# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022416Orig1s000**

# MEDICAL REVIEW(S)

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA Complete Response |
| Application Number(s) | 22416 |
| Priority or Standard | Standard |
| Submit Date(s) | 2/11/13 |
| Received Date(s) | |
| PDUFA Goal Date | 11/8/13 |
| Division / Office | DNP/OND |
| Reviewer Name(s) | Teresa A. Podruchny, M.D. |
| Review Completion Date | 10-10-13 |
| Established Name | Eslicarbazepine Acetate |
| (Proposed) Trade Name | Aptiom |
| Therapeutic Class | Anticonvulsant |
| Applicant | Sunovion |
| Formulation(s) | Immediate release, tablet |
| Dosing Regimen | oral, once daily |
| Indication(s) | Adjunctive treatment of Partial Onset Seizures |
| Intended Population(s) | 18 years of age and older |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

This is the clinical efficacy review of the NDA 22416. The safety review in this cycle was performed by Dr. M. Doi. Based on my review of the submission in this cycle and over three submission cycles (I was the clinical reviewer in the first cycle), I recommend the Agency issue a Complete Response letter to the Sponsor of Eslicarbazepine Acetate (ESL) due essentially to a lack of confidence in data integrity at this time and uncertainty that the processes in place to conduct and/or oversee the trials in a corrective manner and present accurate data functioned/function effectively. This opinion is supported by previous OSI and review findings, evidence of the need for repeated requests and clarification of/from the Sponsor for information in this 3rd submission cycle, and the recent receipt of response(s) from the Sponsor in which the Sponsor did not correctly identify all issues in a finite set of records needed to evaluate for the response (for study 304). Study 304 is the newer study that, at this point, seems to better conducted than the two other studies (301 and 302). The Office of Scientific Investigations' (OSI) review from this cycle is pending as I complete this review.

Earlier in this cycle, there was some concern over a pre-marketing trial case that meets Hy's criteria. The details were not well documented. I note this fact because it speaks in some way to the data issues described in the reviews of several disciplines and perhaps to trial conduct and processes. (In terms of safety, the safety review team concluded that no safety issues were identified that would preclude approval though Dr. Doi noted final approval recommendations were deferred to Dr. Hershkowitz and to me)

This application has received a high level of scrutiny. However, this has largely been driven by the problems encountered in review(s) though there were Sponsor-identified GCP problems in the first cycle with a fourth phase 3 study that is not considered reliable. I recommend the Agency consider whether evaluation of data management reconciliation reports for critical parameters (such as the primary endpoint in the efficacy studies) could provide complementary information to OSI inspections and review findings to assist in determining the integrity of the primary (efficacy) data.

If is determined that the NDA is approvable/may be approved as related to the issues raised above, I still have some questions that primarily are related to the diary type used in the studies. Generally, two adequate and well-controlled trials, statistically positive for the endpoint proposed, are required for regulatory approval of an anticonvulsant for this indication in this Division. Three studies are submitted in this cycle to support the efficacy of ESL at doses of 800 mg and 1200 mg. One of these three studies (304) does not show statistical significance of the 800 mg group when compared to placebo for the primary endpoint (though arguably the p value is just under 0.6). This is the only study of the three that included data from a seizure diary type (daily entry, filled out daily

regardless of the occurrence of a seizure) that generally the Division believes is "better" by design than the type of diary used in the other two studies. The diary type used exclusively in the other two studies is event entry, filled out only when there is a seizure. Event entry diary lends itself to greater uncertainty in distinguishing missing data from zeros in the case of a blank diary page. In study 304, the 800 mg ESL group using the daily entry diary, for which it appears adequately powered, was not statistically different from the placebo group in the primary endpoint analysis while the 1200 mg dose was. This seems to lend some support that dairy type might impact the results of the studies. There are other reasons I question the efficacy of the 800 mg dose, such as comparative rates of serious adverse events of seizure and 50% responder rates in study 304. These are described in more detail in the next section of this review.

A detailed discussion of risk benefit is below.

## 1.2 Risk Benefit Assessment

There are other available approved products for this population and indication. These appear to have similar safety profiles other than the possibly unique occurrence, in pre-marketing, of a Hy's case (of which there appear to mitigating factors and the reader is referred to safety reviews noted later in this section for more details). However, given the totality of the application and an absence of confidence in the data and/or data presentation quality, a final risk-benefit assessment is not made. I do tend to believe there is not a compelling public health need to market this drug at this time.

Quality- In total, efficacy is suggested from the three phase 3 trials that by design are adequate and well-controlled. However, whether there was successful execution of critical elements and processes of trial conduct and oversight to allow for confidence in the integrity of the data and in data presentations remains questionable to me. These issues are listed below and discussed also in sections 2.5 and 3 of this review.

- First cycle- OSI inspections and the existing documentation of Sponsor/CRO oversight issues in trials 301 and 302, Sponsor (then Sepracor, now Sunovion) evaluation of trial 303 as having significant GCP issues while it seems the Sponsor conducting the trial (Bial) did not reach this conclusion, and first cycle review findings as noted in previous discipline reviews. Review concluded in a Complete Response (CR) largely due to concern for data integrity.
- Second submission- received an Incomplete Response- primarily due to adverse event issues similar in concept to those which led to the CR in the first cycle but after Sponsor audits.
- More recently, significant GCP issues at two additional sites in study 301 (additional to those of OSI first cycle review and found in post-Complete Response audits of 2010) and persistent data quality and data presentation issues evidenced by FDA 's multiple information requests to the Sponsor in this cycle (see also Dr. Doi's review of safety and Dr. Lerner's of abuse and

dependency related issues).These types of deficiencies continued to be seen in this review cycle in the face of several audits and efforts by the Sponsor to verify data accuracy.

The OSI review for this cycle is pending at the time of writing of this review, though I have not heard of major inspection findings informally. By the completion of this cycle, OSI will have inspected about 4 sites of 51 in study 302, 3/40 or so in study 301, and 8/160 in study 304. It should be noted that there are inherent limitations in the number of sites (i.e. sampling sizes) and studies that FDA has the resources to inspect (i.e., it is fairly typical for studies outside of the indication not to be inspected though they may contribute safety data) and there is some challenge in site selection in early review cycles. In this case, there are also OSI inspections from the first cycle and an OSI evaluation of audit reports submitted by the Sponsor in the first cycle. OSI's report, from the first cycle, seems to indicate that the number of subjects audited by the Sponsor in all three studies was not sufficient in scope or detail to allow adequate assessment of data reliability and that OSI (then DSI) was concerned that Bial did not exercise adequate oversight of the sites and of the CROs involved in monitoring the sites of the studies submitted in support of the application.

Efficacy: The primary endpoint in all pivotal trials was standardized seizure frequency. This was based on data collected from subjects or caregivers in seizure diaries. In studies 301 and 302, the diary type was an event entry (EE) diary. Diary entries in EE diary are made with the occurrence of a seizure. In the newest study submitted (304), due to FDA concerns about DE diary, a second type of diary was introduced in the then ongoing study, study 304. In this type of dairy, the subject is to note daily whether he/she had a seizure and then is to enter data as appropriate (DE diary).

The final statistical review opinion is that the data overall provided evidence to support the efficacy of ESL as adjunctive treatment in subjects with partial-onset seizures. In study 304, the ESL 1200 mg group was statistically different from placebo for the primary endpoint (standardized seizure frequency). For the 1200 mg group in study 304, the effect remained with a worst-case analysis excluding subjects who used the EE diary types (Dr. Ling's review, p 16/22). Sensitivity analyses indicated that the higher drop-out rate seen in the 1200 mg group "did not appear" to have a drastic effect on the efficacy results or conclusions. For the entire ITT population, the ESL 800 mg group was not statistically significant from placebo on the primary endpoint, though the statistical review states that the results "suggested a trend towards improvement" in standardized seizure frequency. In the ESL 800 mg group, the DE ITT population was not statistically different from the placebo group (unadjusted p value 0.094, adjusted p value 0.167).

The statistical review from this cycle indicates the updated results from 301 and 302 suggests "marginal efficacy of ESL". As I read this statistical review, it cites at least one issue with EE diary use in study 304 data that cannot be resolved with statistical

models. This is important to consider because the event entry diary was the only diary type used in studies 301 and 302.

Study 303 dosed at 800 mg and 1200 mg daily and is the study the Sponsor identified in the first cycle as having significant GCP issues. Therefore, study 303 is mentioned for only for completion. Per the statistical reviewer's analysis in the first cycle, study 303 showed statistical significance at the 1200 mg dose but not the 800 mg dose (her analyses, conservative and non-conservative imputation of the ITT group).

To summarize the primary endpoint data in the three phase 3 studies of adjunctive use in subjects with partial onset seizures submitted to support this application, a table displaying the results is below. The table excludes the 400 mg group as it was tested in two of the studies, 301 and 302, and did not show separation from placebo (Ancova p values, Dunnett multiplicity adjustment, p= 0.33 and 0.42 respectively per study). Also, this dose was not tested in study 304 and is not a proposed maintenance dose.

**Table 1 Efficacy Summary**

| **Study #** | **ESL 800 mg p value** | **ESL 1200 mg p value** |
|---|---|---|
| **304** | 0.058 (NS) | 0.004 |
| **304 DE diary** | 0.167 (NS) | 0.049 |
| **301 1st cycle -Sponsor** | 0.0028 | 0.0003 |
| **1st cycle- Sponsor updated*** | 0.0041 | 0.0009 |
| **301 1st cycle –FDA statistical review** | 0.018 conservative imputation | 0.0010 conservative imputation |
| | 0.0125 nonconservative | 0.0007 nonconservative |
| **301 this cycle -Sponsor** | 0.0468 | 0.0010 |
| **302 1st cycle-Sponsor** | 0.002 | 0.001 |
| **1st cycle- Sponsor updated*** | 0.0095 | 0.0420 |
| **302 1st cycle- FDA statistical review** | 0.0276 conservative imputation | 0.2470 (NS) |
| | 0.0072 nonconservative | 0.1143 (NS) |
| | | |
| **302 this cycle** | .0057 | 0.0424 |

**Sponsor updates in the first cycle were made as response to FDA. NS=not statistically significant**

I tend to think the efficacy of the 800 mg dose is questionable and that the following may support this conclusion.

- The DE ITT in study 304 is not statistically significant at this dose based on adjusted p values and the numbers of subjects is adequately powered.
- The 50% responder rate in study 304 is not statistically different from placebo for the 800 mg group comparison to placebo (p=0.068).

- Rescue medication use in study 304 appears higher in the 800 mg group in this same study.
- The Sponsor's CSS indicates that in the controlled phase epilepsy pooled safety data, 0.2% of both the placebo and ESL 1200 mg groups compared to none of the ESL 400 mg group and 1.4% of the ESL 800 mg experienced partial seizures with secondary generalization. Also, of the treatment-emergent serious adverse events, two met the criterion for partial seizures with secondary generalization. These were in the ESL 800 mg group.
- There is a higher occurrence of serious adverse events of seizure in ESL groups than placebo in the controlled study pool (0.5% compared to 1.4%, Dr. Doi's NDA safety review, Table 61) and it appears there is a higher frequency of these events in the 800 mg group (and 400 mg group) than in the placebo group in study 304 (0.9% to 1.2% compared to 2 or 2.4%, please see review section 7.3.5).
- In study 302, it also appears there are some differences in effect based on seizure type with the 800 mg group not showing a trend in reduction (and in fact has a positive change) when compared to placebo for partial seizures with secondary generalization in one of the three pivotal studies, <u>though</u> the numbers are small enough that interpretation is limited.

In terms of quality and the endpoint efficacy data, Dr. Ling reports that study 304 did not have the extensive hard-coding that was present in studies 301 and 302. Hard-codes in 301 and 302 were used in the creation of the analysis dataset to correct data errors <u>after</u> the database was locked and after unblinded (study 301), "indicating questionable data quality." Dr. Ling's first review of study 301 also noted that in the original submission, the sponsor only mentioned the blinded review, not the unblinded review (p.15-16 of referenced review).

It is acknowledged that one has to be careful not to bias the review by choosing data that only or primarily supports the view one believes is closest to correct. This NDA is a challenge because there are reasons to believe the molecule has efficacy that are related to chemical and class similarity with other product approvals that were based on demonstrations of efficacy in controlled trials and because there is evidence, without regard to quality issues, of an effect.

<u>Safety</u>:

Detailed review of the safety during this cycle was performed by Dr. Mary Doi, with supervisory signature by Dr. S. Yasuda. The reader is referred to this review for the formal evaluation and characterization of the safety data and for the formal discussion of the processes to ensure quality of the safety data across development phases and trials. Dr. Doi's review (p.18) describes that the magnitude and extent of deficiencies in the analysis datasets are concerning. She notes that it is known that data from six studies in the ISS were incorrectly integrated into the ISS datasets. She also notes that

even though all deficiencies identified by the Division were corrected, the potential for additional unidentified deficiencies cannot be ruled out. Dr. Doi states that she did not identify any safety issues that would preclude approval. In terms of quality of data and/or data presentations, as I understand it, the FDA's Drug-Induced-Liver-Injury (DILI) review was impeded by problems with the data when submitting in eDISH

Based on at least one previous internal meeting discussion of the clinical team during the review cycle, the sole safety issue itself that would by its nature possibly have precluded approval is the on-face Hy's case seen in a trial of bipolar subjects. (b) (4) As of the final writing of this section, I am aware of the opinions of the parties engaged in the review of this case (Drs Doi and Yasuda in DNP, Dr. J. Senior, FDA DILI consultant, and Dr. (b) (4), an expert Sunovion engaged). These are summarized as follows. The FDA safety review recommends labeling for this case (please see the review of Dr. Doi for detailed discussion). Dr. J. Senior concludes essentially, that eslicarbazepine acetate is not likely to cause serious liver injury in patients severe enough to damage performance of the liver, that serious liver injury very likely will be very rare, and will probably be preceded by early symptoms of organ dysfunction. He cites both carbamazepine and oxcarbazepine have been reported to cause rare but serious liver injury, including liver failure and death and that there is no evidence provided that this cannot occur with eslicarbazepine (based on consult attached in email from J. Senior 10-8-13, 9:22 AM, please see Dr. Senior's consult for additional details and the appendix of this document for email from Dr. Senior earlier in review cycle). Dr. (b) (4) "a direct effect of ESL, if it in fact accounts for the events observed in this patient," should not represent a health risk to ongoing (b) (4) subjects since they had all been treated for at least 4 months and new subjects were not being recruited. Updated case information did not alter this opinion. As I understand it, there are no DILI cases in the post-marketing experience of Zebinix that meet Hy's criteria.. For a full discussion of this case, the reader is referred to Dr. Doi's review.

This Hy's case is important for process reasons. From a trial process point of view, it appears based on submission content, that detailed exploration to acquire case information came only after FDA inquiry and in the first cycle review this case was captured under the heading "vomiting". Part of the problem with evaluating this case was that some important medical details appear not to have been acquired from the site until FDA inquiry.

As another quality of data point, I am aware of a recent post-marketing European case for Zebinix submitted (b) (4) for an adverse event which appears to be seen in the narrative, "angioedema", (b) (4) but is not coded as an event in the appropriate place on the form.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Please see the safety review of Dr. Doi or the review of her Team Leader, Dr. Yasuda.

### 1.4 Recommendations for Postmarket Requirements and Commitments

If approved, the following may be requested, granted, or considered.

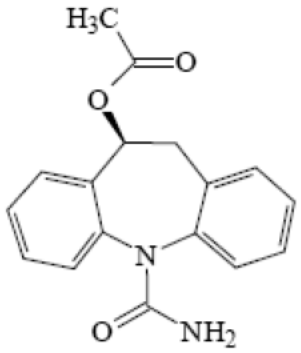
- (b) (4)
- Adequately controlled, randomized, prospective efficacy studies examining POS would be required, but may deferred, for patients > 1 month to < 17 years. This should be accomplished through two studies, one using a diary based endpoint for children older than 2 (or 4) years old and the other EEG based endpoint for younger children. The studies should include a long term extension to collect long term safety data. (This recommendation is mostly based on email from TL to me on 9-12-13).There would need to be stratification by age to represent the entire pediatric age spectrum adequately.
- A waiver will be granted for patient efficacy studies 1 month and younger because there are few patients who can be definitively diagnosed with this condition making such a study highly impractical.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Eslicarbazepine Acetate (ESL) also referred to as SEP-0002093 or (b) (4) or BIA 2-093, is a voltage-gated sodium channel blocker. It can be considered a member of a third generation in the dibenz[b,f]azepine anticonvulsant family represented by drugs like carbamazepine as first generation and oxcarbazepine as second generation.

With oral administration, eslicarbazepine acetate metabolizes to S- and R-licarbazepine and oxcarbazepine, as does Trileptal (oxcarbazepine), just in a different ratio (different proportions). A difference with carbamazepine is that it does not auto-induce its own metabolism and is not metabolized to the epoxide form. A difference with oxcarbazepine is that it is not readily metabolized to a racemic mixture of eslicarbazepine and R-licarbazepine. Following oral administration, eslicarbazepine acetate is metabolized to yield mainly S-licarbazepine (eslicarbazepine, BIA-194) and to minor metabolites, R-licarbazepine (BIA 2-195) and oxcarbazepine.



Molecular weight: 296.32
Molecular formula: $C_{17}H_{16}N_2O_3$

Proposed labeling dosage strengths are immediate release tablets of 200 mg, 400 mg, 600 mg, and 800 mg. The proposed indication is adjunctive in the treatment of partial onset seizures in patients with epilepsy 18 years or older. The proposed dosing is once a day oral dosing initiated at 400 mg daily for one week and increased in increments of 400 mg about weekly to a maximum recommended dose of 1200 mg once a day. The Sponsor's proposed usual maintenance dose is 800 mg daily. The dose can be taken whole or crushed, with or without food.

Dose reduction is recommended in moderate and severe renal impairment and treatment initiation is recommended to be at a 200 mg daily dose for two weeks. (b) (4) a 200 mg dose strength was requested by the Agency to facilitate titration in this population. However, dissolution issues for this dose precluded approval at the as of 8-27-13.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Anticonvulsants used clinically as adjunctive treatment for partial epilepsy are included in the table below.

**Table 2 Anticonvulsants currently available for the proposed indication**

| Clinical use - may or may not be FDA approved for use | Approved for same indication and includes same age |
|---|---|
| phenobarbital | seizure type not specified in label |
| primidone | yes generally |
| phenytoin | yes |
| carbamazepine | yes, though language is general |

| | |
|---|---|
| valproic acid | yes |
| gabapentin | yes |
| lamotrigine | yes |
| topirimate | yes |
| tiagabine | yes |
| levetiracetam | yes |
| lacosamide | yes |
| oxcarbazepine | yes |
| zonisamide | yes |
| pregabalin | yes |
| ezogabine | yes |
| perampanel* | yes (not yet marketed) |
| felbamate | not first line use due to safety issues |
| vigabatrin | yes |

***Perampanel (not yet marketed)**

## 2.3 Availability of Proposed Active Ingredient in the United States

Eslicarbazepine acetate (Zebinix) is available outside of the United States as white tablets in strengths of 200 mg, 400 mg, 600 mg, and 800 mg and is indicated for adjunctive use in adults with partial-onset seizures with or without secondary generalization. The standard dose is 800 mg, starting at 400 mg before increasing. The maximum dose is 1200 mg daily based on treatment response.

Eslicarbazepine acetate was granted marketing authorization on 4/21/09 by the European Medicines Agency (EMA) with the marketing authorization holder as Bial-Portela & Ca, S.A. EMA product information contraindicates use in people with hypersensitivity to the active ingredient or to other carboxamide derivatives and in 2$^{nd}$ or 3$^{rd}$ degree atrioventricular block. EMA product information cautions use in patients with kidney problems, recommends dose adjustment based on kidney function, and is not recommended for patients with severely reduced kidney or liver function. Caution is also recommended in the elderly due to limited safety information in these patients. There is also language about the presence of HLA-B* 1502 allele and HLAA*3101 allele as associated with increased risk of severe cutaneous reactions and/or DRESS in subjects treated with carbamazepine.

Eslicarbazepine acetate alone itself is not approved in the U.S. and is not marketed legally in the U.S. for any indication. As noted, eslicarbazepine and oxcarbazepine (Trileptal® ) have the same active moieties and are chemically related. The reader is referred to the review of the Office of Clinical Pharmacology from the first review cycle for more details.

## 2.4 Important Safety Issues With Consideration to Related Drugs

The table below describes some safety issues either considered by the clinical community based on a fairly recent Continuum Neurology or that are in approved labeling. Please see the safety review, performed by Dr. Mary Doi , for additional discussion of eslicarbazepine related safety issues.

**Table 3 Safety Considerations with Related Drugs**

| | **Clinical safety considerations by practice community or idiosyncratic or labeled** |
|---|---|
| phenobarbital, | induces hepatic enzymes, may be more of problem with elderly patients on multiple concomitants, physical dependence may occur, CNS depression |
| primidone | |
| phenytoin | induces hepatic enzymes, may be more of problem with elderly patients on multiple concomitants, lupus-like reactions, pseudolymphoma |
| carbamazepine | induces hepatic enzymes, may be more of problem with elderly patients on multiple concomitants, serious rash in HLA-B1502 genotype (common in Asian population) |
| valproic acid | teratogenic, risk hepatotoxicity and pancreatitis, needs lab monitoring, weight gain, autism?, cognitive delays |
| gabapentin | weight gain |
| lamotrigine | serious skin reactions, aseptic meningitis |
| topirimate | avoid in presence or history of kidney stones, may cause weight loss |
| tiagabine | non-convulsive spike-wave stupor |
| levetiracetam | irritability and anger with psychiatric adverse events thought to be issue thought not seen in trials of approval |
| lacosamide | Cardiac conduction issues, DRESS (label) |
| oxcarbazepine | SJS, TEN |
| zonisamide | avoid in presence or history of kidney stones, may cause weight loss |
| pregabalin | weight gain |
| ezogabine | urinary retention, blue discoloration, retinitis pigmentosa (label) |
| perampanel* | serious psychiatric and behavioral adverse reactions including homicidal ideation |
| felbamate | SJS, aplastic anemia, hepatic failure |
| vigabatrin | permanent visual field loss, psychosis |

**Source: includes Continuum, June 2010, v16 (3, Epilepsy)**

| | |
|---|---|
| **Eslicarbazepine** | Possible Hy's case in premarketing cannot rule out eslicarbazepine hyponatremia and DRESS and others as per some or all of the anticonvulsants |

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

This is the third submission in this NDA's history. This submission was on 2-11-13.

The first submission of the NDA was 3-30-09.

- Subsequent to the first cycle review, a Complete Response (CR) letter was issued on 4-30-10. The basis for the CR was significant and serious deficiencies in the application and/or data precluding definitive conclusions about safety and efficacy. The letter recommendations included additional audits of clinical sites that enrolled subjects in studies 301 and 302 to provide assurance that safety and efficacy data were reliable. The letter noted the possibility "You should be aware that we are likely to request that you conduct at least one more controlled trial under acceptable and accepted clinical practices".
- End-Of-Review Meeting on 7-30-10. Sepracor and the Agency discussed the proposed audit plan.
- Meeting with the Sponsor on 6-7-11 primarily to discuss the NDA resubmission plan and the outcome of the study 301 and study 302 audits. 76 GCP audits were conducted in 2010, including 37 sites for study 301 and 39 for study 302. For both studies, a higher frequency of potential adverse events were noted in source documents but not entered into case report forms during the 2010 audits as compared to 2008 audits (summ-reg-history. pdf 9-14-12 submission SDN 56, seq 53 to the NDA). *(note to reader: this is potentially important because not all studies in the datasets have undergone the type of audits that these studies underwent)*. In study 301, sites 174 and 175 in Poland were proposed to be excluded from data for the integrated efficacy analyses due to noncompliance at the sites (sites did not maintain original source data to verify the completed patient seizure diary card, p. 19/32 SDN 56, summ-reg-history.pdf). It was decided at the 6-7-11 meeting that ISS would include a separate presentation of adverse events including the potential adverse events identified during the audit. Sunovion also submitted a document that included justification to address data reliability, and a detailed analysis of the impact of protocol violations for each patient with regard to safety and efficacy on 6-24-11.
- A face-to-face meeting to discuss the overall pediatric development plan for use (b) (4) in adjunctive POS in children age 1 month through 17 years was held on 12-14-11. (b) (4) DNP noted that staging was acceptable with two caveats; subjects one month to 2 years must be examined in a separate study and subjects should be stratified by age for a complete representation throughout the full age range. DNP agreed that data from study 202 (a completed open-label, phase 2 study in pediatric subjects 2-17 years old with partial onset seizures) showed that the exposures are similar to those seen in the adults at the studies doses of 800 mg and 1200 mg. DNP noted that due to the limited number of patients and the multiple anticonvulsants patients

received, the conclusions of tolerability might be confounded as a result of pharmacokinetic and/ or pharmacodynamic interactions. (b) (4)

The second submission of the application, dated 8-31-12, was received on 9-4-12.

- There were several teleconferences with the company in September 2012 (9-24 and 9-28). Ultimately this submission received an Incomplete Response letter issued on 11-02-12 with deficiencies that included, similar to the first cycle, missing adverse events from the datasets and what appeared to be a lack of proof-reading of the submission.
- There was a teleconference with the Sponsor on 11-6-12. Meeting discussion included discussion of what appeared to be one factor in the missing adverse events in this cycle; the Sponsor confirmed that CIOMS forms had not been included as source documents in the previous audits. The Division requested 100 randomly selected subjects without narratives to xx.
- On December 12, 2012, the Division requested exposure information for new subjects on eslicarbazepine acetate between 1-31-12 and 8-31-12 to determine the cut-off date of ongoing studies for purposes of submission.

## 2.5 Other Relevant Background Information

Three pieces of additional information that may be informative to the reader; one is an apparent difference in BIAL's assessment of GCP compliance in study 303 versus FDA's and Sunovion's, the second is related to drug interactions with carbamazepine and how this is handled in EMA labeling, and the third that there trials of monotherapy use in partial-onset epilepsy are now completed.

As noted above, eslicarbazepine acetate is authorized in the European Union. Bial submitted the application in Europe and holds the authorization. Sunovion (then known as Sepracor) partnered with Bial to acquire marketing rights in the U.S.

Based on EMA's public assessment report online via the EMA site (see excerpt duplicated below) it appears the original Sponsor (Bial) and Sunovion did not have the same impression of the quality of the data in study 303. EMA did note (not shown in the excerpt below) that study 303 appeared to have higher frequency of major protocol violations than studies 301 and 302 though integrated analysis excluding these data was not significantly from the overall previous integrated analysis.

> "The clinical trials were performed in accordance with GCP "as claimed by the applicant." The clinical development plan included two phase 2 trials and 3 phase 3 trials in epilepsy (301, 302, and 303) and two phase 2 trials in adult with bipolar disorder. "

EMA product information describes that eslicarbazepine acetate dosing may need to be increased in the presence of either carbamazepine or phenytoin and the dose of phenytoin decreased based on individual response. Internally, DNP is considering the language for dosing recommendations in light of carbamazepine –eslicarbazepine drug interactions and the possible implications on pharmacodynamic parameters (efficacy).

The Sponsor has recently completed one or both of the historical- control monotherapy trials of subjects with partial onset seizures.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

In order to provide additional context for the risk-benefit section and the recommendation regarding an action, this section includes a discussion of events from the two previous submissions to this NDA starting with this cycle.

In this cycle, one new additional efficacy trial (304) was submitted and data from the other pivotal trials 301and 302, now audited several times were re-submitted. Also, the sponsor advised that site 952 in study 304 (Dr. Vikram Sharma, Hyderabad, India), selected for routine clinical investigator site audit, was found to significant issues GCP issues (CSR p. 59/2716) and the site was terminated before participation in part 2 .

In this submission cycle, a number of information requests have been made and a (solicited) major amendment was provided to this NDA on 3-27-13. This amendment resulted in an extension of the PDUFA clock.

Several disciplines have required additional information. This in itself is not unique in NDA review cycles. Based on internal meeting discussion and the safety review (finalized since this section was originally written), what appears atypical to me is the amount of additional clarification, information, and data submission that has occurred in this 3rd submission of an NDA. Based on information in DARRTs, the chemistry discipline received two responses to information requests in this cycle. Controlled substance staff have made three requests for information as of 8-30-13 with the second containing multiple questions. Clinical safety made 14 information requests to the Sponsor as of 8-30-13. It appears that many of the safety requests contained more than one question or clarification. For details, please see the review of Dr. Mary Doi. Also, it has required several requests of eDISH data in order to acquire the data as desired by the FDA DILI consultant.

Efficacy review (statistical and/or clinical) resulted in 5-6 information requests. The efficacy related information requests are discussed in the efficacy section of this review but included duplicate entries of seizures (i.e. seizure on the same date and time repeated in the dataset listing) and identification by DNP of the use of both types of diaries in part 1 of the study in one subject (subjects were to use one or the other depending on time of entry into the study). In the both of these inquiries, the sponsor's response did not correctly identify all issues (in the case of the duplicate entries or in the case of the one subject known to DNP when queried specifically as to whether there were any subjects who used both diaries). This is in the context that the data required of the Sponsor to evaluate in order to respond, though tedious, was finite (40 subjects in one case, 653± in the other).These issues are described in much detail in section 6.1.10 of this review.

Data management plans were requested in the IR letter (after the 2nd submission). I requested these thinking that they may provide an understanding of what processes were in place for adverse event capture, transfer, and oversight. This plan was received in the 3RD NDA submission dated 2-11-13. Based on my limited evaluation of the Data Management Plan (DMP) for study 304 (dated 3-9-12, (b) (4), defined acceptable error rates appear to be included. It is unclear whether these were met based on review issues noted (inclusive in a generally way of safety review issues noted in internal meetings).

The second submission of the NDA received an incomplete response (IR) letter due, essentially, to problems with adverse event data similar in nature to those seen in the first cycle (such as adverse events in a narrative not seen in the datasets). It is notable that this type of inadequacy in the adverse event documentation was on a background of an extensive audit program conducted in part because of the same type of issue in the first cycle.

In the first cycle, the scope and degree of inadequacies resulted in a lack of confidence in the integrity of the data and in the submission. The inadequacies found in the clinical safety review included suboptimal characterization of potentially important medical events (SAE, SJS in phase 1 though likely attributable to another drug, not ESL and the potential Hy's case discontinuation as 'vomiting') and adverse events noted in one place, for example, in the CRF, but not in the dataset. There was suggestion of under-reporting of adverse events based on a comparison of the incidence of placebo SAEs between ESL and several other anticonvulsant development programs (admittedly, this is an imperfect approach). OSI Inspection results from the first cycle are summarized in section 3.2 below.

The Sponsor performed audits to address these issues. Though the results may or may not have uncovered any major safety findings or event numbers that changed the results significantly, it did perhaps raise also the question of process (in documentation

and information capture and processing). A summary of the Sponsor's description of the 2010 audits as related to efficacy is in section 3.2 below.

Also in the first cycle, the statistical reviewer noted "extensive" hard-coding in study 301 (less so in study 302) that seemed un-intentional but indicated the study was not well conducted and that data quality/reliability was questionable. The statistical review noted that a second review of seizure data from study 301 was conducted after unblinding (she also notes that in the original submission, the sponsor only mentioned a blinded review, not the unblinded review). Both 301 and 302 have a potential diary issue in that subjects only had to fill out the diaries if they had a seizure (event entry) versus having to fill out the diary daily regardless of whether a seizure occurred (daily entry). Thus, true zeros could not be distinguished from missing data. A worst-case-analysis for study 302 was performed (and the analysis showed favorable results although lost significance for the 800 mg daily dose). The FDA statistical review indicates that such an analysis could not be performed on the data from study 301 because the period of time for which the diaries were missing was not determinable.

In addition to these FDA-identified issues, the Sponsor reported that "Due to Good Clinical Practice (GCP) concerns regarding the conduct of the third Phase III study (2093-303)," the results would be considered supportive but not determinative for the purpose of safety and efficacy evaluation (p. 12/75 clinical overview first NDA submission). The sponsor asserted, essentially, that issues with study 303 were largely due to one CRO who did not perform adequate oversight of the sites it monitored in Mexico and that this CRO was not used in studies 301 and 302. However, the sponsor also noted GCP deficiencies "having less overall significance" (p. 64/75 of clinical overview first NDA cycle) at two sites not in Mexico (so presumably a different CRO). It appears that Bial, the original sponsor, did not conduct any clinical sites audits for study 201 (phase 2, adult, partial-onset seizures) though Sepracor did. Sepracor reported that at two of the five sites audited, certain GCP deficiencies were noted. The U.S. Sponsor (Sepracor, now Sunovion) reports these deficiencies indicated less than full compliance but did not adversely impact interpretation and the ability to fully use the data. I include this information about study 201 because most of the studies used to evaluate safety and efficacy were not conducted in concert with Sunovion and were conducted under Bial sponsorship. The clinical overview in the 9-4-12 submission indicates that Bial conducted 12 audits of phase 1 studies, 4 audits of phase 2 studies, and 27 audits of phase 3 studies.

## 3.2 Compliance with Good Clinical Practices

Whether the pivotal trials proposed to support the indication were conducted in compliance with Good Clinical Practice (GCP) is not established conclusively in my opinion.

With respect to pivotal trials to support the proposed indication, there were initially three studies, 301, 302, and 303. Study 303 was identified by the Sponsor as having significant Good Clinical Practice (GCP) issues (non compliance) such that the Sponsor posited use as supportive but not pivotal. This study was not selected to be OSI inspected. Ultimately, this Division decided that the neither the efficacy nor safety data would be used to support the product's indication. Safety data from 303 that appeared to represent a significant medical finding would be considered, though the absence of such would not be reassuring. The safety data would not otherwise be utilized (for example, it would not be used for common adverse event incidence).

For the other two studies, 301 and 302, based on the first cycle review and inspectional findings of DSI/OSI (summarized later in this section), GCP compliance for studies 301 and 302 was not established. OSI audits indicated that data from two of the four sites audited (1 in each study) were considered insufficiently compliant to rely upon. Based on the problems identified in the first cycle for studies 301 and 302, third party audits of data were recommended. Despite these audits, the second submission of the NDA still contained adverse event disparities and the company received an incomplete response letter. Findings of DSI/OSI from the first cycle are described at the end of this section. This summary is included later in this section (versus the appendix) because it is unclear to me whether certain types of findings are reparable and/or adequately compensated by additional audits of source data. Also, to place them in the appendix, may appear to minimize the findings.

In the current NDA submission, three trials are submitted to support the proposed indication; studies 301, 302, and 304. As of 4-8-13, whether study 304 is sufficiently compliant with GCP is indeterminate and part of the work of this review cycle. Sunovion has reported that one site in study 304 is known to have significant GCP non-compliance (site 952 in India).

In this submission cycle, the NDA underwent more FDA-OSI site inspections than is typical of an NDA. Eight sites in study 304 (9 investigators) were selected for inspection. In order to maximize the scope of FDA inspections within FDA resource constraints (for example, FDA cannot inspect 25% of sites), the Division and OSI chose some sites that allowed for two studies to be inspected with one site visit as the investigator had participated in more than one trial. Thus, three sites in study 301 (307, 336, and 335) and two in study 301 (123 and 152) were also captured in audits in this cycle. An additional consideration in site selection was the size of the site (i.e. if possible, larger numbers to maximize the number of subject records evaluated). As well, OSI created a table displaying how the results of FDA audits in the first cycle compared to Sponsor audit results. This table was used to pick sites that were discrepant in terms of FDA and Sponsor audit results and to provide some balance; sites that were considered good by this table were also included.

The most recent set of audits by DSI are not complete as of 9-5-13. From preliminary indications in internal NDA team meetings, it appears OSI has found no major inspection problems.

In this re-submission, the Sponsor reports the following with respect to GCP compliance.

The original NDA submission of NDA 22416 included 30 studies conducted by Bial-Portela & C., S.A. (Bial). Bial's quality assurance audit program included a total of 42 clinical sites that enrolled subjects (12 of phase 1 studies, 4 of a phase 2 study, and 27 of phase 3 studies).

Prior to the first NDA submission, Sunovion conducted GCP audits in 2008 at 34 clinical sties (including 29 that had participated in phase 3 trials). Based on Sunovion's findings, Sunovion (then Sepracor) advised the Agency that they did not view study 303 sufficiently compliant to be relied upon as a pivotal study for the NDA. Sunovion reported that studies 301 and 302 were sufficiently compliant. Inspections conducted by FDA during the NDA review cycle found significant deficiencies at two of the four sites inspected. The Agency's concerns were described in the CR letter of 4-30-10.

In 2010, Sunovion conducted a number of additional GCP audits in studies 301 and 302 using an independent 3rd party. This audit resulted in examination of nearly 100% of the subject records that were not previously reviewed in 2008. Based on this audit, Sunovion again concluded studies 301 and 302 were sufficiently compliant to support review. Sunovion also reports meeting with the EMA on 6-7-11 and reports that the EMA concluded adequate GCP compliance had been demonstrated to support EU licensure.

Sunovion notes that additional audits found significant GCP deficiencies at two study 301 clinical sites in Poland. The PIs at both sites 174 and 175 directly completed patient diary cards, reportedly to assure dairy card legibility, and original source data were not maintained. This impacted 20 study subjects. Source data could not be verified and the sponsor excluded these sites from efficacy analysis.

The current re-submission includes a new pivotal study, 2039-304. 160 clinical sites, US and non-US, randomized at least one subject. Sunovion and Bial implemented a joint quality assurance program for study 304 and conducted GCP audits at 88 clinical sites. The company summarizes that these audits generally found the sites to be operating in substantial compliance with GCP regulations or with GCP deficiencies that were corrected as a result of the audits. One site in India (site 952) was found to have significant GCP non-compliance. The investigator failed to adhere to certain protocol-specified measure intended to assure patient safety, failed to properly report adverse events and failed to assure adequate completion of key safety-related forms. The company notes that an attempt was made to bring the site into compliance, but on a follow-up audit, the investigator was deemed unreliably adherent to the protocol with respect to patient safety and reporting safety events to the sponsor. The site information was submitted to DSI on 5/4/12 and the site was closed by BIAL. The Sponsor asserts that the study is sufficiently compliant so as to support NDA review. The sponsor notes that more detailed information on the GCP deficiencies observed during the audits conducted, as requested in the CR letter, is provided. Review of this information is deferred to DSI/OSI.

With reference to the 2010 audits, the Sponsor's document complete-response.pdf (found through hyperlink to section 1.1.2.2 in section 2.5 Clinical Overview, p.40/69, submission 2-11-13) provides discussion of the 2010 audits. Formal review is deferred to DSI/OSI. A summary, based on the referenced document is included though formal

review is deferred to OSI. Two tables of possible interest to the reader (Table 1 and Table 2) are copied in the appendix of this review from the document and show a summary tabulation of audit findings.

Study 301:

- 20 subjects enrolled in the study did not meet strict eligibility criteria.
- 35 subjects, auditors not able to confirm eligibility with respect to seizure frequency or stable anticonvulsant use due to inadequate source (reportedly many were at two sites in Poland removed from analysis.
- Audits found 10 subjects did not meet strict entry criteria with respect to seizure type/frequency (4 with seizure-free periods > 21 days, 4 had 2 to 3 seizures (instead of 4) in one of the qualifying periods prior to randomization, 2 had disqualifying seizure types.
- Auditors could not confirm independently that seizure frequency and type met protocol requirements for 26 subjects (20 were at two sites in Poland where original subject-completed diary cards were not available, and 6 were at other sites and were due to inadequate source records
- Auditors found that 10 subjects did not meet strict eligibility with respect to stable anticonvulsant use (2 using more than 2 anticonvulsants, 1 taking disqualifying medications, 7 with unstable doses prior to screening).
- For 9 subjects, documentation issues caused the auditors to be unable to confirm eligibility.

Study 302:

- 92 subjects enrolled in study 302 did not meet strict eligibility. For 48 subjects, audits found he PIs did not have complete information at the time of randomization on certain laboratory work and/or contraceptive methods, “or there were other issues that affected subject eligibility”. The Sponsor states these subjects were qualified for entry based on seizure frequency and stable anticonvulsant use. For 27 subjects (of the 92?), auditors were not able to confirm eligibility with respect to seizure frequency or stable anticonvulsant use, due to inadequate source data. The details are:
    - Audits found 52 subjects did not meet strict entry criteria with respect to seizure type/frequency (9 with seizure-free periods > 21 days, 39 had 2 to 3 seizures (instead of 4) in one of the qualifying periods prior to randomization, 3 had disqualifying seizure types).
    - Audits found that 40 subjects did not meet strict eligibility criteria with respect to stable anticonvulsant use. 14 were taking more than 2 anticonvulsants, 3 were taking disqualifying medications, and 23 were not stable on an anticonvulsant dosage before screening. Another 12 (it seems a separate 12) for whom documentation issues precluded auditors’ ability to confirm eligibility.

- Other eligibility issues-audits found documentation and other issues that affected eligibility determinations for 48 subjects. These appear to be mostly medical/clinical issues (such as 28 due delays in reviews of laboratory tests and 9 subjects incomplete information on contraception methods)

**OSI first cycle:**

OSI inspected four clinical sites; two each in study 301 and 302. Upon inspection, the data at two sites (one per study) were found unreliable. Findings included inadequate record keeping, unorganized medical records, sticky notes used to record observation or to add missing information, and the failure to adhere to protocol eligibility criteria for enrollment. OSI performed the FDA's formal review of the company's submitted audit forms and indicated that the number of subjects audited by the applicant in the studies (301, 302, and 303) was not sufficient in scope or detail to allow for adequate assessment of data reliability. OSI also noted that the audits revealed a broad range of violations regarding safety data, inclusion criteria, poor source documentation, discrepancies between source document and what was in the CRF in terms of adverse events, and inadequate drug accountability records suggesting a systemic problem across all three studies.

**Informed Consent and Ethical Approval of Studies**

In an information request dated 4-24-13, DNP requested confirmation from the Sponsor that all studies conducted in humans, all phases of development, IND or non-IND, epilepsy or other indications, included informed consent and had IRB approval or local equivalent of IRB approval. The Sponsor's response in SDN 87 (sequence 84 to the NDA) states that they confirm this to be the case.

A cross-check of the studies reported in Table 1 of SDN 87 with the study identifier in the table 5.1 of this review indicates that ongoing studies (i.e. 208, 305, 401, 311, 45, 46, and 50) and study 308 (reported in the ISS appendix 7.1.1 of the 2-11-13 submission as clinically completed but not reported as of 1-31-12 cut-off) are not included in Table 1 of SDN 87. Also, the documents hyperlinked to study 116 (QT study) are for study 118 (MTD study) though the ones hyperlinked to study 118 are for study 118. The hyperlink within the study report for study116 also links to 118 documents. The study report section 5.1 and 5.3 report that the protocol and informed consent were reviewed and approved by an IRB and that the nature and purpose of the study were explained to subjects before they provided consent but, as noted, the documents themselves are not present via the hyperlinks provided.

I audited the IRB (or apparently equivalent, and consent) documents as accessed via the hyperlinks in SDN 87 for 11 studies (101, 106, 113, 116, 126, 129, 201, 209, and part 1 of studies 301, 302, 303, and 304 (the extension studies of the pivotal trial were listed separately from the double-blind period in Table 1 of SDN 87).

In some cases, only a lists of the IRB (or local equivalent was provided), such as for studies 303 and 209. For sites with multiple IRB equivalents (local or independent committees listed), I reviewed informed consents at a few sites (such as in study 304, Copernicus, Greece, Poland, and site 952). Some of the consents are, not unexpectedly, more comprehensive than others. The sample informed consent for study 129 (p6-17/29 of the hyperlink) did not appear to discuss the possibility for allergic reactions or serious reactions. Consents for studies 201 and 209 were also less obvious in noting the potential risk of a serious allergic reaction though they did note possibly unknown events/reactions.

*Reviewer's comment: The Bial study consents reviewed could have been better in describing the possibility of allergic reactions or the possibility of serious allergic reactions. The company has reported confirmation that all studies were compliant with IRB and IC issues. Based on SDN 87, this cannot be independently verified by random audit for ongoing studies, study 308, or, utilizing both the study report and SDN 87, for study 116 as the documents do not seem to be present.*

## 3.3 Financial Disclosures

All principal investigators and sub-investigators, except those noted in the financial disclosure document Table 2 (copied from the submission below), listed on the signed FDA 1572 for Sunovion and Bial for the phase 3 trials, 301, 302, 033, and 304, have submitted Financial Disclosure statements indicating the extent to which they received any compensation in any of the four categories:

Category 1 - financial arrangements whereby the value of the compensation could be influenced by the outcome of the clinical trial.

Category 2 - Significant payment of other sorts excluding the costs of conducting the clinical trial or other clinical studies. This could include payments to investigators or institution with a monetary value of > $25,000.

Category 3 - A proprietary or financial interest in the test product, such as patent, trademark, copyright, or licensing agreement.
Category 4 - A significant equity interest in the sponsor of the clinical trial. This would include, for example, any ownership interest, stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or any equity interest in a publicly traded company exceeding $50,000.

The signed financial disclosures made by each of the investigators also certified whether any of the above categories of interest were held, and in what amount (s), by his or her spouse or dependent children.

The Sponsor says that based on the signed financial disclosure forms collected for all principal investigators and subinvestigators who participated in clinical trials that support efficacy and/or safety for Eslicarbazepine acetate, Sunovion and Bial certify that to the best of the company's knowledge, no investigators or subinvestigators received compensation for Categories 1 and 3, or compensation beyond the acceptable limits for Categories 2 and 4 except (b) (6) who received > $25, 000. She was a sub-investigator for (b) (6). at a site in study 304 that randomized (b) (6)

**Table 4 Financial Disclosure**

**Table 2: Financial Disclosure Information Not Available**

| Investigator Name | Study Number/Site Number | Number of Subjects Enrolled at Study Site |
|---|---|---|
| (b) (6) | | |

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

The conclusions of two reviews are described briefly in this section. The first is from the Office of New Drugs and Quality Assessment (ONDQA) regarding dissolution and the second is from the chemistry, manufacturing, and controls (CMC) perspective.

The finished drug product is an immediate release tablet form of four different strengths; 200 mg, 400 mg, 600 mg, and 800 mg. In the initial submission of the NDA, only the three higher strengths (i.e. not the 200 mg) were evaluated. This most recent submission of the NDA includes a 200 mg strength tablet. This dose was made at the request of DNP in order to facilitate up-titration in patients with renal impairment.

As per the review in DARRTs on 8-27-13, by the ONDQA Biopharmaceutical Reviewer, Dr. Elsbeth Chikhale, with supervisory signature of Dr. Angelica Dorantes, the 200 mg strength tablet does not meet dissolution standards for similarity with the drug product used in pivotal trials and the biowaiver, therefore, is not acceptable.

Dr. Chikhale's review also reports that the results from the dissolution studies evaluating the effect of (b) (4) Therefore, the results of clinical studies using (b) (4) may be affected and that the impact of a possible bias on the overall clinical results (safety and efficacy) would need to be further assessed by the Medical Reviewer.

Based on the information in either study reports or protocols for trials 301, 302, and 304, this does not seem to a blinding issue for efficacy analyses in the controlled phases because it does not appear that the 800 mg tablets (or 1200 mg dose group) were used in these phases. This is based on the descriptions of the investigational drug product (SDN 1, 3-30-09, module 5.3.5.1, p. 28/1074 CSR 301, p. 20/17103 CSR 302, and SDN 56, 9-4-12, module 5.3.5.1, 304 amended protocol #2, pages 34-35 and 40-42/81) and a lack of finding (b) (4) terms/word fragment in a search of the study reports for these respective trials. *However*, description of the investigational product in trial 302 notes that the 400 mg and 800 mg tablets were of (b) (4) so corresponding placebo tablets ('placebo 800' and 'placebo 400') were used in part 1.

To confirm that (b) (4) products were not used in the controlled phases, an email was sent to the Sponsor on 9-12-13 and is pending as of writing of this section. Also, as I understood the OCP reviewer (Dr. Bei) in an internal team meeting in this review cycle, in study 304, the to-be-marketed product was bioequivalent to the product used in the clinical trial. Any possible implications for safety data are deferred to Drs. Doi/Yasuda.

The Chemistry review was finalized in DARRTs on 8-29-13. The primary reviewer is Dr. Charles F. Jewell and supervisory signatory is Dr. Ramesh K. Sood. This Chemistry team reports that the chemistry, manufacturing, and controls (CMC) perspective is adequate and that the manufacturing sites received an overall acceptable rating from the CDER Office of Compliance.

## 4.2 Clinical Microbiology

NA

## 4.3 Preclinical Pharmacology/Toxicology

The preclinical review is not completed with supervisory signature as of the writing of this review section on 9-6-13. In informal discussion on 9-6-13 with the primary non-clinical reviewer, Dr. C. Toscano, he noted the only issue from the first cycle CR was the need for an in vitro chromosomal aberration study. This study has been completed and reviewed. Based on his assessment, (his review is not finalized in terms of supervisory signature), the referenced chromosomal aberration study is negative and there are no non-clinical issues to preclude approval.

There is an issue about language in the proposed label which describes juvenile toxicity studies performed in dog, however, this is not critical to the action on this application as there is no proposed pediatric indication in this NDA cycle. The reader is referred to the non-clinical review team for discussion of these studies.

## 4.4 Clinical Pharmacology

As per the summary of clinical pharmacology submitted by the Sponsor in the 9-4-2012 submission, six new clinical pharmacology studies were completed between the original NDA submission and the cut-off for the 9-4-12 submission.

- Four were drug-interaction studies for eslicarbazepine with simvastatin (study 2093-124), combined oral contraceptive (2093-128), carbamazepine (2093-129), and rosuvastatin (093-150).
- One was a study of the PK of ESL and its metabolites in plasma and cerebrospinal fluid in comparison to oxcarbazepine (2093-127).
- One study investigated the PK of eslicarbazepine in healthy recreational central nervous system depressant drug users (SEP093-153). The sponsor indicates there was also an update on PK data from studies 301, 302, and 303.

Formal review of this section is deferred to the Clinical Pharmacology Team.
As of the writing of this section of the review, the clinical pharmacology review is not formalized. Based on internal meeting discussions, as I understand it, there are no issues to preclude approval from a clinical pharmacology perspective though there are labeling issues.

### 4.4.1 Mechanism of Action

See the paragraph following the sub-section heading 4.4

### 4.4.2 Pharmacodynamics

See the paragraph following the sub-section heading 4.4

### 4.4.3 Pharmacokinetics

See the paragraph following the sub-section heading 4.4

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

36 studies were submitted in the first NDA cycle (original application 2009). 17 newly completed or new studies were included in the 9-4-12 submission including one newly completed phase 3 epilepsy pivotal study (study 304).

This submission included only one additional efficacy pivotal study (study 304). However, due to the cumulative review of safety data, tables showing all trials are below. When used, the colored font (blue in my window) shows new studies since the first application cycle with the exception that newly completed extension parts are not in colored font.

**Table 5 Completed Phase 1 Studies**

| Completed PHASE 1 | | | | | |
|---|---|---|---|---|---|
| **PK/Toler-ability and Safety** | **BA Food Effect** | **Comparative BA/BE** | **PK/PD** | **Special Populations** | **Drug-drug interactions** |
| 2093-104 | 2093-103 | 2093-109 | 2093-101 SAD (EEG) | 2093-111 (hepatic impairment) | 2093-107-digoxin |
| 2093-110 | 2093-117 | 2093-122 | 2093-102 MAD (EEG) | 2093-112 (renal impairment) | 2093-108-warfarin |
| 2093-115 | | 2093-130-BE 2 doses healthy volunteers | 2093-116 (QT)-DB, R | | 2093-114-combined contraceptive<br>2093-128 combined contraceptive |
| 2093-113 | | SEP093-155 | 2093-123- | | 2093-119- |

| | | | | | |
|---|---|---|---|---|---|
| | | BA/BE oral whole or crushed tablet healthy volunteers | PD healthy volunteers | | lamotrigine |
| 2093-118 (MTD)-DB, R | | | | | 2093-120-topiramate |
| 2093-105 (elderly included) | | | | | 2093-106- (study was discontinued early) phenytoin |
| | | | | | 2093-121-phenytoin |
| | | | | | 2093-124 simvastatin |
| | | | | | 2093-150 rosuvastatin |
| 2093-127 CSF v plasma ESL and OXC | | | | | 2093-125-metformin |
| SEP093-153-Abuse Potential | | | | | 2093-126-gliclazide |
| | | | | | 2093-129-carbamazepine |

**Table 6 Completed Phase 2 Studies**

| **COMPLETED PHASE 2** | |
|---|---|
| **Epilepsy** | |
| **Children/adolescents POS** | **Adults POS** |
| **2093-202** (OL-PK and tolerability)<br>**0 placebo and 31 ESL** | **2093-201** (DB, PC)<br>**47 placebo and 96 ESL** |
| **Bipolar Disorder** | |
| **2093-203 (acute mania)** | |
| **2093-204 (acute mania)** | |
| **2093-205**- extension of 203 and 204-recurrence of bipolar, 2 part study | |
| | |
| **Phase 2 other indications** | |
| **2093-206-Diabetic Neuropathy**-parts 1 and 2 completed and reported | |
| **2093-307-Diabetic Neuropathy-** part 1-clinically completed but not reported by 1-31-12, part 2 | |
| **2093-207 Post herpetic Neuralgia**-part 1 and 2-clinically completed | |
| **2093-308 Post herpetic Neuralgia –** part 1-clinically completed but not reported by 1-31-12, part 2 | |

| |
|---|
| **2093-209 Migraine-**completed and reported |
| **2093-210 Fibromyalgia-** completed and reported |

**Table 7 Phase 3 Epilepsy Studies and Ongoing Studies**

| **COMPLETED PHASE 3 Epilepsy (some ongoing extensions)** |
|---|
| **Partial Onset adjunctive** |
| **2093-301**-parts 1 – 4 completed and reported. Part 1 DB, R |
| **2093-302**-parts 1 and 2 completed and reported, part 3 in Argentina, Germany, Sweden only. Part 1 DB, R |
| **2093-303**-parts 1 and 2 completed and reported. Part 1 DB, R. |
| **2093-304** Adults, adjunctive use, POS Part 1 DB, R is completed and reported |
| |
| **Phase 2-3 Ongoing or completed since cutoff (POS)** |
| **2093-208 – POS** ages 6-16, assess cognitive function in epileptic children, 1-2 AEDs-parts 1 (DB, R, PCP and 2 (OLE) ongoing |
| **2093-305 Children, adjunctive use**, **POS** parts 1 (DB, PC, PG) and parts 2-4 (OLE) ongoing |
| **2093-304 Adults, adjunctive use, POS** parts 2 and 3 ongoing |
| **2093-401 Elderly, adjunctive use, POS** OL study, ongoing |
| **BIA 2093-311***- **Non-inferiority** to carbamazepine–newly diagnosed, **monotherapy** in adults with **POS** ONGOING |
| **SEP093-045**- **monotherapy** in adults with **POS**, **historical control**-(probably clinically completed since cut-off) |
| **SEP093-046**- **monotherapy** in adults with **POS**, **historical control**-(clinically completed since cut-off) |
| **SEP093-050**-**monotherapy** OLE of 45 and 46- ongoing |

**Except for studies 45 and 46 information, information in this table is based on tabular listing 2-11-13, module 2.7.4 link to ISS appendix 7.1.1. POS=partial onset seizures, SAD=single ascending dose, MAD=multiple ascending dose, EEG=electroencephalogram, OL/OLE=open label/open-label extension, DB=Double Blind, PC=placebo-controlled, PG=parallel group; Blue or colored font =newly completed controlled phase pivotal studies or new pharmacology studies since initial NDA**

## 5.2 Review Strategy

The clinical review was a split review with separate safety and efficacy clinical reviewers. Dr. M. Doi (supervisory signature by Dr. S. Yasuda) performed the primary safety review of this NDA submission. I performed an evaluation of adverse events for seizure worsening or the onset of new seizures types in epileptic subjects and of seizures in non-epileptic subjects.

Two disciplines contributed to the review of efficacy. The primary efficacy review was performed by FDA statisticians and I performed the clinical efficacy review. The primary statistical review in both the first cycle and in this cycle was performed by Dr. Xiang Ling with supervisory signature by Dr. K.Jin and Dr. K. Mahjoob in the first cycle and Drs Jin

and Hung in this cycle. The final signed statistical review was available with supervisory sign-off on 9-10-13. Sections of the clinical efficacy review were performed before the finalized statistical review was available and not all sections of this review were then updated to include the statistical review.

I also reviewed the NDA for purposes of non-safety elements of the clinical reviewer's NDA template.

Given previous review cycles and the extensive quality issues found, data and submission quality is a critical issue of this review cycle. I directed attention to documenting and describing data and submission quality issues that were not safety related. The review of safety data for these purposes is deferred to Dr. Doi.

I used datasets for seizure worsening (ADVENTX.xpt 2-11-13) and efficacy data review (seizure.xpt) as well as the trial (study) report for study 304 and sometimes the ISS or an ISE. Other trial reports, submissions, and datasets were used as needed. I conducted audits on a subset of diaries for consistency with dataset entries. Also, during the review cycle, the statistical reviewer identified duplicate entries in the efficacy data. We requested the sponsor to audit 40 diaries. I also audited a subset of these 40 diaries.

## 5.3 Discussion of Individual Studies/Clinical Trials

Previously, studies 301, 302, and 303 were submitted to support the indication as pivotal and 303 as supportive for safety. Due to GCP issues with 303, identified by the Sponsor, 303 data are not considered reliable to make conclusions. Study 304 is the only new pivotal efficacy study submitted in this cycle. Primary endpoint trial data from studies 301 and 302 were reanalyzed and re-submitted.

The design, demographics, and results of studies 301 and 302, and to a lesser degree of 303, were described in the statistical and/or clinical reviews performed during the first cycle review. Study 304 has not been reviewed before and will be the focus of this review with integration of the updated 301 and 302 data and "old" data results described as appropriate for integration in section 6 of this review.

**Study 304**
**Title**: "Efficacy and Safety of Eslicarbazepine acetate (BIA-2093) as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multicenter clinical trial"

**Sponsors**: The original sponsor was Bial which had planned the study to be conducted in Europe and South America. The study was expanded in December of 2009 in amendment 2 Sunovion sponsored the North American sites and Bial sponsored the rest-of-the world (ROW) sites.

**Study period**: First subject first visit: 12-2-2008
Last subject last visit (part 1, controlled phase): 1-12-12

**Study centers**: 173 sites in 19 countries (North America, 89 sites; ROW, 84 sites) screened and enrolled subjects. 160 of these sites randomized subjects. A total of 936 subjects were screened at all sites with 653 randomized.

- North America (Canada and the U.S.): Canada- three sites screened 12 subjects and randomized 7 subjects. U.S. 86 sites screened 365 subjects. 229 were randomized at 78 U.S. sites. The three largest U.S. sites randomized 20 (site 5), 12 (site 10), and 10 (site 11) subjects each.
- ROW- 559 subjects were screened and 417 were randomized. Argentina randomized 37 of 43 screened subjects, Australia randomized 6 of 7 screened, Belgium randomized 4 of 4 subjects screened, Brazil randomized 75 of 111 screened, Cyprus randomized 6 of 7 subjects screened, France 20 of 24, Germany 2 of 4, Greece 9 of 12, Hungary 9 of 11, India 59 of 91, Italy 26 of 33, Poland 20 of 22, Romania 21 of 26, South Africa 9 of 15, South Korea 58 of 85, Turkey 3 of 4, and the Ukraine 53 of 60

**Objectives**: The primary objective of the study was to evaluate the efficacy of ESL administered daily at doses of 800 mg and 1200 mg compared with placebo as adjunctive therapy in subjects with refractory partial epilepsy over a 12-week maintenance period.

**Primary Endpoint:** The primary endpoint was the standardized seizure frequency over the 12-week maintenance period. Seizure frequency for all of the periods (baseline, titration, and maintenance) was standardized on a 28 day basis. The protocol referred to this as 'standardized seizure frequency'. Data were natural log transformed.

**Secondary Endpoints:** There were a number of secondary endpoints including proportion of subjects with a ≥ 50% reduction in standardized seizure frequency from baseline period to the 12-week maintenance period (responders) and relative change from baseline (percentage change) in standardized seizure frequency during the 2-week titration period, the 12-week maintenance period, and both periods combined.

**Methodology:** This was an international, double-blind, randomized, multicenter, placebo-controlled, parallel-group study of two doses of eslicarbazepine acetate in subjects with refractory partial-onset seizures. There was an 8-week observational baseline and a two-period double-blind phase (periods B and C). Period B included randomization which occurred at Visit 2. Subjects were randomized 1:1:1 to ultimately receive either placebo, eslicarbazepine acetate 800 mg daily, or eslicarbazepine acetate 1200 mg daily. Period B included a 2- week titration period starting up to the final doses noted. Period C was a 12-week maintenance phase starting at Visit 3. Visit

5 corresponded with the end of Period C. Additionally, patients could enter an open-label extension after the double-blind phase.

**Inclusion Criteria**: Generally, subjects were male and female, 16 years or older, with a documented diagnosis of epilepsy at least 12 months before screening. They were to have ≥ 4 partial-onset seizures (including simple, complex, or partial with secondary generalization) in the 28 days prior to screening and to be on 1 or 2 AEDS on a stable dose (except oxcarbazepine) for at least a month before screening (vigabatrin use required stability for a year. VNS was allowed if implanted at least 6 months before screening and with stable parameters for at least one month before screening. VNS was not counted as a concomitant anticonvulsant (this change occurred with amendment 3). At visit 2 (randomization), subjects had to have at least 8 partial-onset seizures during baseline with at least 3 partial-onset seizures in each 4-week period of the 8-week baseline period prior to randomization, documented in the diary, and no seizure-free period greater than 28 days.

**Exclusion Criteria**: exclusion criteria included subjects with only simple partial seizures with no motor symptoms, primary generalized seizures, history of status epilepticus or cluster seizures within 3 months before screening, benzodiazepine use more than 2x per week unless used as an anticonvulsant, non-compliance with concomitant medications during baseline, and inadequate diary completion.

**Drug administration:** The study drug was an immediate release tablet to be swallowed daily by mouth about the same time without chewing or crushing and with or without food. Tablets were in blister cards and each day a subject was to take tablets from the blister cards. In the ROW, eslicarbazepine was administered as 400 mg and 800 mg white oblong tablets. Matching placebos were supplied for part 1. The manufacturer was Bial. Per the protocol dated 12-01-09, protocol #2 of study 304, in North America, eslicarbazepine was administered for part 1 as 400 mg white, plain-face, round tablets. Matching placebo was supplied. The manufacturer was (b) (4) for the drug or placebo used in North America.

I**n the ROW**: Each blister card had two columns-labeled A and B-and was to contain a 7-day supply of the investigational product. Each daily dose consisted of two tablets, 1 from A and 1 from B, which were to be taken once daily. Blister cards were grouped in carton boxes, per subject. Subjects were given the boxes at visits.

In titration, subjects in group 1 had placebo “400” and placebo “800” tablets in columns A and B respectively. Subjects in group 2 had ESL 400 mg tablets in column A and placebo “800” in column B, and subjects in group 3 had placebo “400” in column A and ESL 800 in column B. Subjects were instructed to take two tablets QD.

In maintenance, the ROW subjects took the tablets as per the figure copied from the study report below.

Illustration of the blister card contents

| Group 1 (Placebo) | |
|---|---|
| A | B |
| ○ | □ |
| ○ | □ |
| ○ | □ |
| ○ | □ |
| ○ | □ |
| ○ | □ |
| ○ | □ |

| Group 2 (800 mg) | |
|---|---|
| A | B |
| ○ | ■ |
| ○ | ■ |
| ○ | ■ |
| ○ | ■ |
| ○ | ■ |
| ○ | ■ |
| ○ | ■ |

| Group 3 (1200 mg) | |
|---|---|
| A | B |
| ● | ■ |
| ● | ■ |
| ● | ■ |
| ● | ■ |
| ● | ■ |
| ● | ■ |
| ● | ■ |

● BIA 2-093 400 mg ■ BIA 2-093 800 mg ○ Placebo "400" □ Placebo "800"

**In North America**, eslicarbazepine was administered for part 1 as 400 mg white, plain-face, round tablets. Matching placebo was supplied. In NA, in titration the blister cards had two tablets in them for each day and in maintenance, they had 3 tablets. Pictures of the blister cards used in North America are not shown in this review.

**Visit Schedule**: In part 1, which included the controlled phase, there were 5 study visits.

1. Visit 1 was at screening
2. Visit 2 was randomization, 2 week up-titration began.
3. Visit 3 was at week 2 and was the beginning of the maintenance period.
4. Telephone contact occurred about two weeks after Visit 3 during the 12-week maintenance phase for all subjects. . At the first contact, investigators were to telephone the subjects and inquire about any problems taking the study drug or completing the diary. Additional unscheduled visits were initiated following telephone contact as needed.
5. Visit 4 was at week 8
6. Visit 5 was at week 14. Last visit in maintenance, beginning OL as applicable.
7. The second telephone contact -at week 16, about 2 weeks after Visit 5 for subjects who continued into open-label and about 2 weeks after the last dose of study drug for subjects not continuing on treatment after part 1.

The efficacy related **assessment schedule** is displayed below as per the submission.

**Table 6: Schedule of Assessments - Part I (Continued)**

| DOUBLE-BLIND (PART I) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit** | **V1** | **V2** | **V3** | **TC1** | **V4** | **V5** | **EDV** | **PSV** |
| **Weeks/Months** | **-8 wks** | **Day 1** | **2 wks** | **4 wks** | **8 wks** | **14 wks** | **-** | **-** |
| **Visit windows** | **-** | **± 3 days** | **± 3 days** | **± 3 days** | **± 3 days** | **± 3 days** | **-** | **-** |
| CGI Severity of Illness | - | X | - | - | - | X[f] | X | - |
| MOS-SS | - | X | - | - | - | X | | - |
| 12-lead ECG | X | X | X | - | - | X | X | - |
| C-SSRS[e] | X | X | X | - | X | X | X | X |
| Dispense Study Drug | - | X | X | - | X | X | X | - |
| Medication Accountability | - | - | X | - | X | X | X | X |
| Distribute Diary | X | X | X | - | X | X | X | - |
| Collect and Review Diary | - | X | X | - | X | X | X | - |

**Concomitant Medication and Rescue Medication Use During Maintenance:**

Not allowed:

1. more than 2 current anticonvulsants (no oxcarbazepine), changes in anticonvulsants generally not allowed for one month prior to screening and during the entire trial except as noted below for carbamazepine and phenytoin
2. VNS not allowed if not implanted 6 months before and at stable parameters at least one month
3. other experimental drugs
4. per exclusion criterion, benzodiazepine on more than an occasional basis (defined as more than 2x per week except as chronic anticonvulsant

Investigator Discretion:

1. any concomitant deemed necessary to provide adequate supportive care was allowed
2. allowed carbamazepine reduction up to 25% of total daily dose at study entry in last week of titration or first week of maintenance in case of intolerable adverse events considered associated to with carbamazepine and with Medical Monitor approval-amendment #3 (9-16-10)
3. allowed phenytoin reduction up to 15% of total daily dose at study entry in last week of titration or first week of maintenance in case of intolerable adverse events suggestive of phenytoin toxicity with Medical Monitor approval-amendment #5 (7-28-11)

**Protocol Amendments:** The initial protocol was dated 3-13-2008. A second initial version is dated 4-15-2008. There were 5 protocol amendments. Important efficacy related changes are described below. The discussion of safety related protocol amendments is deferred to the safety review (Dr. Doi).

- Amendment 1, VNS still considered a concomitant anticonvulsant but the amendment detailed how long VNS should be implanted and how parameters should be stable before screening (6 months and 1 month respectively). Defined “more than an occasional basis” use of benzodiazepine as more than 2 times per week.
- Amendment 2 was dated 12-1-2009 and included introduction of a sponsor for North America such that “The Sponsor” referred to either BIAL (Europe and South America) or Sunovion (North America). The primary and secondary efficacy analyses were “clarified” as change of seizure frequency rather than seizure frequency and stratification by region was introduced.
- Amendment 3 was dated 9-16-2010 (submitted 11-01-10) and included the implementation of the daily entry diary for new subjects (those subjects already using the event entry diary continued to use event entry diaries), noted that VNS was not to be counted as an anticonvulsant drug, and increased the sample size so that the number of subjects using the DE diary was adequate to support about 90% power and addition of separate statistical analyses for subjects using event entry versus those using daily entry diaries. An option to reduce concomitant carbamazepine was added (was to require approval from the Medical Monitor). At the time of amendment 3, about 168 subjects were enrolled.
- Amendment #4-(2-15-11) allowed the maximum number of subjects recruited per site to be > 18 with the Sponsor’s written approval. The name change from Sepracor Inc. to Sunovion Pharmaceuticals Inc was noted.
- Amendment #5 (7-28-11) included additions to the statistical analyses which added summarizing seizure frequency also for the combined 2-week titration and 12-week maintenance period and during each week of the titration and maintenance periods for 4 efficacy populations, allowed a dose reduction of phenytoin of up to 15% for intolerable adverse events suggestive of phenytoin toxicity. The withdrawal criterion for “exacerbation of seizures” was changed so that increase in seizure frequency of 100% versus baseline was deleted. The number of sites was modified from 150 to about 200.
- The SAP was amended March 2, 2012 following audit findings at site 952.

Additionally, there were amendments in certain countries as requested by the local regulatory authorities. The Sponsor reports these were administrative and did not alter study conduct. Five countries had 10 local amendments (Belgium, Turkey, Argentina, Germany, and South Korea).

# 6 Review of Efficacy

Efficacy Summary

## 6.1 Indication

The sponsor is seeking an indication as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.

### 6.1.1 Methods

Three efficacy studies (301, 302, and 304) are submitted in this cycle in support of the indication. Only study 304 is new though there was an update on studies 301 and 302, which is discussed later in this section. Studies 301 and 302 were previously reviewed by statistics.

For ease of reading, studies 301 and 302 are also briefly described below in terms of efficacy evaluation, similarity to study 304 (the new study), and significant/noteworthy differences between the three studies. Study 303 was similarly designed but due to major non-compliance with GCP, this study is not considered as pivotal. After the summary section, there is discussion of the new information in this submission cycle. The updated data itself (results for the primary endpoint from studies 301 and 302) are presented at the end of section 6.1.4.

**Summary of studies submitted in the first cycle and results:**
Similar in all three trials:

- All three of the pivotal phase 3 trials, (301, 302, and 304) are randomized, placebo-controlled, multicenter, parallel group, multi-phase studies.
- The double-blind phase is part 1 of each study which consisted of an 8-week baseline, 2-week titration (though studies used somewhat different titration regimens), and 12 -week maintenance period.
- A randomization criterion in trials 301, 302, or 304 was that subjects have at least 8 seizures in the baseline 8 weeks or minimum of 4 per month during baseline to qualify for randomization though some of the details of frequency differed between studies.
- In 301, 302, and 304, the times of diary review were at visit 2, at 2 weeks (visit 3), at 8 weeks (visit 4), and at 14 weeks (visit 5). Visit schedules had a 3 day window.
- The primary efficacy endpoint was standardized seizure frequency per 4 weeks over the 12-week maintenance period. The primary and secondary endpoints generally were the same in studies 301 and 302 and 304.

Significant or Noteworthy Differences between studies included:

Trial issues:

- Studies 301 and 302 included three ESL dose groups (400 mg, 800 mg, and 1200 mg). Study 304 (and 303) had 800 mg and 1200 mg ESL groups (no 400 mg ESL group).
- Studies 301 and 302 used only event entry (EE) diary (seizures recorded with occurrence of a seizure compared to daily entry (DE), in which the diary requires a response daily regardless of whether there is a seizure). Study 304 started with EE diaries but was amended (# 3) from EE to DE diary for new subjects enrolling. 'Old' subjects already using the EE diary were to continue to use this type of diary. 304 powered at about 90% for the DE diary.
- In studies 301 and 302, no changes were to be made to background anticonvulsants while in study 304, amendment #3 allowed a dose reduction of concomitant carbamazepine for intolerable adverse events and amendment #5, allowed dose reduction of phenytoin.
- In studies 301 and 304, the 800 mg group started on 400 mg and then increased to 800 mg after 1 or 2 weeks respectively. In study 302, the 800 mg group started on 800 mg. In study 301, the 1200 mg group started on 400 mg, moved to 800 mg daily and then to 1200 mg daily in weekly steps. In studies 302 and 304, the 1200 mg dose group started on 800 mg and then increased up to 1200 mg daily after 2 weeks.
- Baseline was single-blind in study 301 and observational in studies 302 and 304.
- There was a 4 week tapering off in studies 301 (and 303). None in studies 302 and 304.
- More subjects used concomitant carbamazepine at baseline in studies 301 and 302 (about 60%) than in 304 (about %35 to 42%). For concomitant anticonvulsant use at baseline, there were differences in the percentages of subjects using carbamazepine between NA and ROW and maybe in number of subjects with VNS (304 indicated more subjects in NA with VNS than in ROW, though could be time of study effect also).

General:

- Bial was sole sponsor of 301,302, and 303. Sunovion (previously Sepracor) partnered with Bial for study 304.
- Studies 301 and 302 conducted completely outside of the U.S. with no North American (NA) subjects. Study 304 included NA sites. Differences were seen in the rest -of –the- world (ROW) and NA in use of some baseline concomitant anticonvulsants (and VNS) in study 304.
- Studies 301 and 302 were smaller in size with an ITT of about 400 subjects each (397 and 393 respectively) compared to ITT of 640 in study 304.
- Time of study conduct was a little earlier for studies 301 and 302 than for 304 and closer in time to each other. Study 301 initiated in 2004 (July 15) and completed last visit for last subject in part 1 in 2005 (November 9). Study 302

initiated in 2004 also (September 1) and completed in late 2006 (December 19). Study 304 had the first subject visit in 2008 (December 12) and the last subject in 2012 (last visit for part 1 on January 12).

Dr. Ling reported the following in her first cycle review of study data from studies 301 and 302.

- p-values reached statistical significance for 800 mg and 1200 mg comparisons to placebo in study 301 but not in study 302 for the 1200 mg dose group comparison to placebo.
- the results were robust to the handling of drop-outs in study 301 and "slightly" sensitive to the handling of dropouts for the 1200 mg group in study 302.
- Analyses excluding the site from each study that DSI found in non-compliance showed similar results.
- The 400 mg daily dose was not statistically different from placebo in either trial (301 and 302).

During the first cycle, Dr. Ling concluded that "the data seem to support the efficacy of ESL as adjunctive therapy to subjects with refractory simple or complex partial seizures." In both studies, she indicated that the 800 mg daily dose resulted in statistically significantly lower standardized seizure frequency over a 12-week maintenance period compared to placebo and stated that there was no compelling evidence that the 1200 mg daily dose provided additional improvement over the 800 mg daily dose with the incremental efficacy seen in the 1200 mg group when compared to the 800 mg group in study 301 not seen in study 302.

In terms of the quality of the efficacy data/conduct, in the first cycle, Dr. Ling noted:

- extensive hard-coding in the program in study 301 which she describes as indicating that the study was not well conducted and that data quality/reliability was questionable.
- one unblinded review of seizure data as well as a blinded review and some hard-codes were generated from the unblinded review. As per her review, in the original submission, the Sponsor only mentioned the blinded review, not the unblinded review.
- Sensitivity analysis for the hard-codes was performed by the Sponsor, which is reported as having no difference in data interpretation or conclusions.
- Issues related to the seizure diary format of EE in that a failure to record a seizure could not be differentiated from the absence of seizure. The statistical reviewer performed a worst-case imputation analysis for missing data and reported a p-value change from 0.0041 t o 0.0599 for the 800 mg group and from 0.0009 to 0.0144 for the 1200 mg group.

**Update on studies 301 and 302 in this submission:**

As per the Sponsor (CSE 9-4-12), 76 GCP audits were independently conducted in 2010 using (b) (4) and third-party auditors supervised by (b) (4) These were performed as a result of the Agency's concerns in Question 2 of the CR letter dated 4-30-10. These audits reportedly resulted in examination of "nearly" 100% of the study subject records not previously reviewed in the 2008 audit program.

The Sponsor's 2010 audits uncovered two sites in Poland for study 301 considered non-compliant. The principal investigators (sites 174 and 175, records for 20 subjects) directly completed seizure diary cards and did not maintain source data. These non-compliant sites were discussed at a 6-7-11 meeting between FDA and the Company. Meeting minutes from that meeting reflect that the Company reported the source documents not maintained were those used to verify seizure data and that the audits verified that all subjects were exposed to study drug and source documents were available to verify the validity of the safety data. (see quality of data sections, 3.1, 3.2, 6.1.10).

In terms of the audit findings of seizures, the referenced CSE reports that studies 301 and 302 included 50, 109 seizures (22,538 from study 301 and 27,571 from study 302). The audit findings added 115 seizures to the database (0.23%). The CSE reports that subjects impacted were evenly distributed among the dose groups and that these seizure additions did not represent a source of bias. From a quality point of view, the sponsor reports finding a low number of seizures in the audits; low enough that they are unlikely to alter the final results in terms of statistical significance from positive to negative, for example. Based on Dr. Ling's update of these studies, it appears this rather modest addition of seizures to the data did alter the p-values in study 301 for the ESL 800 mg group from 0.003 to 0.047 in the ISE resubmission and the p-value for the 1200 mg group in study 302 changed from 0.001 to 0.042.

The FDA statistical review of the updated results of the primary endpoint analyses from studies 301 and 302 is in the section below immediately before discussion of secondary analyses begins (before section 6.1.5).

**'New' efficacy study: Study 304**

### 6.1.2 Demographics

Subjects in study 304 were generally 38 to 39 years old with a range from 16 to 71 years. A little more than half of each group (placebo, ESL 800 mg, and ESL 1200 mg) was < 40 years old and about 43-47% were 40 to 65 years old. There were only 8 subjects > 65 years old. Around 64% of subjects were Caucasian and about 20% were Asian. Less than 4% were black. The sponsor's table of demographic information is copied from the ISE below.

**Table 8 Study 304 Demographics**

**Table 20: Demographics and Body Measurement Characteristics Study 2093-304 Part 1 (ITT Population)**

| Characteristic | Placebo (N=220) | ESL 800 mg (N=215) | ESL 1200 mg (N=205) |
|---|---|---|---|
| **Age[a] (years)** | | | |
| n | 219 | 215 | 205 |
| Mean | 39.0 | 38.9 | 37.8 |
| SD | 12.73 | 12.11 | 12.02 |
| Median | 39.0 | 39.0 | 38.0 |
| Min | 16 | 16 | 16 |
| Max | 67 | 71 | 69 |
| **Age Category** | n (%) | n (%) | n (%) |
| < 40 years | 113 (51.6) | 112 (52.1) | 114 (55.6) |
| 40 - 65 years | 103 (47.0) | 100 (46.5) | 89 (43.4) |
| > 65 years | 3 (1.4) | 3 (1.4) | 2 (1.0) |
| Missing | 1 | 0 | 0 |
| **Sex** | n (%) | n (%) | n (%) |
| Male | 110 (50.0) | 108 (50.2) | 103 (50.2) |
| Female | 110 (50.0) | 107 (49.8) | 102 (49.8) |
| **Race** | n (%) | n (%) | n (%) |
| Caucasian | 141 (64.1) | 136 (63.3) | 130 (63.4) |
| Black or African American | 8 (3.6) | 3 (3.7) | 8 (3.9) |
| Asian | 46 (20.9) | 41 (19.1) | 39 (19.0) |
| Other | 25 (11.4) | 30 (14.0) | 28 (13.7) |
| **Baseline BMI ($kg/m^2$)** | | | |
| n | 218 | 214 | 203 |
| Mean | 25.63 | 26.25 | 26.48 |
| SD | 5.728 | 5.633 | 7.035 |

a Subjects in Belgium, Germany, and Turkey had to be 18+ years to enter the study, but only 16+ years in the other countries.

Note: Percentages are calculated based on the number of subjects with non-missing data in the ITT population in each treatment group.

Source: Section 14.1, Table 14.1.4.2 of the CSR for Study 2093-304.

Disease History at Baseline:

The etiology of seizures for subjects in the safety population is unknown in about 25-30% of each group (placebo and the two ESL groups) and idiopathic in about 20 to 25%. Cranial trauma/injury was recorded as the possible etiology in 11 to 14% and "other" in another 12 to 19%.

Mean time since onset of epilepsy in each group was about 21 years (SD=13 to 15). The median time was 18 to 20 years and the minimum time in each drug group was 1.1 to 1.4 years. History of epilepsy in a parent, sibling, or child was negative in 85 to 91% of subjects.

Seizure Type and Frequency in the four weeks prior to screening V1, ITT:

As per the Table 14 of the CSR for study 304, in the four weeks prior to screening, 79.5% to 82.9% of each group experienced complex partial seizures and about a quarter to a third of each group experienced partial seizures that generalized. About 30-40% of each group experienced simple partial seizures.

**Table 9 Study 304 Seizures in Screening**

**Table 14: Seizure Type and Frequency During the Four Weeks Prior to Screening (V1) (ITT Population)**

| Seizure Type | Placebo (N = 220) | ESL 800 mg (N = 215) | ESL 1200 mg (N = 205) |
|---|---|---|---|
| Seizure Type[a] | | | |
| Simple Partial | 81 (36.8%) | 84 (39.3%) | 66 (32.2%) |
| Complex Partial | 175 (79.5%) | 170 (79.4%) | 170 (82.9%) |
| Partial Evolving to Secondary Generalized | 57 (25.9%) | 59 (27.6%) | 63 (30.7%) |
| Unclassifiable | 2 (0.9%) | 0 | 3 (1.5%) |
| Other | 2 (0.9%) | 1 (0.5%) | 0 |
| Missing | 0 | 1 | 0 |
| Seizure Frequency: Total per Subject | | | |
| n | 220 | 214 | 205 |
| Mean | 18.1 | 18.0 | 17.6 |
| SD | 28.68 | 35.86 | 30.15 |
| Median | 8.0 | 8.0 | 9.0 |
| Min | 4 | 1 | 4 |
| Max | 282 | 420 | 351 |

Abbreviations: ESL = eslicarbazepine acetate; Max = maximum; Min = minimum; SD = standard deviation; V = visit.
[a] Subjects may have more than one type of seizure.
Note: These data were collected at screening on the CRF (independent of the diary card data).
Note: Percentages are calculated based on the number of subjects with non-missing data in the ITT population in each treatment group.
Source of Data: Table 14.1.7 and Listing 16.2.4.3.

**Regional impact**:

Most subjects, regardless of region, experienced partial complex seizures though they may also have experienced other seizure types. Percentage-wise, more NA subjects experienced simple partial seizures than in the ROW. This was also the case generally with secondary generalized seizures though the ESL 1200 mg group did not show much of a regional difference (30% NA vs. 31% ROW). Table 10 below shows seizure type (percentage of subjects) per group by region ROW or NA.

**Table 10 Seizure type -regional differences**

| Seizure Type | Placebo total/ROW/ NA | Eslicarbazepine 800 mg total/ROW/ NA | Eslicarbazepine 1200 mg total/ROW/ NA |
|---|---|---|---|
| Simple Partial | 37/32/45 | 39/33/50 | 32/28/41 |
| Complex Partial | 80/76/86 | 80/75/88 | 83/79/89 |
| Secondary Gen | 26/20/36 | 28/25/32 | 31/31/30 |
| Unclassifiable | 0.9/0.7/1.3 | 0/0/0 | 1.5/2.3/0 |
| Other | 0.9/0/2.6 | 0.5/0.7/0 | 0/0/0 |
| Missing | 0/NR/0 | 1/NR/1 | 0/NR/0 |

Total=rest of world (ROW) + North America (NA). Data from table 14.1.7 of CSR for 304, NR=not reported. Numbers rounded.

Based on data from Table 14.1.7 in the CSR, by randomized drug group, for the placebo group, the mean number of simple and the mean number of complex partial seizures was about the same. North America had a larger mean number of complex partial seizures than of simple partial seizures and for both types of partial seizures, North America sites had higher means than the ROW (about 3-4% higher). The mean number of secondarily generalized seizures in the ROW was 4.7 (SD=3) compared to 5.1 in NA (SD=6).

Based on data from Table 14.1.7 in the CSR, in the ESL 800 mg group, the mean number of simple partial seizures was greater than that of complex partial seizures in the ROW (about 21 vs. about 10) but not in NA (about 12 vs.15.5). In NA, the mean # of complex partial seizures was greater than the mean # of simple seizures. The mean # of secondarily generalized seizures was greater in the ROW than in NA (5.9 compared to 5.3).

Based on data from Table 14.1.7 in the CSR, in the ESL 1200 mg group, the mean number of partial complex seizures was higher for the ROW than for NA and higher than the mean number of simple seizures in both NA and ROW. The mean number of secondarily generalized seizures was about the same in NA and the ROW and was about 4.5 in each. The median in NA was lower at 3.

Standardized Seizure Frequency During Baseline Period

Based on the Sponsor's Table 15, reproduced below, the mean standardized seizure frequency in baseline was between 16 and 18 in each group. The ESL 800 mg group has an outlier with a maximum at 412 seizures compared to maximum placebo or 1200 mg groups of 132 and 164 respectively.

**Table 11 Standardized Seizure Frequency During Baseline**

**Table 15: Standardized Seizure Frequency During the Baseline Period (ITT Population)**

| Parameter | Placebo (N = 220) | ESL 800 mg (N = 215) | ESL 1200 mg (N = 205) |
|---|---|---|---|
| Baseline Period | | | |
| n | 220 | 215 | 204 |
| Mean | 16.31 | 18.22 | 17.23 |
| SD | 19.285 | 34.486 | 21.084 |
| Median | 9.00 | 8.62 | 8.92 |
| Min | 2.4 | 2.0 | 3.7 |
| Max | 131.8 | 412.3 | 163.5 |

Abbreviations: ESL = eslicarbazepine; Max = maximum; Min = minimum; SD = standard deviation.
Source of Data: Table 14.2.4.1.1.

Prior Anticonvulsant Treatment:

Prior anticonvulsant use was defined as anticonvulsants received prior to enrollment and either stopped prior to enrollment or not ongoing at the start of the study. For the total population, the most commonly used anticonvulsants (≥ 20% of subjects) were carbamazepine (~79%), valproic acid (~53%), levetiracetam and lamotrigine (~51% each), phenytoin (~50%), topirimate (~42%), phenobarbital (~34%), oxcarbazepine (~25%), and clobazam or Zonisamide at ~23% and 22% respectively.

Ongoing anticonvulsants at baseline:

**Study 304:**
Table 14.1.4.1 in the CSR (via CSR links) indicates that at baseline, 70.5% to 72% of subjects were on two anticonvulsants, and 28 to 29% were on one anticonvulsant. Four subjects (1 placebo and 3 eslicarbazepine 800 mg) were on no other anticonvulsants and one placebo and no eslicarbazepine subject was on three or more anticonvulsants at baseline. The most commonly used concomitant anticonvulsants in descending order of use were carbamazepine (about 34-42%), levetiracetam (about 20.5% to 29.5%), lamotrigine (about 24% to 27%), and valproic acid (about 19% to 21%). About 9% to 13% of each group was using concomitant phenytoin.

Table 12,(Sponsor Table 13) reproduced from the Sponsor's submission, displays this information.

**Table 12 Anticonvulsant Use at Baseline**

**Table 13: Other Baseline Characteristics - Seizure Treatments and Anti-Epileptic Drugs (Safety Population)**

| Characteristic | Placebo (N = 224) | ESL 800 mg (N = 216) | ESL 1200 mg (N = 210) |
|---|---|---|---|
| Number of AEDs[a] at Baseline | | | |
| 1 AED | 64 (28.6%) | 60 (27.8%) | 59 (28.1%) |
| 2 AEDs | 158 (70.5%) | 153 (70.8%) | 151 (71.9%) |
| 3 or more AEDs | 1 (0.4%) | 0 | 0 |
| Carbamazepine Use at Baseline | | | |
| Yes | 77 (34.4%) | 84 (38.9%) | 89 (42.4%) |
| No | 147 (65.6%) | 132 (61.1%) | 121 (57.6%) |
| Phenytoin Use at Baseline | | | |
| Yes | 26 (11.6%) | 19 (8.8%) | 28 (13.3%) |
| No | 198 (88.4%) | 197 (91.2%) | 182 (86.7%) |
| VNS Use at Baseline | | | |
| Yes | 11 (4.9%) | 17 (7.9%) | 14 (6.7%) |
| No | 213 (95.1%) | 199 (92.1%) | 196 (93.3%) |
| AEDs during the Baseline Period Used by > 15% of Subjects[b] | | | |
| Carbamazepine | 77 (34.4%) | 84 (38.9%) | 89 (42.4%) |
| Levetiracetam | 66 (29.5%) | 58 (26.9%) | 43 (20.5%) |
| Lamotrigine | 57 (25.4%) | 51 (23.6%) | 57 (27.1%) |
| Valproic acid[c] | 42 (18.8%) | 46 (21.3%) | 41 (19.5%) |

Abbreviations: AED = anti-epileptic drug, ESL = eslicarbazepine acetate; VNS = vagus nerve stimulation.

[a] An AED was considered to be used at baseline if it was started at any time prior to first dose of study drug and continued into the titration period. Anti-epileptic drugs used as rescue medication at baseline are not included.

[b] Most commonly used AEDs at baseline are background AEDs that were used by at least 15% of subjects.

[c] The incidence of valproic acid is based on subjects who were taking AEDs with preferred drug names of ergenyl chrono, valproate semisodium, valproate sodium or valproic acid.

Note: Percentages are calculated based on the number of subjects with non-missing data in the Safety population in each treatment group.

Source of Data: Table 14.1.4.1

There are some differences between the treatment groups in study 304 based, on region (ROW or NA) as to which specific concomitant therapies were used at baseline (see table below)

- In North America, concomitant VNS was more common in all groups than in the ROW (placebo NA 3x that of ROW, and 9 and 7x that in the ROW for the Eslicarbazepine 800 mg and 1200 mg daily groups).
- Carbamazepine was used in about 45-50% of the subjects in the ROW and in about 15 to 29% of the subjects in NA. Valproic acid was a more common anticonvulsant in the ROW than in NA, at about 25% in all treatment groups in the ROW and 7-12% in NA.

**Table 13 Concomitant Anticonvulsant Use**

**Percentage of subjects per group using concomitant drug or concomitant VNS**

| Concomitant treatment | Placebo total/ROW/ NA | Eslicarbazepine 800 mg total/ROW/ NA | Eslicarbazepine 1200 mg total/ROW/ NA |
|---|---|---|---|
| Carbamazepine | 34/46/15 | 39/50/19 | 42/50/29 |
| Levetiracetam | 30/28/32 | 27/23/35 | 21/20/22 |
| Lamotrigine | 25/22/31 | 24/22/27 | 27/28/26 |
| Valproic Acid | 19/25/9 | 21/27/12 | 20/27/7 |
| VNS | 5/3/9 | 8/2/18 | 7/2/14 |

Total=rest of world (ROW) + North America (NA). Data from table 14.1.4.1 of CSR for 304

**Studies 301 and 302 concomitant anticonvulsant use**:

About 60% of the ITT subjects in these trials were on concomitant carbamazepine at baseline. Concomitant lamotrigine use was overall higher in study 301 than 302 at about 24 to 28% in study 301 and 17 to 24% in study 302. Valproic acid was used in 22 to 28% of study subjects in 301 and 13 to 28% in study 302.

The tables below are excerpted from ISE presentations (Tables 17 and 19, for studies 301 and 302 respectively) displaying baseline concomitant medication use.

**301**

**Table 14 Study 301 Concomitant Anticonvulsant Use**

| | | | | | |
|---|---|---|---|---|---|
| Most Common[a] Types of AED | %Carbamazepine | 62 | 56 | 60 | 56 |
| | %Lamotrigine | 26 | 24 | 27 | 28 |
| | %Valproic acid | 28 | 26 | 22 | 26 |
| | %Topiramate | 16 | 9 | 19 | 11 |

**Dose groups placebo, 400 mg, 800 mg, and 1200 mg respective columns.**

**302:**

**Table 15 Study 302 Concomitant Anticonvulsant Use**

| | AEDs | | | | |
|---|---|---|---|---|---|
| Most Common Types of AED | %Carbamazepine | 58 | 61 | 61 | 59 |
| | %Valproic acid | 26 | 13 | 28 | 21 |
| | %Lamotrigine | 24 | 22 | 17 | 22 |
| | %Clobazam | 16 | 20 | 21 | 12 |
| | %Levetiracetam | 16 | 16 | 13 | 20 |
| | %Phenytoin | 14 | 11 | 15 | 12 |
| | %Phenobarbital | 18 | 11 | 13 | 9 |
| | %Topiramate | 12 | 11 | 11 | 15 |

**Dose groups placebo, 400 mg, 800 mg, and 1200 mg respective columns.**

A discussion of the possible impact of concomitant carbamazepine, phenytoin, and rescue medication use is included in section 6.1.8 of this review.

Diary Compliance:

Based on the dataset review, diary compliance was < 80% per dataset for 9 subjects in the eslicarbazepine 1200 mg group (with 5 subjects considered overall non-compliant, meaning non-compliance in baseline, titration, and maintenance), 9 subjects in the eslicarbazepine 800 mg daily group (with 1subject overall non-compliant ), and 11 (12) placebo subjects (with 4 overall non-compliant). The number of subjects with overall noncompliance was about the same for placebo and the 1200 mg ESL group and for other non-compliance (not overall) are similar between groups. Assuming adequate randomization, this likely is of minimal impact in the totality of the data.

**Table 16 Diary Compliance**

| Diary Compliance | N Rows | N(USUBJID, Eslicarbazepine Acetate 1200 mg) | N(USUBJID, Eslicarbazepine Acetate 800 mg) | N(USUBJID, Placebo) |
|---|---|---|---|---|
| < 80% | 31 | 9 | 10 | 12 |
| Between 80% and 120% | 649 | 208 | 216 | 225 |

Clinical reviewer, data from dccomp.xpt 9-4-12 submission

Diary type used:

Although not a true demographic, most subjects in study 304 used DE type diaries (about 69%). Studies 301 and 302 only employed the EE diary type.

**Table 17 Diary Type Used Study 304**

| | Placebo n (%) ITT 220 | ESL 800 mg n (%) ITT 215 | ESL 1200 mg n (%) ITT 205 |
|---|---|---|---|
| EE | 62 (27.4%) | 67 (31%) | 56 (26.5%) |
| DE | 158 (69.9%) | 148 (68.5%) | 149 (70.6%) |

Source: Table 10 CSR 304

### 6.1.3 Subject Disposition

Study 304: 936 subjects were screened for the study. Around 70% of these were randomized (n=653) and 30% were screen failures (n=283). A greater percentage of those screened in NA were considered screen failures than of those screened in the ROW (141 screen failures of 377 screened in North America (37.4%) and 142 screen failures of 559 screened in the ROW (25.4%)). As per the Sponsor, 198 of the 283 screen failures did not meet the eligibility criteria for randomization.

The CSR includes a discussion of screening failures. The number one reason for screen failure was “subject did not meet the eligibility criteria for randomization” at n=198. Reasons #2-6 in descending order of frequency were: at the request of the

caregiver or subject (n=31), other reason ( n=17), subject non-compliance (n=14), and suicide attempt or significant ideation or treatment with more than 2 concomitant anticonvulsants at the same time (n=6 each). There were subjects who were eligible at visit 1 but not at visit 2, many of these are listed as “not meet the selection criteria for randomization” in Listing 16.2.1.2.

The dataset of disposition for study 304 generally was not granular for the category “patient does not meet the selection criteria for randomization”. Therefore, the exposure dataset was utilized. In the dataset (IE.xpt in the 9-4-12submission), there are 230 unique subjects not randomized (seems to be missing 53 subjects based on numbers). The largest single category reason that led to not being randomized was not having enough partial seizures in the baseline period (48 subjects in NA and 65 in the ROW). Another approximately 30 subjects from each group (ROW and NA) were not randomized due to medical reasons. Four subjects in NA and none in the ROW were not randomized due to having primary generalized seizures.

In study 304, about ~84% of the placebo subjects compared to 80% of the 800 mg group and 67% of the 1200 mg group completed the study. In all groups, the most common category of reason for discontinuation was adverse event (4% of the placebo group compared to ~10% and ~21% of the 800 and 1200 mg groups respectively.) For randomized subjects, the following disposition table is copied from the CSR for study 304 and displays disposition data.

**Table 18 Subject Disposition Study 304**

**Table 9: Number (%) of Subjects in Part I Study Periods**

| Disposition | Placebo n (%) | ESL 800 mg n (%) | ESL 1200 mg n (%) | Total n (%) |
|---|---|---|---|---|
| Randomized | 226 (100.0%) | 216 (100.0%) | 211 (100.0%) | 653 (100.0%) |
| Randomized and Received at Least 1 Dose of Study Drug (Safety Population) | 224 (99.1%) | 216 (100.0%) | 210 (99.5%) | 650 (99.5%) |
| Entered the Maintenance Period | 212 (93.8%) | 201 (93.1%) | 184 (87.2%) | 597 (91.4%) |
| Completed the Double-Blind Period | 189 (83.6%) | 173 (80.1%) | 142 (67.3%) | 504 (77.2%) |
| Prematurely Discontinued from the Double-Blind Period | 37 (16.4%) | 43 (19.9%) | 69 (32.7%) | 149 (22.8%) |
| Entered the 1-Year Open-Label Period | 187 (82.7%) | 171 (79.2%) | 140 (66.4%) | 498 (76.3%) |
| Primary Reason for Discontinuation from the Double-Blind Period[a] | | | | |
| Administrative Reasons | 1 (0.4%) | 2 (0.9%) | 1 (0.5%) | 4 (0.6%) |
| Adverse Event | 9 (4.0%) | 21 (9.7%) | 45 (21.3%) | 75 (11.5%) |
| Lack of Efficacy | 0 | 0 | 1 (0.5%) | 1 (0.2%) |
| Non-Compliance with Study Drug | 5 (2.2%) | 1 (0.5%) | 3 (1.4%) | 9 (1.4%) |
| Physician Decision | 1 (0.4%) | 0 | 3 (1.4%) | 4 (0.6%) |
| Pregnancy | 2 (0.9%) | 1 (0.5%) | 0 | 3 (0.5%) |
| Protocol Violation | 4 (1.8%) | 3 (1.4%) | 3 (1.4%) | 10 (1.5%) |
| Withdrawal by Subject | 7 (3.1%) | 7 (3.2%) | 12 (5.7%) | 26 (4.0%) |
| Other | 8 (3.5%) | 8 (3.7%) | 1 (0.5%) | 17 (2.6%) |

Abbreviations: ESL = eslicarbazepine acetate.

[a] Reasons for discontinuation from the double-blind period include subjects who discontinued from either the titration or maintenance periods. One subject was discontinued in the ESL 1200 mg group for reason reported as 'lack of efficacy'. This reason on the case report form had been interpreted differently during the study depending on the protocol amendment in effect. Until Protocol Amendment No. 5, “lack of efficacy” required at least a 100% increase in seizure frequency.

Note: Percentages are calculated based on the total number of randomized subjects.

Note: Subjects could have more than one reason for discontinuation.

Source of Data: Table 14.1.2, Listing 16.1.7, and Listing 16.2.1.1.

The category "other" was the reason for discontinuation in 3.5% of placebo, 3.7% of the 800 mg group and 0.5% of the 1200 mg group.

- In the placebo group, based on Listing 16.2.1.1, the "other" category was used for two subjects who were lost to follow-up and one each to the following: EKG showed 2nd degree block, change in concomitant medications, death (subject 30301), product marketed, mistakenly not taking the investigational product, and stopping 2nd AED.
- In the eslicarbazepine acetate 800 mg group, one subject each discontinued for the following reasons: subject was admitted to hospital for back pain and did not want to continue, death (00901), generalized tonic-clonic seizure (01902), patient changed carbamazepine dose (protocol violation captured as other), "treatment abandon", withdrew consent and later was lost to follow-up, subject to undergo surgery for aneurysm of thoracic aorta, and lost to follow-up.
- In the eslicarbazepine 1200 mg group, the one subject categorized as "other" was non-compliant with the protocol.

Lack of efficacy was noted as a reason for discontinuation in only one subject in the trial. This was a subject in the 1200 mg group, who had an increase in seizure frequency by 100% or more during the treatment periods (Listing 16.2.1.1).

Important Protocol Deviations included (as per the SAP, final version 4.1);

- less than seven partial-onset seizures in baseline and/or less than three in each 4-week period of the 8-week baseline prior to randomization (as per diary card) and a seizure-free interval > 28 consecutive day
- diary not satisfactorily completed by the subject or caregiver (compliance overall < 75%)
- diary compliance overall < 80% or > 120% during the titration and maintenance periods
- subject received a treatment different than the randomized treatment
- subject use of > 2 anticonvulsants during the study, other than rescue medication
- subject use of oxcarbazepine
- change in anticonvulsant during the study period other than as allowed
- At Visit 1 (week -8) -Violation of criteria related to seizures (could not have simple partial with no motor, not have primary generalized, not have seizures of non-epileptic origin, not have diagnosis of epilepsy < 12 months, not have epilepsy secondary to progressive cerebral lesion), progressive neurologic diseases, current treatment with more than 2 anticonvulsants or using oxcarbazepine or the anticonvulsant was not stable for ≥ 1 month before screening, and creatinine clearance < 60 mL/min

Table 14.1.3 of the CSR for study 304 indicates that, overall, similar percentages of subjects in each group had at least one important protocol deviation. More of the

placebo group compared to either ESL group did not meet an important inclusion/exclusion criteria or did not meet baseline eligibility (combined 6.3% compared to 4.7% and 4.4% respectively). Slightly more ESL 800 mg subjects received a disallowed medication.



**Table 19 Protocol Deviations**

Important Protocol Deviations
ITT Population

| | Placebo (N=220) | Eslicarbazepine Acetate 800 mg (N=215) | Eslicarbazepine Acetate 1200 mg (N=205) |
|---|---|---|---|
| Patients with at Least One IPD | 32 (14.5%) | 31 (14.4%) | 30 (14.6%) |
| Important Protocol Deviation | | | |
| Does not Meet Important Inclusion/Exclusion Criteria | 4 (1.8%) | 3 (1.4%) | 3 (1.5%) |
| Does not Meet Important Baseline Eligibility Criteria | 10 (4.5%) | 7 (3.3%) | 6 (2.9%) |
| Received Disallowed Concomitant Medication | 10 (4.5%) | 12 (5.6%) | 9 (4.4%) |
| Lack of Compliance (Study Treatment and/or Seizure Diary) | 13 (5.9%) | 10 (4.7%) | 13 (6.3%) |
| Other | 0 | 0 | 1 (0.5%) |

## 6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy analysis was natural logarithmically transformed (ln) standardized seizure frequency (lnSSF) over 28 days derived from seizure diary data for the maintenance period. lnSSF during the maintenance period was analyzed on the ITT population using an ANCOVA model that included treatment as a fixed effect, ln standardized seizure frequency at baseline, and diary version as covariates.

The ITT population was all randomized subjects who received at least one dose of study drug after randomization and had at least one post-baseline seizure frequency assessment, regardless of dairy type.

**Sample size determination:** Sample size estimation and power calculations were based on the natural log transformation (ln) of the standardized seizure frequency (or seizure frequency per 28 days). The original sample size calculation for this study was powered at 80% based on the change from baseline in standardized seizure frequency during the maintenance period. The alpha level was 0.025 based on a Bonferonni adjustment for two comparisons of the 2 doses of active drug with placebo (0.05 alpha level each). The assumptions yielded a sample size of 100 subjects for the placebo group and 100 subjects for each of the two active treatment groups. A 15% early discontinuation rate in the double-blind period was assumed. The required number of subjects to be randomized was 120 in each treatment group. 360 subjects were to be randomized in order to have 306 complete the double-blind period.

When the protocol was amended to incorporate the DE diary, the sample size was re-calculated from that in the original protocol to detect a treatment difference of 0.174 in the DE diary group with a standard deviation of 0.4. With a Bonferonni adjustment for

multiple comparisons (2 comparisons of 2 doses of active drug with placebo (alpha=0.025 for each), 130 subjects in each group were needed to achieve 89.4% power. A 10% drop-out rate was assumed, reportedly based on the drop-out in studies 301 and 302. A sample size of 435 subjects using DE diary (145 per group) were to be randomized across all sites in North America and the ROW in addition to those subjects already randomized and using the EE diary. It was projected this would result in 175 additional subjects randomized in North America and 260 in the ROW. Given the increase in the sample size, the primary analysis based on the ITT population has > 90% power.

The primary efficacy variable was calculated by the following formula:

(total number of seizures reported during maintenance period/total number of days with non-missing seizure data during the maintenance period) x 28.

All seizures, regardless of type, were to be used. Seizures occurring after visit 1 but more than 56 days before the date of visit 2 were not to be included in the calculation of standardized seizure frequency during the baseline.

The end of a seizure evaluation period was defined for subjects using the EE diary as the last date that the patient returned the diary as per the seizure diary tracking log. If there were missing diaries for patients during an evaluation period, the numbers of days in which diaries are missing were not to be included in the calculation of the average daily frequency for that period. The absence of seizures was to be assumed only in cases where the diary card was returned.

For subjects using the DE diary, if the diary was returned and there were no seizure data available for a particular day during the evaluation period, it was to be assumed that the seizure data were missing and the day was to be excluded from the calculation of the standardized seizure frequency (i.e. imputed as having the average daily rate for the period).

Multiplicity was adjusted using a 2-stage gate-keeping procedure for the ITT and DE populations. In stage 1, pair-wise comparisons of ESL 800 mg and ESL 1200 mg to placebo using alpha level of 0.0025. If both comparisons were significant, Dunnett's method was to be conducted at alpha 0.05 in stage 2. If only one comparison was significant, alpha of 0.025 remained in stage 2. If neither comparison was significant, no additional analyses were to be done.

**Sensitivity analyses of the primary endpoint:**

1. The *ln* SSF analysis of the primary analysis was repeated for each of the four efficacy populations.
2. A secondary analysis used the standardized seizure frequency from the titration phase in the maintenance analysis if there was missing standardized seizure

frequency during the maintenance period due to early discontinuation during the titration period. Also utilized nl data prior to analysis.

3. To examine the impact of missing DE diary data, missing seizure diary data in the placebo group was to be assumed to be zero for the day while the eslicarbazepine group was to have the average seizure count used. This was to be performed for the ITT population only on *ln* transformed data in an ANCOVA model.
4. To evaluate the impact of early drop-outs, imputations of standardized seizure frequency data were to be performed on the ITT population
- in subjects who dropped out by using the standardized seizure frequency during the baseline to impute the missing data and
- by using the standardized seizure frequency over the last two weeks prior to study discontinuation.
- The observed pre-discontinuation frequencies and the imputed post-discontinuation frequencies would be weighted according to the number of days of seizure diary data collected prior to discontinuation and the remaining scheduled time post-discontinuation to the end of the maintenance period.

5. subgroup analyses of the primary endpoint used ANCOVA models and ln standardized seizure frequency in the maintenance period and evaluated covariates including region, age, race, sex, carbamazepine dose reduction in maintenance, phenytoin dose reduction in maintenance, and rescue medication use (binary).
6. Sensitivity analyses added to the SAP: amended on March 2, 2012, following audit findings at site 952. Due to non-compliance at site 952 which ultimately led to site closure due to sufficient concern for subject safety, primary efficacy analyses were also performed excluding all data from site 952 (ITT and DE Diary ITT populations without Bonferroni and Dunnett's adjustment to ρ values and 95% CI's for the differences between treatment groups).
7. Post hoc efficacy analyses: p. 85/2539 CSR
    - Standard errors (SE) for the Least Standard Means (LSM) were added to all ANCOVA analysis tables. For all seizure efficacy analyses, the SE was calculated using the Delta Method.
    - For subjects who discontinued early from the study, DE seizure diary card compliance and the number of days of missing DE diary data were calculated up to and including their last scheduled visit.
    - A sensitivity analysis of the primary analysis of the primary efficacy variable, standardized seizure frequency during the maintenance period, was performed excluding extreme values that were greater than the mean + 3 *SD of the mean. This was performed on the ITT without multiplicity adjustment.
    - An additional analysis with the missing seizure data (identified after database lock) for subject 03905 hard-coded in the programming. The analysis was performed for the ITT with no adjustment for multiplicity.

- Regional analyses of standardized seizure frequency and CGI scale for the overall ITT were performed.

Per the Statistical Analysis Plan (SAP), sites and countries were pooled by region (North America versus ROW) in order to perform by- region analyses for selected efficacy variables and to investigate for regional differences. Smaller regional differences *could have been* investigated (p. 62/2716) based on geographical areas of Eastern Europe (including the Czech Republic, Hungary, Poland, Romania, Russia, and the Ukraine), Latin America (including Argentina and Brazil), and Western Europe (including Austria, Belgium, Denmark, France, Germany, Italy, Portugal, Spain, Sweden, Switzerland, United Kingdom, Greece, Cyprus), North America (including the U.S. and Canada) and Others (including Australia, South Africa, India, South Korea, and Turkey). Analyses by region were to be performed for the primary efficacy variable for the ITT population only if the treatment- by- sub-region interaction was statistically significant at an alpha level of 0.10.

**Results per Sponsor of Primary Analysis**

The analysis populations are shown as per the Sponsor's Table below. The primary analysis was performed on the ITT population and again, by diary type.

**Table 20 Analysis Populations Study 304**

**Table 8: Analysis Populations for Study 2093-304 Part 1**

| Data Analysis Sets | Placebo N=226 n (%) | ESL 800 mg N=216 n (%) | ESL 1200 mg N=211 n (%) | Total Randomized N=653 n (%) |
|---|---|---|---|---|
| Safety Population | 224 (99.1) | 216 (100.0) | 210 (99.5) | 650 (99.5) |
| ITT Population | 220 (97.3) | 215 (99.5) | 205 (97.2) | 640 (98.0) |
| EE ITT Population | 62 (27.4) | 67 (31.0) | 56 (26.5) | 185 (28.3) |
| DE ITT Population | 158 (69.9) | 148 (68.5) | 149 (70.6) | 455 (69.7) |
| PP Population | 188 (83.2) | 184 (85.2) | 175 (82.9) | 547 (83.8) |

Note: Percentages are calculated based on the number of randomized subjects.
DE diary=Daily entry diary, EE diary=Event entry diary
Source: Section 14.1, Table 14.1.2 of the CSR for Study 2093-304

The results will be described first based on the Sponsor's material and then, summarized based on the FDA statistical review.

The standardized seizure frequency was statistically positive for the 1200 mg group and not statistically positive, per the Sponsor's table below, for the 800 mg group. Based on the Sponsor's presentation, there is treatment-by-dairy version interaction

**Table 21 Standardized Seizure Frequency During the Maintenance Phase**

**Table 19: Standardized Seizure Frequency During the Maintenance Period (ITT Population)**

| Parameter | Placebo (N = 220) | ESL 800 mg (N = 215) | ESL 1200 mg (N = 205) |
|---|---|---|---|
| Standardized Seizure Frequency During Maintenance Period | | | |
| n | 212 | 200 | 184 |
| Mean | 12.99 | 13.70 | 12.05 |
| SD | 16.675 | 27.212 | 16.793 |
| Median | 7.44 | 5.56 | 5.49 |
| Min | 0.0 | 0.0 | 0.0 |
| Max | 103.6 | 294.0 | 106.0 |
| LS Mean (SE) | 7.88 (0.49) | 6.54 (0.41) | 6.00 (0.40) |
| 95% CI for LS Mean | (6.98, 8.90) | (5.77, 7.40) | (5.26, 6.84) |
| Log Difference in LS Mean | - | -0.18 | -0.26 |
| Unadjusted 95% CI for Log Difference | - | (-0.34, -0.02) | (-0.42, -0.10) |
| Unadjusted *P* value for Pairwise Comparison with Placebo | - | 0.029 | 0.002 |
| Adjusted 95% CI for Log Difference[a] | - | (-0.36, 0.00) | (-0.45, -0.07) |
| Adjusted *P* value for Pairwise Comparison with Placebo[a] | - | 0.058 | 0.004 |
| *P* value for Treatment-by-Diary Version Interaction[b] | - | 0.764 | - |
| *P* value for Treatment-by-Baseline Standardized Seizure Frequency Interaction[b] | - | 0.623 | - |

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ESL = eslicarbazepine acetate; LS = least squares; SD = standard deviation; SE = standard error.

[a] Bonferroni's procedure used to calculate the *P* values and the 95% CIs for the log differences.

[b] From separate ANCOVA models as described below, but including the respective interaction term as a fixed effect.

Note: Results are based on an ANCOVA model with log-transformed baseline standardized frequency and diary version as covariates and treatment as a fixed effect. The pairwise comparisons are each ESL dose versus placebo. LS means and CIs are back-transformed via the exponential function and subtracting 0.333. SEs for LS means are back-transformed via the Delta Method. Subjects who discontinued from the study during the titration period are not included.

Source of Data: Table 14.2.1.1.1.

**Primary Analysis -FDA statistical review**:

As noted, for the ITT population in study 304, there was statistical separation between the ESL 1200 mg group and placebo (adjusted p value = 0.004). The difference between the ESL 800 mg group and the placebo group was not statistically significant (adjusted p value =0.058). She indicates the dose response appeared to be monotone.

Dr. Ling notes the following with respect to diary types and the primary analysis for study 304. As studies 301 and 302 only used EE diary type, no additional discussion of diary type results is applicable.

In study 304, for the DE diary type, the adjusted p values for the comparisons of 800 mg to placebo and of 1200 mg to placebo were not statistically significant for either at the 0.25 alpha level used in the second stage Dunnett procedure. Of note, the statistical review indicates that in a worst case analysis in which EE diary data were excluded, the DE dairy ITT showed as statistically significant separation between the ESL 1200 mg group comparison to placebo (adjusted p value = 0.049 in the table below). Dr. Ling notes that a significance level of 0.05 should be used in this case since the EE diary was excluded and the analysis of the DE diary was ITT was treated as the primary analysis. Of note, the statistical reviewer confirmed the data in the Sponsor's table 4 below which displays the data just described.

**Table 22 Standardized Seizure Frequency ITT and DE Populations**

**Table 4. Primary Analysis of Standardized Seizure Frequency during the Maintenance Period (ITT and DE Population)**

| | Placebo | ESL 800 mg | ESL 1200 mg |
|---|---|---|---|
| ITT population | | | |
| N [a] | 212 | 200 | 184 |
| LS mean (SE) | 7.88 (0.49) | 6.54 (0.41) | 6.00 (0.40 |
| 95% CI | [6.98, 8.90] | [5.77, 7.40] | [5.26, 6.84] |
| Log difference in LS mean | | -0.18 | -0.26 |
| Unadjusted p-value | | 0.029 | 0.002 |
| Adjusted p-value [b] | | 0.058 | 0.004 |
| DE ITT population | | | |
| N [a] | 154 | 137 | 136 |
| LS mean (SE) | 7.54 (0.54) | 6.32 (0.48) | 5.96 (0.46) |
| 95% CI | [6.55, 8.68] | [5.44, 7.35] | [5.12, 6.94] |
| Log difference in LS mean | | -0.17 | -0.22 |
| Unadjusted p-value | | 0.094 | 0.026 |
| Adjusted p-value [c] | | 0.167 | 0.049 |

a Subjects who discontinued from the study during the titration period were not included.
b Bonferroni's procedure was used to calculate the p- values.
c Dunnett's procedure was used to calculate the p-values (assessed at 0.025 level).
Source: Table 19 & 20 of the CSR for Study 304, confirmed by the reviewer.

Page 14 of the FDA statistical review of study 304 cites other issues around missing data and zeros that might not be accommodated by the measures attempted to overcome the issues with the EE diaries. These are described below.

- For subjects using EE diaries, when no seizures were reported, their seizure data were considered zero (0) if the dates were covered by a Diary Tracking Log CRF. However, when the diary card was returned, it was possible that some seizure data were missing. She notes this type of missing data cannot be identified due to the limitation of the EE diary and she notes this cannot be accounted for in the analysis. This could be accounted for in DE diaries which reported compliance rates of 77%, 80%, and 80% for placebo, 800 mg, and 1200 mg subjects respectively.
- For EE diaries, seizure data were considered missing if the dates were not covered on the Diary Tracking Log CRF by the dates that the EE diary cards were dispensed and returned, for example, subject 20101 had 32 seizures recorded on 28 days between 2-19 and 5-14, 2009 (baseline). However, the diary tracking log did not contain records of diaries dispensed or returned during this period. Days without seizures was set to be missing. Dr. Ling opined that it was likely the subject did not have seizures and that the seizure

data was set to missing due to error in the diary tracking log. She notes that only 3 subjects had similar situation and the impact on efficacy was minimal.

- The sites were instructed to transcribe seizures records on the EE diaries onto CRF pages and errors could occur in this process. She provides an example of subject #00405 between 7-29-10 and 8-4-10 whose data was transcribed twice in the CRF giving duplicate seizures in the dataset. She notes the Division requested the sponsor to audit a total of 40 subject diaries and the corresponding database entries, including this subject. She notes the Sponsor found some duplicates but failed to identify the problem for this subject.
- The use of the end of a seizure evaluation period as the last date the subject returned the diary is a reasonable assumption but there may be exceptions, such as subject #00405, the last seizure was reported on the CRF as 9-12-10 and the dairy was returned on 10-12-10. It was assumed no seizures occurred during the period of 9-12 and 10-12. This subject, however, had 169 seizures during the 80 days prior to 9-12 so it is questionable whether he/she did not have a seizure versus he/she did not record the seizure. Dr. Ling notes that the extent of this problem cannot be known for certain, as these zero seizures may or may not be accurate.

Dr. Ling reports that based on review of the dataset (presumably for study 304) and selected CRFs, these problems were not deemed common.

Dr. Ling notes that there may be other unidentified problems and posits that it is not clear whether collectively they could undermine the credibility of the EE diary. However, she indicates that the evidence to date may not be enough to dismiss the EE diary data entirely, though Dr. Ling also indicates some sort of discounting may be reasonable.

Diary type as related to regional impact and study populations in studies 301 and 302 is discussed in the section following discontinuation below.

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**Analysis for Impact of early discontinuation in study 304**:

**Sponsor:**
Per the CSR, three analyses were performed to evaluate the impact of early discontinuation. One included only those who completed maintenance (completer's analysis). One imputed missing scores from the baseline period data and one imputed missing scores from the 2 weeks prior to discontinuation.

Based on the Sponsor's presentation (Table 14.2.15.2 of the CSR, not shown in this review), the bottom line results using the completer's analysis was a p value of 0.03 for the 800 mg to placebo comparison and a p value of <0.001 for the 1200 mg to placebo comparison.

Based on the Sponsor's presentation (Table 14.2.15.3 of the CSR, not shown in this review), with imputation based on baseline data, the p value was 0.045 for the 800 mg to placebo comparison and 0.016 for the 1200 mg to placebo comparison.

Based on the Sponsor's presentation (Table 14.2.15.4 of the CSR, not shown in this review), the imputation using the data from two weeks prior to discontinuation, the p value is 0.03 for the 800 mg to placebo comparison and a p value of <0.001 for the 1200 mg to placebo comparison.

**FDA statistical review:**

The statistical reviewer performed several additional analyses to assess the impact of early drop-outs (combined titration and maintenance and imputation with the last 2 week seizure frequency for subjects with < 14 days of maintenance seizure data). She posited that analyses of the combined titration and maintenance might overestimate treatment effects in the 1200 mg group due to early drop-outs and that the imputation using the last 2-week seemed more reasonable. The results of the latter analysis were consistent with the primary analysis.

**Impact of Region on study 304 data**:

**Sponsor**: In an analysis performed by the Sponsor, in North America, there were 78 placebo subjects, 77 ESL 800 mg subjects, and 74 ESL 1200 mg subjects p value. In the analysis, there were 75 placebo subjects, 70 ESL 800 mg subjects, and 66 ESL 1200 mg subjects. Neither ESL group separated statistically from placebo.

In an analysis performed by the Sponsor, in the ROW, with 137 placebo subjects, 130 800 mg ESL subjects, and 118 ESL 1200 mg subjects, both ESL groups separated statistically from placebo.

**Table 23 Standardized Seizure Frequency During the Maintenance Period by Region**

**Table 22: Standardized Seizure Frequency During the Maintenance Period for Each Region (ITT Population)**

| **Region: North America** | **Placebo (N = 78)** | **ESL 800 mg (N = 77)** | **ESL 1200 mg (N = 74)** |
|---|---|---|---|
| Standardized Seizure Frequency During Maintenance Period | | | |
| n | 75 | 70 | 66 |
| Mean | 13.26 | 20.06 | 13.23 |
| SD | 16.490 | 41.214 | 16.211 |
| Median | 7.61 | 6.96 | 7.49 |
| Min | 0.0 | 0.0 | 0.0 |
| Max | 79.3 | 294.0 | 79.6 |
| LS Mean (SE) | 7.90 (0.80) | 7.63 (0.80) | 6.57 (0.73) |
| 95% CI for LS Mean | (6.48, 9.63) | (6.20, 9.37) | (5.26, 8.17) |
| Log Difference in LS Mean | - | -0.03 | -0.18 |
| Unadjusted 95% CI for Log Difference | - | (-0.29, 0.22) | (-0.44, 0.08) |
| Unadjusted *P* value for Pairwise Comparison with Placebo | - | 0.794 | 0.181 |
| ***P* value for Treatment-by-Diary Version Interaction**[a] | - | 0.935 | - |
| *P* value for Treatment-by-Baseline Standardized Seizure Frequency Interaction [a] | - | 0.860 | - |
| **Region: Rest of World** | **Placebo (N = 142)** | **ESL 800 mg (N = 138)** | **ESL 1200 mg (N = 131)** |
| Standardized Seizure Frequency During Maintenance Period | | | |
| n | 137 | 130 | 118 |
| Mean | 12.85 | 10.27 | 11.38 |
| SD | 16.833 | 14.140 | 17.142 |
| Median | 7.33 | 5.16 | 4.69 |
| Min | 0.0 | 0.0 | 0.0 |
| Max | 103.6 | 89.9 | 106.0 |
| LS Mean (SE) | 7.80 (0.61) | 5.87 (0.47) | 5.59 (0.47) |
| 95% CI for LS Mean | (6.68, 9.09) | (5.01, 6.86) | (4.72, 6.60) |
| Log Difference in LS Mean | - | -0.27 | -0.32 |
| Unadjusted 95% CI for Log Difference | - | (-0.48, -0.07) | (-0.53, -0.11) |
| Unadjusted *P* value for Pairwise Comparison with Placebo | - | 0.010 | 0.003 |
| *P* value for Treatment-by-Diary Version Interaction[a] | - | 0.686 | - |
| *P* value for Treatment-by-Baseline Standardized Seizure Frequency Interaction [a] | - | 0.589 | - |

Abbreviations: ANCOVA = Analysis of Covariance; CI = Confidence Interval; ESL = eslicarbazepine acetate; LS = Least Squares; Max = maximum; Min = minimum; SE = Standard Error.

[a] From separate ANCOVA models as described below, but including the respective interaction term as a fixed effect.

Note: Results are based on an ANCOVA model with log-transformed baseline standardized frequency and diary version as covariates and treatment as a fixed effect. The pairwise comparisons are each ESL dose versus placebo. LS means and CIs are back-transformed via the exponential function and subtracting 0.333. SEs for LS means are back-transformed via the Delta Method. Subjects who discontinued from the study during the titration period are not included. Source of Data: Table 14.2.1.1.1.

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## FDA statistical review:

Dr. Ling's review indicates there were no statistically significant interactions between treatment and diary version or between treatment and region at the 0.10 level. She notes, however, that the EE diary ITT had a numerically larger treatment effect in the ROW than in NA. The largest treatment effect was seen in subjects using the EE diary in the ROW. *This (ROW and EE) is the population in studies 301 and 302.*

The table below, made by Dr. Ling, shows the treatment effect on standardized seizure frequency by diary type and region. Dr. Ling indicates that in NA there were fewer subjects using the EE diary and the placebo response seemed greater compared to the ROW, and in the ROW, there was a significant effect of Diary Type (p of 0.01) suggesting that the type of diary impacted seizure frequency regardless of treatment.

**Table 24 Standardized Seizure Frequency By Diary Type and Region-FDA Statistical Reviewer**

**Table 7. Treatment Effect on Standardized Seizure Frequency (Log Difference in LS Mean) by Diary Type and Region**

| | North America | | | Rest of World | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|
| | | ESL 800 mg | ESL 1200 mg | | ESL 800 mg | ESL 1200 mg | | ESL 800 mg | ESL 1200 mg |
| **EE** | N=44 | -0.10 | -0.16 | N=125 | -0.34 | -0.46 | N=169 | -0.21 | -0.36 |
| **DE** | N=168 | -0.05 | -0.17 | N=260 | -0.24 | -0.26 | N=428 | -0.17 | -0.22 |
| **Total** | N=212 | -0.03 | -0.18 | N=385 | -0.27 | -0.32 | N=597 | -0.18 | -0.26 |

N is the number of subject with maintenance seizure data for each subgroup.
Source: The FDA reviewer.

**Update on primary endpoint analysis from data from studies 301 and 302:**

The statistical review notes the efficacy endpoints were reanalyzed in the ISE resubmission to account for the effect of seizure diaries not previously analyzed and to exclude two sites found non-compliant by the Company (sites 174 and 175). {*Clinical reviewer's comment: reanalysis did not also include OSI sites found non-compliant in the first cycle (site 112 from study 301 and site 395 from study 302)}*. In the re-analysis, the last diary card return date was used to cap the end of the study period instead of the way it was handled in the initial CSR analysis, which was according to the length of time they had participated in the study and if no seizures were reported for a day, it was assumed that no seizure had occurred while the subject was still in the study.

The table below is from this cycle's statistical review; the source appears to be an ISE table. The statistical reviewer indicates that though the updated results still reached statistical significance for the doses of 800 mg and 1200 mg, the monotone dose-response was seen only in study 301 and not in 302 and that "the significance of ESL 800 mg group in Study 301 and ESL 1200 mg group in study 302 became marginal." (p. 18/22 of the statistical review). The reader is deferred to her initial review of 301 and 302 for discussion of her results from the first cycle review.

**Table 25 Study 301 and 302-Updated Primary Endpoint Results**

**Table 10. Updated Results for Study 301 and Study 302**

| | Placebo | ESL 400 mg | ESL 800 mg | ESL 1200 mg |
|---|---|---|---|---|
| **Study 301** | | | | |
| N | 95 | 91 | 88 | 87 |
| LS mean (SE) | 6.6 (0.54) | 5.8 (0.48) | 5.0 (0.43) | 4.3 (0.38) |
| Adjusted p-value | - | 0.4969 | 0.0468 | 0.0010 |
| **Study 302** | | | | |
| N | 99 | 94 | 87 | 81 |
| LS mean (SE) | 8.6 (0.62) | 8.1 (0.60) | 6.2 (0.48) | 6.6 (0.53) |
| Adjusted p-value | - | 0.9043 | 0.0057 | 0.0424 |

Source: Table 31 of ISE.

## 6.1.5 Analysis of Secondary Endpoints(s)

Include:
As per the SAP, all seizures, regardless of type were included in the seizure-related secondary efficacy variables.

- Proportion of responders during the maintenance period-defined as patients with ≥ 50% reduction in standardized seizure frequency from the 8-week baseline period to the 12-week maintenance period. The variable was derived based on calculation of percentage change from baseline in the standardized seizure frequency during the maintenance period.
- Relative change from baseline in standardized seizure frequency-for the ITT population, the summaries and analyses were also to be performed by carbamazepine dose reduction
- Standardized seizure frequency
- Seizure reduction (<50%, ≥50 % to ≤ 75%, and >75%) during the maintenance period
- Proportion of seizure-free patients during the maintenance period
- Proportion of patients with ≥ 25% increase (exacerbation) in standardized seizure frequency during the maintenance period
- Seizure frequency by week
- Standardized seizure frequency and relative change from baseline (percent) in seizure frequency over the 12-week maintenance period by seizure type (per body CSR)
- Proportion of patients remaining on treatment for the duration of part 1 of the study (the controlled phase)
- Clinical Global Impressions
- Seizure severity questionnaire
- Quality of Life in Epilepsy Inventory (QoLIE-31)
- Montgomery Asberg Depression Rating Scale

**Results:**
The results of the secondary analyses of responder rate (Sponsor followed by FDA statistical reviewer), relative change in baseline standardized seizure frequency during maintenance phase for the ITT population, and the Sponsor's presentations/analyses of standardized seizure frequency in the maintenance period by type are discussed below.

## Sponsor's Responder analysis:

The table duplicated below is from the CSR for study 304. This table indicates that more of the 1200 mg ESL group experienced a reduction of ≥ 50% than either the 800 mg or placebo group (~43% compared to ~31% of the 800 mg group and 23% of the placebo group). Only the comparison between the 1200 mg group and placebo was statistically significant.

Most subjects did not have an increase of seizures by ≥ 25% (~15% of the placebo group compared to ~13% of either ESL dose group). Most subjects did not become "seizure free" defined as 100% reduction in seizures and completing the maintenance phase (0.9% in the placebo group and about 2% in each of the ESL groups).

**Table 26 Sponsor's Responder Analysis Study 304**

**Table 23: Summary of Percent Changes from Baseline in Seizures During the Maintenance Period (ITT Population)**

| Parameter | Placebo (N = 220) | ESL 800 mg (N = 215) | ESL 1200 mg (N = 205) |
|---|---|---|---|
| Distribution of Percentage Change from Baseline in Standardized Seizure Frequency | | | |
| 100% Reduction | 3 (1.4%) | 7 (3.5%) | 6 (3.3%) |
| > 75% - < 100% Reduction | 15 (7.1%) | 24 (12.0%) | 25 (13.7%) |
| ≥ 50% - ≤ 75% Reduction | 31 (14.6%) | 30 (15.0%) | 47 (25.7%) |
| 0% - < 50% Reduction | 107 (50.5%) | 83 (41.5%) | 62 (33.9%) |
| > 0% - < 25% Increase | 25 (11.8%) | 30 (15.0%) | 19 (10.4%) |
| ≥ 25% Increase | 31 (14.6%) | 26 (13.0%) | 24 (13.1%) |
| Not Evaluable | 8 | 15 | 22 |
| *P* value[a] | - | 0.156 | 0.002 |
| ≥ 50% Reduction (Responder) | | | |
| Yes | 49 (23.1%) | 61 (30.5%) | 78 (42.6%) |
| No | 163 (76.9%) | 139 (69.5%) | 105 (57.4%) |
| Not Evaluable | 8 | 15 | 22 |
| Exact 95% CI for Percentage of Responders | (17.6%, 29.4%) | (24.2%, 37.4%) | (35.4%, 50.1%) |
| *P* value[a] | - | 0.068 | < 0.001 |
| 100% Reduction and Completed the Maintenance Period (Seizure Free) | | | |
| Yes | 2 (0.9%) | 4 (2.0%) | 4 (2.2%) |
| No | 210 (99.1%) | 196 (98.0%) | 179 (97.8%) |
| Not Evaluable | 8 | 15 | 22 |
| Exact 95% CI for Percentage of Seizure-Free Subjects | (0.1%, 3.4%) | (0.5%, 5.0%) | (0.6%, 5.5%) |
| *P* value[a] | - | 0.336 | 0.235 |
| 100% Reduction and Received at Least 28 Days of Treatment in the Maintenance Period (Seizure-Free) | | | |
| Yes | 2 (0.9%) | 5 (2.5%) | 6 (3.3%) |
| No | 210 (99.1%) | 195 (97.5%) | 177 (96.7%) |
| Not Evaluable | 8 | 15 | 22 |
| Exact 95% CI for Percentage of Seizure-Free Subjects | (0.1%, 3.4%) | (0.8%, 5.7%) | (1.2%, 7.0%) |
| *P* value[a] | - | 0.191 | 0.068 |
| ≥ 25% Increase (Exacerbation) | | | |
| Yes | 31 (14.6%) | 26 (13.0%) | 24 (13.1%) |
| No | 181 (85.4%) | 174 (87.0%) | 159 (86.9%) |

| Parameter | Placebo (N = 220) | ESL 800 mg (N = 215) | ESL 1200 mg (N = 205) |
|---|---|---|---|
| Not Evaluable | 8 | 15 | 22 |
| Exact 95% CI for Percentage of Subjects with Exacerbation | (10.2%, 20.1%) | (8.7%, 18.5%) | (8.6%, 18.9%) |
| *P* value[a] | - | 0.514 | 0.647 |

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; ESL = eslicarbazepine acetate.
[a] From a CMH test stratified by region and diary version comparing each ESL dose versus placebo.
Note: Percentages are calculated based on the number of subjects with non-missing data in the ITT population in each treatment group.
Note: The Not Evaluable category includes subjects who discontinued during the titration period or who entered the maintenance period but have missing data. These subjects are not included in the denominator for the percentage calculations.

By region: When considered by region NA versus ROW, for the NA sites (n=78 placebo, 77 at 800 mg eslicarbazepine, and 74 at 1200 mg eslicarbazepine) all of the parameters above are negative, no difference between placebo and the eslicarbazepine groups (Table 14.2.3.1 of the CSR). For the ROW sites (n=142 placebo, 138 eslicarbazepine 800 mg and 131 eslicarbazepine 1200 mg), the same table indicates that only the 50% responder rate is statistically positive for both the 800 mg and 1200 mg eslicarbazepine groups when either is compared to the placebo group.

**FDA statistical review 50% responder:**

The FDA statistical review notes that the Sponsor's analysis of subjects who had a ≥ 50% reduction from baseline in standardized seizure frequency during the maintenance period (responders) excluded subjects without data during maintenance phase. Dr. Ling performed a sensitivity analysis in which subjects without maintenance data were considered non-responders. She indicates the results were similar. The percentage of responders was 22.3% placebo, 28.4% in the ESL 800 mg group, and 30.1% in the ESL 1200 mg group. The unadjusted p value was 0.123 for the 800 mg group and <0.001 for the ESL 1200 mg group.

## Relative Change in Baseline Standardized Seizure Frequency During the Maintenance Period (ITT population)

**Sponsor:**

Section 11.2.2 of the CSR for study 304 reports the relative change from baseline in standardized seizure frequency during the maintenance period. Median percentage changes are reported as -21.78 in the placebo group, -29.7 in the ESL 800 mg group, and -35.56 in the ESL 1200 mg group. The unadjusted p values from non-parametric analysis were 0.249 for the comparison of placebo to 800 mg ESL and 0.012 for the comparison of placebo to ESL 1200 mg. The sponsor reports that these results were supported by the parametric analysis results.

**FDA statistical review relative change from baseline data**:

The FDA statistical review notes that both the parametric and non-parametric analyses performed by the Sponsor achieved statistical significance for the 1200 mg group.

## Sponsor's analyses of standardized seizure frequency in the 12-week maintenance period by seizure type:

It is difficult to know how to interpret the data below. In study 304, the sample sizes are larger than in the other studies for each seizure type. For the seizure types, simple partial, complex partial, partial with secondary generalization, the ESL groups have slightly greater reductions than the placebo group in maintenance. In study 301 (n sizes of 39,39, 40), the means (not clear LS means) seem to suggest no worsening in seizure types with ESL treatment compared to placebo treatment. In study 302 (n sizes of 29 – 35), with sample sizes not that much smaller than those in 301 for partial evolving to secondarily generalized, the LS mean change comparison ESL 800 mg to placebo does not show reduction and is positive while the ESL 400 mg and ESL1200 mg group mean differences are negative.

## Study 304:

The Sponsor's analysis of standardized seizure frequency during the maintenance period by seizure type for the ITT population is in Table 26 of the CSR for study (reproduced below). Based on this table, for all three seizure types the log difference in LS mean trended in the direction that ESL groups showed a greater reduction when compared to placebo. The unadjusted p values for the comparisons between ESL 800 mg daily and placebo and for ESL 1200 mg versus placebo for simple partial seizures and for partial seizures generalizing did not separate statistically. For complex partial seizures, the 1200 mg group comparison to placebo for log difference in LS mean did reach statistical significance.

Table 14.2.7.1.1 is the source table for Table 26 above and includes descriptive statistics for "unclassifiable" and "other" seizures. The number of subjects with "unclassifiable" seizures is 4-6 per group and with "other" seizures is 1-4 per group (numbers too small to interpret).

**Table 27 Standardized Seizure Frequency During Maintenance- Study 304**

**Table 26: Standardized Seizure Frequency During the Maintenance Period by Seizure Type (ITT Population)**

| Parameter | Placebo (N = 220) | ESL 800 mg (N = 215) | ESL 1200 mg (N = 205) |
|---|---|---|---|
| Simple Partial During the Maintenance Period | | | |
| n | 101 | 98 | 88 |
| Mean | 9.41 | 9.71 | 10.89 |
| SD | 13.739 | 19.432 | 19.293 |
| Median | 4.44 | 3.15 | 3.46 |
| Min | 0.3 | 0.3 | 0.3 |
| Max | 75.5 | 126.7 | 97.1 |
| LS Mean (SE) | 4.77 (0.53) | 3.99 (0.44) | 4.12 (0.49) |
| 95% CI for LS Mean | (3.82, 5.93) | (3.20, 4.94) | (3.26, 5.20) |
| Log Difference in LS Mean | - | -0.17 | -0.13 |
| Unadjusted 95% CI for Log Difference | - | (-0.44, 0.11) | (-0.41, 0.14) |
| Unadjusted *P* value for Pairwise Comparison with Placebo | - | 0.230 | 0.343 |
| *P* value for Treatment-by-Region Interaction[a] | - | 0.885 | - |
| Complex Partial During the Maintenance Period | | | |
| n | 164 | 158 | 148 |
| Mean | 9.21 | 9.40 | 7.44 |
| SD | 13.930 | 25.239 | 8.693 |
| Median | 4.94 | 4.39 | 3.95 |
| Min | 0.3 | 0.3 | 0.3 |
| Max | 101.4 | 294.0 | 42.0 |
| LS Mean (SE) | 5.18 (0.34) | 4.74 (0.32) | 4.22 (0.30) |
| 95% CI for LS Mean | (4.55, 5.89) | (4.16, 5.41) | (3.67, 4.85) |
| Log Difference in LS Mean | - | -0.08 | -0.19 |
| Unadjusted 95% CI for Log Difference | - | (-0.25, 0.09) | (-0.36, -0.02) |
| Unadjusted *P* value for Pairwise Comparison with Placebo | - | 0.343 | 0.031 |
| *P* value for Treatment-by-Region Interaction [a] | - | 0.523 | - |
| Partial Evolving to Secondary Generalized During the Maintenance Period | | | |
| n | 71 | 58 | 56 |
| Mean | 3.89 | 4.89 | 2.71 |
| SD | 7.592 | 10.480 | 2.743 |
| Median | 1.65 | 1.49 | 1.84 |
| Min | 0.3 | 0.3 | 0.3 |
| Max | 46.1 | 67.9 | 12.0 |
| LS Mean (SE) | 2.10 (0.24) | 1.99 (0.24) | 1.59 (0.21) |
| 95% CI for LS Mean | (1.67, 2.62) | (1.55, 2.52) | (1.22, 2.05) |
| Log Difference in LS Mean | - | -0.05 | -0.23 |
| Unadjusted 95% CI for Log Difference | - | (-0.31, 0.22) | (-0.51, 0.04) |
| Unadjusted *P* value for Pairwise Comparison with Placebo | - | 0.726 | 0.091 |

| Parameter | Placebo (N = 220) | ESL 800 mg (N = 215) | ESL 1200 mg (N = 205) |
|---|---|---|---|
| *P* value for Treatment-by-Region Interaction [a] | - | 0.603 | - |

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ESL = eslicarbazepine acetate; LS = least squares; Max = maximum; Min = minimum; SD = standard deviation; SE = standard error.

[a] From a separate ANCOVA model as described in the note below, but including region and the interaction term as fixed effects.

Note: Results are based on an ANCOVA model on log-transformed baseline standardized seizure frequency and diary version as covariates and treatment as a fixed effect. The pairwise comparisons are each ESL dose versus placebo. LS means and CIs are back-transformed via the exponential function and subtracting 0.333. SEs for LS means are back-transformed via the Delta Method.

Source of Data: Table 14.2.7.1.1.

## Study 301:

The sponsor's table in the CSR for study 301(Table 42) shows descriptive summary statistics of the number of seizures (standardized to a "frequency per 4 weeks") by seizure type (simple partial, complex partial, secondarily generalized, and unclassified) for the ITT population. This table is not reproduced in the text of this review though a sample of the formatting is included in the appendix of this document. There is a summary below.

- Simple seizures: the mean number of simple partial seizures, standardized to a frequency per 4 weeks, increases over baseline in the titration period and decreases in the 12-week maintenance phase (compared to baseline and titration) for the placebo group and for all ESL groups. For the combined 12-week maintenance + titration, all groups show a mean reduction from baseline.

  The baseline mean for the ESL 1200 mg group and for the ESL 800 mg group was 8.5. For the ESL 400 mg group the baseline mean was 9.7 and for the placebo group, the baseline mean was 10. In maintenance, the mean for the 1200 mg group was 5.4 (Δ -3.1) and for the 800 mg group was 6.1 (Δ - 2.4) compared to a change in the means of -1.5 for the 400 mg group and for the placebo group. The means went up in taper for two ESL groups (1200 mg and 400 mg) when compared to that groups baseline.

- Complex partial seizures: for each ESL group, the mean number of complex partial seizures decreases in both maintenance (Δ -0.6 in the 1200 mg group, Δ -2.4 in the 800 mg group, Δ -.13 in the ESL 400 mg compared to Δ +0.2 in the placebo group) and in the combined titration+ maintenance when compared to baseline. For the placebo group, there is a small increase from baseline to maintenance but a small decrease from baseline to the combined titration and maintenance (Δ -0.5). The means went up in taper for all groups

except the ESL 800 mg group (Δ -0.3) when compared to that group's baseline and for all ESL groups when compared to that group's maintenance number. The largest taper increase from baseline was in the ESL 1200 mg group (from baseline mean 8.4, maintenance mean of 7.8 and to taper mean 10.5).

- Partial evolving to secondarily generalized seizures: for each ESL group (ns of 39, 39, and 40) and for placebo (n=48), the mean number of partial seizures that generalize increases in titration when compared to baseline (less of an increase in the placebo group than in the ESL groups) and all groups (including placebo) decrease in both maintenance and in the combined maintenance + titration when compared to baseline. The change (Δ) between baseline and maintenance means for the ESL 1200 mg group, ESL 400 mg group, and the placebo group is -0.8. For the 800 mg group, the Δ is -1.4. The Δ between baseline and the period of maintenance plus titration is -1 for the ESL 1200 mg and for the placebo group and is -1.4 for the ESL 800 mg group and -0.8 for the ESL 400 mg group.

  The numbers of subjects per group providing data on taper are smaller (17 to 33 per group). As per Table 42, for the 17 subjects who tapered from the ESL 1200 mg group and for the 33 who tapered from placebo, the table indicates an increase in mean seizure frequency over baseline (4 compared to 3.2 at baseline for the ESL 1200 mg group and 4.1 compared to 3.5 at baseline for the placebo group).

- Unclassified seizures: Table 42 indicates the numbers of subjects are small with a maximum n of 10.

## Study 302:

- Simple partial seizures: The Sponsor's Table 14.2-2.8.2 in the CSR for study 302 provides an ANCOVA analysis of the frequency of simple partial seizures per 4 weeks over the 12 week maintenance period for the ITT population. Table 14.2-2.8.3 is the corresponding table representing the combined titration + maintenance periods. These tables are not shown in this review but the data are summarized.

  In maintenance, the LS mean changes (LS mean difference to placebo) is negative for each ESL group (400 mg, 800 mg, and 1200 mg) and the ESL 800 and ESL 1200 mg comparisons are statistically different from placebo (the ESL 400 is not). The 800 mg group has the biggest mean difference (-3 compared to -2.5 for the 1200 mg group and -0.8 for the 400 mg group). In combined titration + maintenance, it is similar. The 800 mg group and the 1200 mg group show greater reductions compared to placebo change that are

statistically significant. The ESL 800 mg group reduction is numerically bigger than the 1200 mg group (-3.8 compared to -2.9 in the 1200 mg group).

- Complex Partial Seizures: The Sponsor's Table 14.2-2.9.2 is an ANCOVA analysis for frequency of complex partial seizures per 4 weeks over the 12-week maintenance period and Table 14.2-2.9.3 is the corresponding analysis using the combined titration + maintenance period. These tables are not shown in this review.

  In maintenance, the LS mean changes (LS mean difference to placebo) is negative for each ESL group (400 mg, 800 mg, and 1200 mg) when compared to placebo and the ESL 1200 mg comparison is statistically different from placebo (ESL 400 and ESL 800 mg are not). The LS mean differences to placebo are – 0.6, -1, and -1.7 for the ESL 400 mg, ESL 800 mg, and ESL 1200 mg to placebo respectively. In combined titration + maintenance, the 800 mg group and the 1200 mg group show greater reductions compared to placebo that are statistically significant.

- Partial seizures evolving to secondarily generalized seizures: Data in the Sponsor's Table 14.2-2.10.2 is the Sponsor's ANCOVA analysis for frequency of partial evolving to secondarily generalized per 4 weeks over the 12- week maintenance period and Table 14.2-2.10.3 is the corresponding analysis using the combined titration + maintenance period. These tables are not shown in this review.

  For this analysis, there are 29 to 35 subjects in each group (about out of 97 to 100 per treatment group). In maintenance, the LS mean changes (LS mean difference to placebo) is positive in the ESL 800 mg group when compared to placebo (0.6). Both the ESL 400 mg and the ESL 1200 mg LS mean differences are negative (-0.4 and -0.7 respectively). None of the comparisons of ESL to placebo is statistically significant.

  In the combined titration + maintenance, all of the ESL groups are negative when compared to placebo (LS mean difference to placebo). No difference is statistically significant. The 800 mg group LS mean difference s -0.1. Both the ESL 400 mg and the ESL 1200 mg group LS mean differences to placebo were -0.7.

  Unclassified:
  Data in the Sponsor's Table 14.2-2.11.2 is the Sponsor's ANCOVA analysis for frequency of partial evolving to secondarily generalized per 4 weeks over the 12- week maintenance period and Table 14.2-2.11.3 is the corresponding analysis using the combined titration + maintenance period. These tables are not shown in this review.

For this analysis, there are 19 to 27 subjects in each group (about out of 97 to 100 per treatment group). The number of subjects contributing data per group is small and the following is reported with the understanding that it is of limited interpretability. In maintenance, the LS mean changes (LS mean difference to placebo) is positive in the ESL 1200 mg group when compared to placebo (0.7). Both the ESL 400 mg and the ESL 800 mg LS mean differences are negative (-0.2 and -0.6 respectively). None of the comparisons of ESL to placebo is statistically significant.

In the combined titration + maintenance, the LS mean differences to placebo for both the ESL 800 mg and ESL 1200 mg groups are positive when compared to placebo (0.4 and 1.1). The ESL 400 mg group comparison is negative (-0.1). No difference is statistically significant.

### 6.1.6 Other Endpoints

Not applicable.

### 6.1.6 Subpopulations

For the primary efficacy variable, subgroup analyses were conducted for the covariates of region (NA versus ROW), age (< 40 years, 40 to 65, and > 65 years), sex, race (Caucasian, non-Caucasian), most common anticonvulsant at baseline, carbamazepine dose reduction in maintenance (yes or no), phenytoin dose reduction in maintenance (yes or no), and use of rescue medication during maintenance (yes or no). These groups are discussed in limited way below.

**The Sponsor:**

**Race and Sex**:

By Race- standardized seizure frequency during the maintenance period for the ITT population, as per the Sponsor's CSR Table 14.2.14.2.2 indicates that for both Caucasians and non-Caucasians, the unadjusted p value for the comparison of ESL 1200 mg to placebo was ≤ 0.05 but not significant (> 0.05) for he ESL 800 mg comparison to placebo.

By Sex- standardized seizure frequency during the maintenance period for the ITT population, as per the Sponsor's CSR Table 14.2.14.2.3 indicates that standardized seizure frequencies were lower in males compared with females. In females, the unadjusted p value comparison between ESL 800 mg and placebo was not statistically

significant (0.311) and was 0.045 for the ESL 1200 mg to placebo comparison. For males, the p-values were < 0.05 or both comparisons.

**Dose reductions of anticonvulsants during the trial**:

In trials 301 and 302, changes in concomitant anticonvulsants were not allowed.
In trial 304, reductions in both carbamazepine (amendment #3) and phenytoin (amendment # 5) were allowed (up to 25% and 15% of the total daily dose respectively. The phenytoin amendment was fairly late in the trial.

Per the CSR, in 304, 45 subjects changed concomitant anticonvulsant use in some manner. Fewer changes were noted in the placebo group (3.1%) when compared to the eslicarbazepine 800 mg and 1200 mg groups (7.4% and 10.5%) respectively. It is not clear whether this table includes benzodiazepines and/or psycholeptics.

**Study 304**

**Table 28 Anticonvulsant Medication Changes in Study 304**

| | Placebo n=224 | 800 mg n=216 | 1200 mg n=210 |
|---|---|---|---|
| any change | 7 (3.1%) | 16 (7.4%) | 22 (10.5%) |
| change in dose | 2 (0.9%) | 9 (4.2%) | 13 (6.2%) |
| AED stopped | 6 (2.7%) | 14 (6.5%) | 17 (8.1%) |
| new/previous AED started | 1 (0.4%) | 1 (0.5%) | 5 (2.4%) |

**Data source: Table 14.1.12.1 CSR (link)**

For the specific concomitant anticonvulsants carbamazepine, data in Table 14.2.14.2.5 of the CSR indicates that 0 placebo patients, 6 eslicarbazepine 800 mg and 12 eslicarbazepine 1200 mg subjects had reductions of carbamazepine during the maintenance period (appears dose –relationship). Data in Table 14.2.14.2.6 (link via the CSR) indicates that no dose reductions in phenytoin occurred in the maintenance period (it should be noted that the amendment to allow dose reduction was fairly late in the study (7-28-11, last subject visit in part 1 was 1-12-12, based on my use of conmed.xpt, 88 subjects were randomized on or after 7-28-11 and 11 of these were on a concomitant phenytoin or diphenylhydantoin).

**Use of Rescue Medication in 304**:

The CSR for 304 defines rescue medication use in several ways. An anticonvulsant was considered rescue if it was taken intermittently as needed for less than 2 days, multiple occurrences of the same rescue medication are counted once per subject within a drug class and preferred drug name, use of the medication is on or after the start date of maintenance or it is ongoing at baseline and into maintenance.

The CSR reports that the use of rescue medication during the maintenance period was reported for a total of 46 subjects with greater use in the ESL 800 mg group. The Sponsor's tables showing these data are not optimal/complete in that 'benzodiazepine derivatives' and clonazepam' are under 'antiepileptics' and other benzodiazepines including diazepam are under 'psycholeptics'. Also, one cannot tell whether there is a difference in the frequency of use between the subjects as multiple occurrences of the same rescue medication are counted once per subject.

**304-ITT population # and percentage of subjects using rescue**

**Table 29 Rescue Medication Use - Study 304**

| | placebo n=220 | ESL 800 mg n=215 | ESL 1200 mg n=205 |
|---|---|---|---|
| at least 1 rescue med | 15 (6.8%) | 18 (8.4%) | 13 (6.3%) |
| any benzodiazepine | 17 (7.7%) | 17 (7.9%) | 13 (6.3%) |
| phenytoin/fosphenytoin | 0 | 2 (.01) | 0 |
| | | | |
| | | | |

**Data source: Table 14.1.13.2 CSR link**

Tables linked from the CSR for study 304 indicate that a lower percentage of the ITT EE subjects (3.6% to 7.5%) are reported as using rescue when compared to the ITT DE subjects (all 7.4% to 8.8%). Whether this represents a real difference (i.e. under-reporting of rescue use when using EE diary) is unclear and unknown.

**FDA statistical Review:** The statistical review (Dr. Ling, p.16) reports that no significant effects were seen for age group, region, or race in analyses with additional covariates for the primary endpoint. The covariates of sex, baseline carbamazepine use, baseline lamotrigine use, and baseline valproic acid use were found to be statistically significant covariates based on ANCOVA analyses (p value ≤ 0.05). The only treatment-by-covariate interaction that was statistically significant was treatment-by-carbamazepine use interaction. The potential impact on dosing recommendations is in section 6.1.8 immediately to follow.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This section discusses carbamazepine use in studies 301 and 302 as well as 304. If approved, ESL labeling should address concomitant carbamazepine use. As I understand it , the language (i.e. will there be a specific dosing recommendations/instruction) is still under discussion as of the writing of this section of the review.

**Concomitant Anticonvulsant use:**

As noted previously in this review, in study 304, most subjects were on two anticonvulsants at baseline and the top four anticonvulsants used concomitantly at baseline were, carbamazepine (about 34-42%), levetiracetam (about 20.5% to 29.5%), lamotrigine (about 24% to 27%), and valproic acid (about19% to 21%). About 9% to 13% of each group was using concomitant phenytoin.

**Carbamazepine and standardized seizure frequency during the maintenance period** for subjects who were and were not using concomitant carbamazepine at baseline (ITT): Based on the Sponsor's analysis and the FDA statistical reviewer's description, the use of carbamazepine appears to impact the treatment effect.

**Table 30 Baseline Carbamazepine Use and Treatment Effect**

| **YES on Carbamazepine** | Placebo n=76 | ESL 800 mg n=83 | ESL 1200 mg n=87 |
|---|---|---|---|
| n | 73 | 77 | 77 |
| mean (SD) | 9.6 (9) | 11.7 (17.8) | 13.6 (18.5) |
| median | 6.26 | 6 | 5.86 |
| range | 0- 42.5 | 0-126.7 | 0.3 to 100.8 |
| LS mean | 7.23 | 6.51 | 7.35 |
| unadjusted p value for pair wise comparison to Placebo | | 0.4 | 0.889 |

**Data source: Table 14.2.14.2.4 of CSR**

| **NOT** on Carbamazepine | Placebo n=144 | ESL 800 mg n=132 | ESL 1200 mg n=118 |
|---|---|---|---|
| n | 139 | 123 | 107 |
| mean (SD) | 14.8 (19) | 14.9 (31.7) | 10.9 (15.4) |
| median | 7.81 | 5.33 | 5.35 |
| range | 0- 103.6 | 0-294 | 0 to 106 |
| LS mean | 8.29 | 6.55 | 5.14 |
| unadjusted p value for pairwise comparison to Placebo | | 0.04 | <0.001 |

**Data source: Table 14.2.14.2.4 of CSR**

Dr. Ling provided analyses of subjects only on carbamazepine at baseline in study 304 (at clinical reviewer's request). The numbers of subjects eligible for the analyses is too small to allow meaningful interpretation (sample sizes in 304 of 17 placebo, 23 of the ESL 800 mg, and 21 of the ESL 1200 mg and sample sizes in combined 301-302 of 28-34 subjects) and the results are not described secondary to this limitation.

**Baseline carbamazepine use-Trials 301 and 302:**

As noted previously, in studies 301 and 302, carbamazepine use at baseline was higher at roughly 60% of each group in both studies (ISE data). Concomitant lamotrigine use was overall higher in study 301 than 302 at about 24 to 28% in study 301 and 17 to 24% in study 302. Valproic acid was used in 22 to 28% of study subjects in 301 and 13 to 28% in study 302.

Dr. Ling's first statistical review indicates that in study 301, the analysis of seizure frequency with carbamazepine use and treatment- by -carbamazepine use as factors showed that treatment-by-carbamazepine interaction was not significant but the use of carbamazepine had a significant effect on the seizure frequency during the maintenance period (p=0.0318) but not in the combined titration + maintenance period for the ITT population and not for the PP population.

For study 302, Dr. Ling's previous statistical review indicates that results showed some significant interactions between treatment and region, race, and carbamazepine use.

Dr. Ling's referenced review notes that in the pool of studies 301 and 302, carbamazepine use and treatment-by-carbamazepine use interaction did not have a significant effect on seizure frequency (p. 0.17 and 0.87 respectively).

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long term controlled studies are not performed to address this issue given ethical considerations. Open-label data available is not able scientifically to address conclusively these issues for reasons including drop-outs (i.e. those subjects who think they are not receiving a benefit may discontinue early and those who may not tolerate the drug may leave early) and confounding due to the ability of patients to be managed as medically appropriate (changes in medications) without leaving the trial.

There is a presentation in the study report for **study 304** of standardized seizure frequency by study period for the ITT population (Table 14.2.4.1.1). This table is reproduced from the study report below. There is no obvious increase in seizure frequency means over the three time epochs of the controlled phase (M 1 -4 weeks, M5-8 weeks, M9-12 weeks) in any group.

**Table 31 Standardized Seizure Frequency By Study Period Study 304**

Table 14.2.4.1.1
Standardised Seizure Frequency by Study Period
ITT Population

| | Placebo (N=220) | Eslicarbazepine Acetate 800 mg (N=215) | Eslicarbazepine Acetate 1200 mg (N=205) |
|---|---|---|---|
| Maintenance Period: Weeks 1 to 4 | | | |
| n | 212 | 200 | 184 |
| Mean | 13.48 | 14.03 | 12.51 |
| SD | 16.956 | 27.515 | 18.012 |
| Median | 7.00 | 6.00 | 6.50 |
| Min | 0.0 | 0.0 | 0.0 |
| Max | 94.0 | 294.0 | 132.0 |
| Maintenance Period: Weeks 5 to 8 | | | |
| n | 207 | 194 | 175 |
| Mean | 12.69 | 12.82 | 11.79 |
| SD | 17.554 | 21.241 | 17.791 |
| Median | 7.00 | 5.59 | 5.25 |
| Min | 0.0 | 0.0 | 0.0 |
| Max | 121.0 | 147.0 | 140.0 |
| Maintenance Period: Weeks 9 to 12 | | | |
| n | 194 | 179 | 146 |
| Mean | 12.36 | 12.40 | 10.30 |
| SD | 17.630 | 19.625 | 13.091 |
| Median | 6.74 | 4.83 | 4.91 |
| Min | 0.0 | 0.0 | 0.0 |
| Max | 126.5 | 154.0 | 60.0 |



**Studies 301-302:**

The Clinical Study report for study 301, Table 38 (p.151/1074), displays the Sponsor's analysis of seizure frequency per week, by week, during the two week titration and the maintenance period (baseline frequency and treatment as covariates using ANCOVA and Dunnett's multiplicity adjustment). As per this table, there is suggestion that the difference between ESL 1200 mg and placebo is generally not worse and often greater over time in maintenance in terms of reduction in the standardized seizure frequency throughout the trial period. This is not seen for the comparison to between the 400 mg ESL group and the placebo group and generally not seen for the comparison between the 800 mg ESL group and the placebo. The comparisons are weekly which render definitive interpretation difficult.

**Table 32 Study 301 Difference between treatment groups in seizure frequency per week over the two week titration and 12 week maintenance period**

Table 38: Difference between treatment groups in seizure frequency per week over the 2-week titration period and 12-week maintenance period by ANCOVA (ITT population)

| Study week | Differences (by ANCOVA) between active treatment groups and placebo group in seizure frequency | | | | | |
|---|---|---|---|---|---|---|
| | ESL 1200 mg | | ESL 800 mg | | ESL 400 mg | |
| | Difference between means | p value | Difference between means | p value | Difference between means | p value |
| T1 | –0.0927 | 0.5308 | –0.2153 | **0.0234** | –0.1501 | 0.1616 |
| T2 | –0.1246 | 0.3180 | –0.1714 | 0.1044 | –0.0296 | 0.9708 |
| M1 | –0.2270 | **0.0283** | –0.1303 | 0.3206 | –0.0820 | 0.6705 |
| M2 | –0.0790 | 0.7086 | –0.1443 | 0.2424 | –0.0184 | 0.9936 |
| M3 | –0.1533 | 0.1923 | –0.1588 | 0.1568 | –0.0781 | 0.6784 |
| M4 | –0.1569 | 0.1928 | –0.2398 | **0.0171** | –0.1726 | 0.1162 |
| M5 | –0.2683 | **0.0085** | –0.2119 | **0.0435** | –0.0631 | 0.8103 |
| M6 | –0.1949 | 0.0880 | –0.1128 | 0.4523 | –0.0788 | 0.7032 |
| M7 | –0.0944 | 0.6301 | –0.1386 | 0.3081 | –0.0235 | 0.9884 |
| M8 | –0.2995 | **0.0055** | –0.2580 | **0.0146** | –0.1687 | 0.1558 |
| M9 | –0.1774 | 0.1594 | –0.1625 | 0.1853 | 0.0737 | 0.7529 |
| M10 | –0.0965 | 0.6066 | –0.0019 | 1.0000 | 0.1048 | 0.4949 |
| M11 | –0.2086 | 0.0983 | –0.1145 | 0.4956 | –0.0136 | 0.9979 |
| M12 | –0.2552 | **0.0342** | –0.1207 | 0.4747 | –0.0333 | 0.9728 |

Note: natural logarithm of seizure frequency was tested.
Note: p values <0.05 are typed in bold.
Statistical Report (Section 17.5), Table F10.1

Study 302: Mean data by week were presented. These were not reviewed.

## 6.1.10 Additional Efficacy Issues/Analyses

Additional efficacy issues are related primarily to data quality and the type of diary used.

For study 304 data, there were several efficacy related information requests made to the Sponsor. One request was precipitated by the statistical reviewer's finding of duplicate entries in the efficacy dataset. It appeared the number of these duplications would not likely change the outcome, however, it was felt important to know how this happened, whether the duplicates were as recorded by subjects or were errors in the dataset, and if dataset errors, whether they suggest larger or systemic problems. The Sponsor was asked to perform a comparison of the seizure diary data to the dataset for each subject in a JMP table of 40 subjects, some of whom had duplicate dataset entries. In the Sponsor's initial response to this request, the Sponsor did not report/identify at least two subjects with duplicates (of the 40 subjects' records audited).

In the process of review of the Sponsor's submitted diary cards for this audit request, I ran across a subject who used both types of diaries (an event entry diary and a daily entry diary). As a reminder, subjects early in the trial, before the amendment changing to DE diary, were given EE diaries while subjects enrolled after the amendment, were given DE diaries. It was not intended for subjects already on the EE diary to switch. We later queried the Sponsor as to whether any subjects in study 304 had used both types of diaries. The Sponsor's initial response was essentially no. We then queried them with the one subject that we had rather incidentally discovered. The response explained their methods for evaluation for other cases and basically stated that the identified subject was the only one in that study (304) who had used both diary types.

Also, during audits, I noted a page number for a dairy that was out of sequence or mis-numbered (numbered as diary card 000203). The Sponsor was queried. The Sponsor's response noted, essentially, that this was an error and that the subject had two diaries with the same entries. Both of the diaries were in the 00300 number ranges. The sponsor did report, in this response, that the duplicated seizures were counted accurately in the maintenance period.

The requests and responses are described in more detail below. Statistics asked for clarification as to how missing data were handled. The request is copied below. The review of the Sponsor's response is deferred to FDA statistical review staff.

Information Requests efficacy diary related:

1. **A request made March 26, 2013 for the sponsor to clarify how they determined if seizure data was missing for event entry diary subjects.**

**"Please clarify how you determine if seizure data is missing (SEIZURE.DAYMISS=1) for patients using EE (event entry) diary. For example, the transcription of the seizures for patient '20101' at Visit 2 (Baseline) had 32 seizures recorded on 28 days between 2/19/2009 and 4/14/2009 (about 8 weeks in the baseline period). The days without a seizure recorded were assigned 'Missing diary' in your dataset, hence excluded from calculating the seizure frequency. The resulting standardized seizure frequency was 32 (per 28 days) for the baseline.**

**However, the reviewer could not find anything in the CRF (attached below) that indicates missing diary for the days without recorded seizures. It seems that the patient did not experience any seizure on the days for which no seizure was recorded in the diary and the baseline seizure frequency should be 16 if all 8 weeks of baseline are counted in the calculation.**

**If you decide that it is an error in deriving this key variable, please submit updated analysis datasets, results and SAS codes (including all SAS macro code so that the programs could be run to generate the analysis datasets and tables)."**

*Clinical Reviewer: Defer to the statistical team for formal review.*

*2.* Databases duplications were noted by the statistical reviewer as a possible issue. The following seizure data are excerpted from dataset seizure.xpt for subject 301-30103 to show the reader the type of

issue. I moved the subjid column over for orientation purposes. These are not the only duplicate entries for this subject.

| SUBJID | **STUDYDT** | **STUDYDTC** | **SEIZTM** | **SEIZTMC** |
|---|---|---|---|---|
| 30103 | 07/17/2010 | 17JUL2010 | 21:00:00 | 21:00 |
| 30103 | 07/17/2010 | 17JUL2010 | 21:00:00 | 21:00 |
| 30103 | 07/18/2010 | 18JUL2010 | 16:30:00 | 16:30 |
| 30103 | 07/18/2010 | 18JUL2010 | 16:30:00 | 16:30 |
| 30103 | 07/19/2010 | 19JUL2010 | 11:05:00 | 11:05 |

The following request was made of the sponsor on 4-24-13. The JMP dataset included usubjids for 40 subjects.

> ***We are conducting an audit of diary data. In order to complete this audit, please send the CRFs for the subjects from study 304 that are included in the JMP table under the column "subjid". Please send these CRFs within 1 week of receipt of this email. Also, perform a comparison of the seizure diary data to the dataset data for each subject in the JMP table. Fill out the JMP dataset that is attached and send this back to us. Please submit the completed JMP table results within 3 weeks.***

The CRFs of 10 subjects (EE diary CRFs did not contain diary cards) did not contain diary cards. DNP sent a follow-up request on 5-11-13.

> ***Sequence 84 to NDA 22416 is a response to an information request DNP made which included a request for certain CRFs. It appears the CRFs of 10 subjects (see the table below) are missing diary cards. We note that sequence 87 indicates that event entry diaries were kept on site as source documents. Send the diary cards for these 10 subjects. To be clear, we are interested in the part 1 diary cards (not just the transcriptions of the diary cards) for the double-blind, placebo controlled phase. If the diary cards are in the CRF for any of the subjects in the table below, provide the location in the CRF (i.e., the page number in the viewbox of the CRF). Also, check the CRFs for diary cards for the other subjects in sequence 84. If any other subjects are missing diary cards, send these also. Please respond by COB, 5 days within receipt. Thank you.***
>
> ***004-00405, 004-00403, 004-00407, 301-30106, 301-30103, 301-30108, 016-01602, 019-01901, 307-30711, 507-50701***

***Sponsor's Responses and Perspective:***

*The Sponsor's reports in SDN 94 (5-20-13, sequence 91, module 1.11.3, response document) that they performed comparison of seizure diary data to the SDTM dataset, including a review of the source diary pages for EE diaries (note: n=10) requested in the 5-11-13 clarification.*

*Sunovion outlined the process used to address the request. The seizure data review was conducted by a team of 7 Sunovion employees from Data Management and Clinical Operations. The Sponsor explained that they also reviewed seizure diary pages from a list of subjects not chosen by the FDA as a quality*

*check on the training of the7 personnel who were to perform review of the FDA-requested subjects. Based on this pilot training and review, the Sponsor concluded that the reviewers were appropriately trained and the other review proceeded. The Sponsor reports that the review was conducted using the same published diary pages sent to the Division on May 3, 2013 and that, following the 5-11-13 request from FDA, they confirmed that seizures from source diaries had been transcribed to the CRF. They report "no obvious discrepancies in seizure counts between the subject source diary and the Transcription CRF page were noted."*

*The Sponsor detailed that 4378 seizures were correctly reported (99.7%) based on the comparison of the Transcription CRF page and the SDTM SAS dataset. They report that discrepancies were noted for 16 seizure records in 3 subjects for an overall error rate of 0.4% (16/4393). Of the 16, 1 seizure was recorded in the CRF but was missing from the dataset and 15 seizure records were included in the dataset in error as duplicate entries. Specifically, the Sponsor reports the discrepancies as below:*

- *Subject 85601 (ESL 800 mg)-noted to have 14 seizures during the maintenance period with duplicate entries in the dataset*
- *Subject 00409 (ESL 1200 mg) – noted to have 1 seizure during the baseline period with duplicate entry into the dataset*
- *Subject 75103 (placebo)- noted to have 1 seizure recorded in the CRF in titration which was not entered into the dataset*
-

*The company concludes there was no apparent pattern in the distribution of the subjects noted to have discrepancies among treatment groups or study periods. The Sponsor concluded that the small number and distribution of the seizures discrepancies has no meaningful effect on efficacy conclusions.*

***Reviewer audit:***
*While reviewing this response, I noted one subject who appeared to have completed both EE and DE diary types and a subsequent set of requests was made about this (subject 304-004-00407-see #5 below).*

*As related to the issue of duplication in the dataset, subject 304-301-30103 was not identified in the 5-20-13 response (SDN 94) as a duplicate. This is detailed below and some of the source documents are included below also. I am aware that the statistical reviewer also identified a subject (405-00405) with duplications in the dataset (which are not in the source document data) and that the Sponsor had not identified in this response.*

Subject 304-301-30103- *Appendix 2 in SDN 94 includes the stop and start dates for each of the phases and is an adobe document of the JMP sheet the Sponsor was asked to fill out. For the subject 304-301-30103, baseline started on 3-24-10 and ended on 5-18-10. Titration started on 5-19-10 and ended on 6-1-10, and maintenance started on 6-2-10 and ended on 8-23-10.*

*The sponsor's audits findings are shown below for this subject as taken from Appendix 2 in the response in SDN 94 (p.17-19).*

- *304-301-30103 --CRF baseline # seizures: 13, CRF titration # seizures 4,* ***CRF maintenance # seizures 32****, dataset baseline # seizures 13, dataset titration # seizures 4,* ***dataset maintenance # seizures 32****.*

*My audit findings for this subject using the CRF transcription cards (CRF) and the dates in Appendix 2 for stop and start of the study epoch are – CRF baseline # seizures 13, CRF titration # seizures 4,* ***CRF maintenance # of seizures, 20.*** *Counting from the diary cards themselves and using the visit and dates, the number for baseline is 13, titration and maintenance are 4 and* ***20*** *respectively. The dataset has 32 seizures in maintenance.*

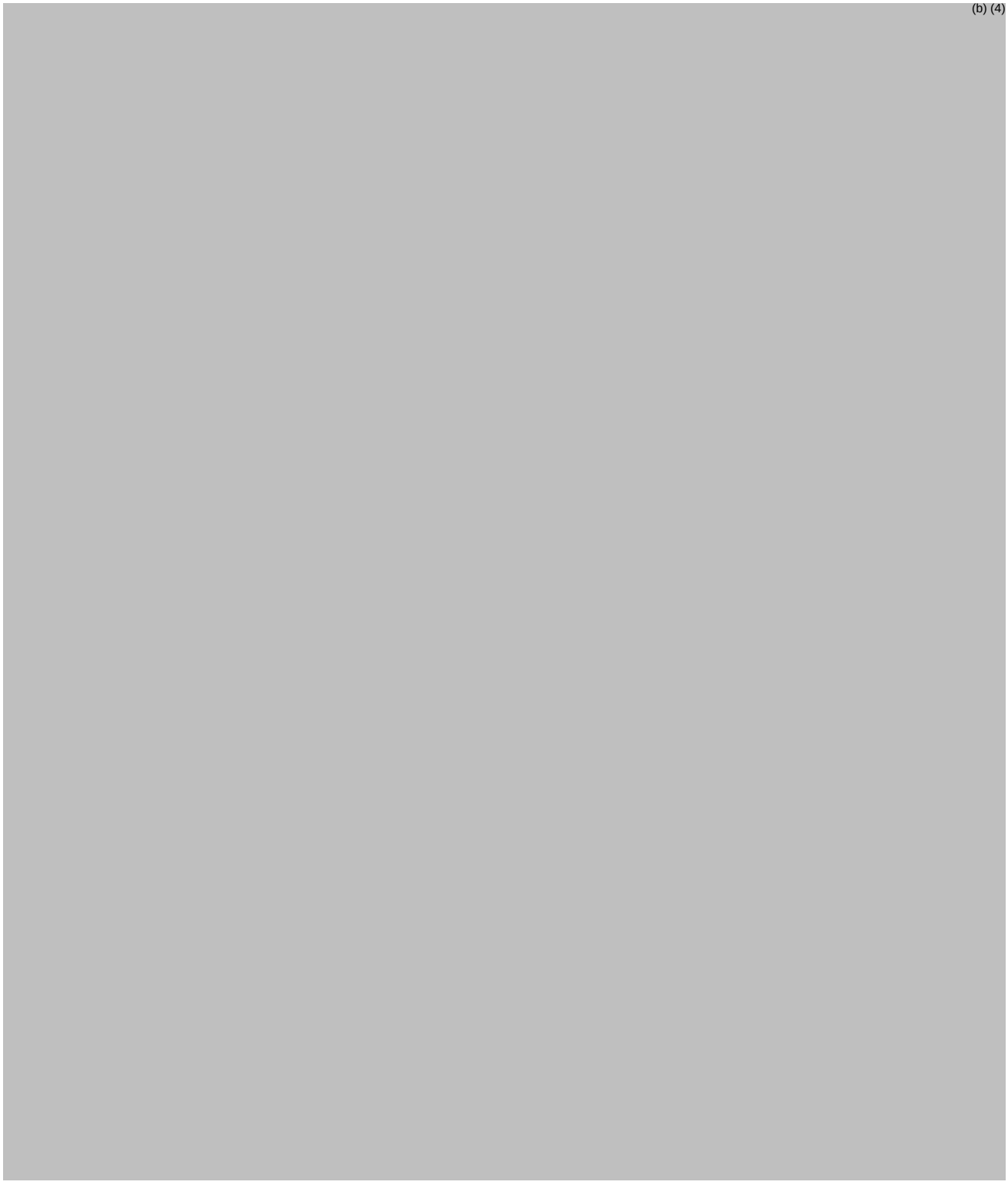
- *Specifically, in subject's 304-301-30103 diary, the dairy cards show that the subject made duplicate entries (seizures between the dates of 7-17-10 and inclusive of 8-22-10 are recorded on two separate books; in book labeled as 000203, which should be book number 00304, and also in book 00305 (again, see #4 below). The CRF transcription pages for each visit reflect the seizure..*

*In a subsequent information response, submitted on 7-1-13 ( seq 103, SDN 106) in response to 6-19-13 inquiry about the card numbering in which we had also included that there were identical entries on two diary cards, the sponsor reported that the 12 seizures listed on both diaries are identical. One diary was in double-blind (D00304) and the other diary card, D00305, was for visit 6 and duplicated entries of D00304. The Sponsor states that these duplicated seizures were counted in the efficacy analysis but as the subject was in the double-blind on 800 mg ESL, this would only have hurt the treatment effect of drug. There is not an explanation for how this was missed at transcription, in quality checks after, and in dataset incorporation.*

***Diary cards 304-301-30103 (000203 linked to the bookmark "diary card D00304)***

3 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)



3. A request was made on 5-2-13 for the diary itself and for clarification of the diary transcription information and dataset information for subject 30505. The request is copied below:

***Please clarify the possible data discrepancy for subject 30505 between the diary transcription information and the dataset information. Though we are unable to locate the seizure diary itself, the "Transcription of Patient's Seizures" in the CRF indicates that not all seizures were documented between visits 3 and 4 (p.66/184) and between visits 4 and 5 (p 81/184). The dataset seizure.xpt and Listing 16.2.6.1.1 of the CSR indicate that there were no seizures on 2-4-10 (Visit 3 date) and none for the remainder of the maintenance phase. Also, send the diary for this subject or reference the CRF page numbers for the diary if the diary is already present.***

Clinical Reviewer: The diary cards are somewhat confusing and there are 60 data clarifications for this subject. The diary cards are EE and are often blank. Otherwise, I performed a manual comparison of the diary data (untranslated diary with reference to the translated diary as needed). There were some differences between the entries in the diary and those in the dataset (two instances where the exact time of the seizure on a certain date is different; one is on 12/10/09 with dataset noting time at 14:00:00 and diary showing time on this date of 14:08 and on 12/13/09 with dataset showing **19:56:00 a**nd diary showing **18:56**).

The transcription page (p.81/184) has both an "x" in the box for both responses yes and no to the question "Are all seizures between Visit 4 and Visit 5 documented?" The yes "x" is marked out with single slash, so it appears the intended answer to the question was no. This illustrates an issue with the EE diary in that it is hard to feel confident of the missing data as zeros. In this case, the Sponsor noted that the Seizure Severity Questionnaire (SSQ) was used in the study and was completed by the subject. The SSQ capture whether there had been no seizures in the previous 4 weeks and could allow a check of the diary in that way. The SSQ for visits 3, 4, and 5 was referenced. The subject indicated having no seizures in the past 4 weeks (the time since the prior visit) at visit 4 and at visit 5. The image below is copied from the submission shows the way the SSQ queried this response.

**Figure 3 Seizure Severity Questionnaire-Excerpt**

**Figure 2 SSQ for Subject 304-305-30505, Visit 4**


4. A request was made on 6-19-13 to clarify a discrepancy in the diary card page numbers for a subject (304-301-30103).

***Sequence 92 to NDA 22416 provides the diary cards of six subjects in study 304. For subject 301-30103, the diary card that is labeled as # 304 in the bookmark and on the front cover is numbered "000203" in the top right hand corner of the diary card. The diary tracking log (p 221-223/298 of CRF in sequence 84) indicates that the diary numbers of the dispensed diaries were all in the 300's (301-307). Clarify.***

***Twelve of 14 of the entries on diary card "000203"/ 304 (p. 103/115 of diary card) are identical to those in diary card #305 (p. 111/115 of diary card). Based on the dates in the diary tracking log and the dates of the maintenance period (6-2-10 through 8-23-10), diary card # 304 should be the last one in the maintenance period (last in part 1). We understand that some of the entries for part 2 may be on the same page as the end of part 1, however, it is not clear why the twelve entries are on both diary cards. Please clarify.***

Clinical Reviewer:

*The Sponsor responded on 7-1-13 (seq 103) and noted that BIAL contacted the CRO and investigator and were told that the diary card #000203 for this subjects was erroneously written in the header on 2 pages (704B and 705B) when it should have been card #000304 as on the cover page and bookmark. The company reports the following:*
*● -it appears this subject had two separate diaries with the same entries as follows: Diary D00304 (first seizure 7-17-10 and last seizure 8-22-10) between visits 4 on 7-14-10 and visit 5 on 8-23-10. The diary card was reviewed and signed on 8-23-10 and transcribed at visit 5 of the double-blind period. Diary 00305 (the same set of 12 seizures as above plus additional seizures from 8-27-10 through 9-25-10. The visit 6 date was 9-27-10 and the diary was reviewed and signed on 9-27-10 and the seizures transcribed at visit 6 during the OLE.*

*● -The 12 seizures in both diaries are identical and the period when they were registered is the same; therefore the company determined that Diary 00304 is accurate and should be considered the last diary of part 1 of study 304. The subject received ESL 800 mg. The 12 duplicated seizures from Diary 00305 for Visit 6 were included in the maintenance period and counted in the efficacy analysis.*

5. A request was made on 8-1-13 due to the discovery of a subject who appeared to have used both a daily entry diary and an event entry diary. This was noted while performing an audit for the duplicate entry issue noted in #2 in this list of requests made to the Sponsor for efficacy purposes.

***Amendment 3 dated 9-16-10 implemented the daily entry diary (DE) versus the event entry diary (EE). Table 20 of the CSR for study 304 indicates that 154 placebo, 137 of the 800 mg eslicarbazepine acetate group, and 136 of the 1200 mg eslicarbazepine acetate group provided DE dairy data in the ITT population. Table 14.2.1.2 indicates that 48 to 63 subjects from each group included in the analyses of the ITT population used EE diary. Did any subjects use both diaries? If so, identify these subjects. Please respond within one week of receipt of this request.***

Clinical Reviewer: T*he Sponsor's response is in SDN 113 (sequence 110) to the NDA.*

*The Sponsor stated that there no subjects in part 1 who used both EE and DE diary formats. The Sponsor stated there "are no instances where a single patient's actual seizure data over time comes from both an EE and a DE diary source".*

*The Sponsor indicated that for 12 subjects listed in Table 1 of the submission (4 placebo subjects, 5 of the 800 mg subjects, and 3 of the 1200 mg subjects) the diary data could be "initially confusing". This was further explained by the Sponsor but includes that for some DE dairies, the site also transcribed the events into the CRF though the transcriptions were only to be done for EE diary subjects.*

*The Sponsor reports that during data cleaning, the erroneously transcribed seizure records and header information were queried and removed. However, for the 12 subjects in Table 1, the header data remained in the dataset which suggested that both diary types had been used even though these 12 were all assigned to the DE diary and had their seizures recorded and analyzed as DE diary subjects.*

*The Sponsor noted that subjects 304-16-1602 and 304-21-2102 were assigned to DE diary type but consistently used the EE type throughout the study due to site error. These subjects were included as EE diary type subjects in analyses.*

*The Sponsor did not identify the subject using the processes they described. Secondary to locating this subject, I subsequently perused through the diaries from the same site as that subject and about diaries of <5 other subjects and did not find another diary of the ones I reviewed in which a subject used both diary types.*

6. A request was made on 8-23-13 due to the sponsor's response to the previous request that included that there were no instances where a patient's actual seizure data over time came from both an event entry and daily diary entry source. The request provided the subject number of the subject for whom the diary appeared to be of both types: event entry and daily entry.

***The response in sequence 110 to NDA 22416 indicates that there were no instances where a patient's actual seizure data over time comes from both an EE and DE diary source. However, upon our review of diary data submitted in sequence 91 for subject 304-004-00407, it appears that baseline diary data are from an EE diary (diary D00701 in the CRF bookmark) and other maintenance data are from DE diaries (N84338). Please explain.***

Clinical Reviewer: T*he sponsor' response is in SDN 117 (seq 114) to the NDA. The Sponsor explained how they had approached the response in sequence 110 and described the search criteria used for the response. The Sponsor's approach included that they "looked for subjects with evidence of data entered into the original raw seizure data collection datasets (per-SDTM) form both EE and DE diary." They note finding a number of subjects with data that made it appear as if both diaries may have been used. Upon CRF review of those subjects, they concluded that all subjects were DE diary patients where EE diary transcriptions were completed in error and no actual use of EE diary had been recorded.*

*The Sponsor's explanation for why they did not identify subject 304-004-00407 is that there are no records from the DE diary in the clinical database, so the patient's data reflected use of only the EE diary. Upon further review, they noted that this subject did use both types of diaries in the double-blind phase. They note that this was not apparent in their review of the part 1 data because the site transcribed the DE diary entries onto the CRF as if they had been EE source diaries. Also, the site is reported as having erroneously recorded EE diary numbers on the CRF diary tracking log rather than the DE diary number (N84338) that was used by the subject.*

*The company reports that in response to this request, they did an additional investigation to identify other subjects who might have used both types of diaries. Their method was:*

*1) To review protocol deviation logs for mention of use of incorrect diaries. They note that subject 304-004-00407 is on that log and the use of two diary types is noted. Three other subjects were noted as having used two diaries but the company reports that the switch occurred only after*

*entering part 2 of the study (subject 304-004-00403, 304-304-008-00802, and 304-306-30608). Therefore, the switches in these subjects were not part of the controlled data. They also note that the log indicated three more subjects 304-16-01602, 304-21-02102 (screen failure), and 304-35-03504 (screen failure) who were initially dispensed an incorrect diary at Visit 1. They report that the first two were included in their previous submission. [note –subject 304-004-00403 and 304-306-30608 are ESL 1200 mg group, subject 304-304-00802 is placebo, and subject 304-16-01602 is ESL 800 mg group- based on variable Trt01p in seizure.xpt dataset].*

2) *To review the EE Diary Tracking Log for diary numbers starting with "N" indicating a daily entry diary was dispensed. Two subjects (304-008-00802 and 304-903-90303) were found to have used both types of diaries. One of these was also in the protocol deviation log (304-008-00802). The company reports both switches as occurring in part 2 of the study. [note -304-008-00802 and 304-903-90303 are on placebo in part 1, based on variable Trt01p in seizure.xpt dataset, which if this only occurred in part 2, is irrelevant].*

*The company summarizes that they found only one subject, 304-004-00407 to have switched source diary types during part 1. They report that systematic searches of the database, diary tracking logs, and protocol deviation log did not reveal any other subject who had switched diary types during Part 1. They note that risk minimization for this type of error was "comprehensive" training of investigators.*

*The actual impact on the primary endpoint of the one subject found (Subject 304-004-00407) would be insignificant and would not favor the drug (based on variable trt01p in seizure xpt, the subject was on ESL 1200 mg). I have not looked at every diary and this one was found rather incidentally. There are 653 randomized subjects in the trial. It is not clear to me that this is the only subject or that the methods described would detect this and apparently previous methods to detect this for the response did not. Is this important as a possible process issues?*

# 7 Review of Safety

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The review of safety is deferred to Dr. Doi.

I was asked to evaluate seizure events from an efficacy point of view for the possibility of seizure worsening or new onset seizure types on active drug product compared to placebo. It should be noted that my analyses and evaluations may be limited as described to follow.

It appears that in cases of fall or fracture that may have been associated with seizure, seizure may not have been coded also as an adverse event in ADEVENTX.xpt. This is based on a spot-check using Appendix 7.9 of the ISS submitted 2-11-13 ("Subjects with Head Injuries and Fractures"). I chose several subjects who, by the Sponsor's assessment might had the injury as a result of a seizure or in the dataset it indicates seizure. For several of these subjects, the dataset did not also have a 'seizure' term coded at all.

- subject 301-211-90300-fractured bone in the foot, sponsor assessment probably related to secondarily generalized seizure. Date is (b) (6). There is no seizure event in the dataset. (part 1 event, ESL 800 mg)
- subject 301-113-90398-this subject sustained several injuries including fracture and contusion of face and "brain contusion" on (b) (6) and a skull fracture on (b) (6) The Sponsor's assessment of the (b) (6) adverse events is that the CIOMS report indicated the injury was secondary to a seizure and that there were no adverse events of dizziness, etc, "that could have contributed to it". This was a part 1 event on ESL 400 mg. For the skull fracture, the Sponsor's assessment notes the CIOMS form indicates this event was due to a seizure. This was a part 2 event. For both sets of injuries, there is a seizure event in the dataset on the same day or the day before.
- subject 302-304-80601-this subject sustained a clavicle fracture on (b) (6) The Sponsor's assessment is that the fracture was probably caused by a seizure that occurred that day. This was a part 2 event. There is no seizure adverse event in the dataset for this subject (on (b) (6) or otherwise).
- Subject 304-307-30715 has several AETERM listings noting a head contusion injury and occipital laceration secondary to seizure. There is no separate AE Term of seizure coded for this subject and the AEHLGT and AEHLT terms are injury related (e.g. Injuries NEC). This subject is in the Sponsor' s ISS Appendix 7.9 and noted to have had complex partial seizure on the day of injury and to not repot other events of dizziness, balance or gait disorder, or fall.

### 7.1.2 Categorization of Adverse Events

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

### 7.2.2 Explorations for Dose Response

#### 7.2.3 Special Animal and/or In Vitro Testing

#### 7.2.4 Routine Clinical Testing

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

## 7.3 Major Safety Results

#### 7.3.1 Deaths

#### 7.3.2 Nonfatal Serious Adverse Events

#### 7.3.3 Dropouts and/or Discontinuations

#### 7.3.4 Significant Adverse Events

#### 7.3.5 Submission Specific Primary Safety Concerns

Adverse event data are limited in interpretability for efficacy purposes due to nature of reporting though the adverse events of seizure are potentially helpful if there are obvious trends in the drug groups that would appear discordant with the primary analysis.

As seizures may occur secondary to hyponatremia and this drug may be associated with hyponatremia, the reader is referred to the safety review for discussion of hyponatremia as possibly related to seizures with administration of ESL.

The review for the evaluation of seizure worsening or significant events that may reflect on efficacy considerations is summarized below and detailed in the sections to follow. The more detailed discussion starts with the Sponsor's presentations of seizure events as per the Clinical Summaries (such as the ISS or CSS). This is followed by results of my analyses using one of the ISS adverse events' datasets, ADEVENTX.xpt (dataset integrates audit findings of potential events, review events, and signs and symptoms). As noted previously, my analyses of the dataset is limited if not all events of seizure-related injury were also recoded to a seizure term.

In the controlled phase 3 epilepsy pool, based on my analysis of the dataset, somewhat more ESL 400 mg subjects experienced "worsening of seizures' (4%) followed by placebo (3.5% or 3.8%) and ESL 800 mg (3.45%).

In the phase 3 controlled epilepsy studies, most events of status epilepticus were in placebo subjects (6). One ESL 800 mg subject experienced status. This apparently resulted in death. There are no reported adverse events of status epilepticus in phase 1 studies or in non-epileptic populations based on adverse event terms in the ISS.

More serious adverse events of seizures occurred in the pooled ESL groups in epilepsy studies when compared to the placebo group in these studies (0.5% compared to 1.4%, (Dr. Doi's review). Both the ESL 400 mg and ESL 800 mg groups experienced more SAEs of seizures than the placebo group based on my analyses of studies 301, 302, and 304 controlled data.

The Sponsor's CSS indicates that in the controlled phase epilepsy pooled safety data, 0.2% of both the placebo and ESL 1200 mg groups compared to none of the ESL 400 mg group and 1.4% of the ESL 800 mg experienced partial seizures with secondary generalization and that of the treatment-emergent serious adverse events, two met the criterion for partial seizures with secondary generalization. These were in the ESL 800 mg group.

In terms of new onset seizure types or adverse events of absence, as per the Sponsor, there were no AEs of absence in the combined controlled epilepsy study pool. There were two subjects in the open-label epilepsy study (study 202) who experienced EEG findings consistent with generalized seizure disorders with one of these having continuous spike and wave activity. Both were hospitalized for worsening seizures. There was one AE term in study 201 indicating new generalized tonic-clonic seizures.

By phase in the controlled epilepsy studies 301, 302, and 304, more subjects experienced seizures in the maintenance phases than in the titration phases of these studies. A few more subjects discontinued in titration compared to maintenance due to a seizure event.

In phase 1 and non-epilepsy studies, based on adverse event terms of seizures, there was only one subject with an event of treatment emergent seizures. This subject was in a phase 1 pharmacokinetic study, had a history of epilepsy, and experienced the event while on phenytoin and ESL.

**Per the Sponsor: ISS (2-11-13 submission) or CSS**

Seizures as an adverse event:

Per the Sponsor's Table 14 of the ISS, "Treatment Emergent Adverse Events with an Incidence of ≥ 2%" in either the ESL 800 mg or 1200 mg treatment group and greater than placebo for phase 3 epilepsy controlled study pool, there were no explicit seizure terms meeting the criterion (i.e. no status, seizure of any type, convulsion).

Falls were 1% in placebo compared to 3% in the ESL 800 mg group, and 1% in the ESL 1200 mg group. (ESL 400 mg group is not in the table). The fall rate may be a kind of indicator of seizure activity as Sponsor Table 59a of the ISS (p 253/465) indicates that in ESL groups 11/19 (58%) falls were related to seizure (placebo 5/6 (83%) falls were related to a seizure, 1/3 (33%) in the ESL 400 mg group, 7/11 (64%) in the ESL 800 mg group, and 3/5 (60%) in the ESL 1200 mg group). In the phase 3 controlled epilepsy pool, the majority of fractures and head injuries reported were within 3 days of a major seizure. It also appears that more non-seizure associated falls, fractures, and injuries occurred in ESL subjects than placebo.

In the phase 3 controlled study pool, the Sponsor considered as a topic of special interest, the term "complex partial seizures increased'. The adverse event terms subsumed under this are complex partial seizures, convulsion, epilepsy, and grand mal convulsion (based on Table 7.7.1.15.1 -link from ISS). These events are treatment-emergent with preferred terms as per medical review by the company. The reported incidences of "Complex Partial Seizures Increased" is 1.4% in the placebo group compared to 3.1%, 1%, and 1.5% in the ESL 400 mg, 800 mg, and 1200 mg group respectively. The Sponsor reports that time to onset was longer and duration of events was shorter in ESL groups when compared to placebo.

Study 201, a phase 2 epilepsy study reports a higher incidence of "Complex Partial Seizures Increased" in ESL-treated subjects (29.2%) when compared with placebo subjects (21.3%). In study 201, by dose group, 21.3% placebo (10/47), 20% of the ESL < 600 mg (n=4/20), 31.6% of the ESL 500-<1000 mg (24/76), and 0/0 in the ESL 1000 - <1400 mg group). "Grand mal convulsion" was one of these in the ESL 600 to < 100 mg group.

The Sponsor also reports the following:
Epilepsy:

- Status and SUDEP: In the phase 3 epilepsy pool, controlled and uncontrolled, there were 2 cases of status epilepticus "which may have been more accurately described as" SUDEP. One of these is an unwitnessed death of a subject for whom the autopsy diagnosis is status epilepticus. The subject was titrating to ESL 800 mg after taking ESL 400 mg for 8 days. The subject was found dead, in bed, with a tongue bite. This may have been SUDEP. One other unwitnessed death was of a placebo subject found dead (b) (6) 75 days after starting placebo (b) (6). Apparently, the autopsy report finding was "total supercooling of the body". The sponsor considers it SUDEP. The company reports that the cases of SUDEP and of status epilepticus were in the placebo group, the 400 mg ESL group, and the ESL 800 mg group. In study 201, no subject experienced SUDEP.

- Serious Adverse Events of seizure -phase 3 controlled epilepsy pool (studies 301, 302, and 304), the most frequently reported treatment emergent serious adverse events were partial seizures (and ataxia). The only treatment emergent serious adverse event of 'partial seizures with secondary generalization' in the phase 3 controlled studies with incidence ≥0.2% was in the ESL 800 mg group with 2 subjects (0.5%) (*note, based on the data in the ISS table 33, it seems it would take only 1 subject to reach ≥0.2% in any group except the ESL 400 mg where 1 subject would be 0.5%).*

  Treatment-Emergent SAEs with an incidence of ≥ 0.2% for ESL for the phase 3 epilepsy controlled pool are displayed in Table 33 of the ISS. Based on this table, in the phase 3 epilepsy controlled study pool, there were no subjects with treatment-emergent serious adverse events of "partial seizures" in either the placebo group (0/426) or the ESL 1200 mg group (0/410) compared to 1% in the ESL 400 mg and 800 mg groups (2/196 (1%) in the ESL 400 mg group and 3/415 (0.7%) in the ESL 800 mg group. Partial seizures with secondary generalization are discussed below.

  In study 201, there were no SAEs that have seizure-related adverse event terms.

  In the pediatric study 202 (open-label study), two severe TEAEs were seizures in the 30 mg/kg/day group. These were serious adverse events.

- Partial Seizures with Secondary Generalization: Table 14 of the Clinical Summary of Safety (CSS, 9-4-12 submission) indicates that in the phase 3 epilepsy controlled study safety pool, there was 1/426 placebo subjects (0.2%) with partial seizures with secondary generalization compared to none in the ESL 400 mg group, 6 (1.4%) in the ESL 800 mg group, and 1 (0.2%) in the ESL 1200 mg group. In the updated CSS of 2-11-13, Table 7.1.11.1.s1 shows treatment-emergent serious adverse events. This table indicates that

only two subjects met table criterion as noted for 'partial seizures with secondary generalization'. Both were in the ESL 800 mg group (2/415=0.5%).

- Discontinuation of study medication: Adverse events leading to discontinuation *of study medication* in the phase 3 controlled study safety pool with an incidence of ≥ 0.5% in any ESL group is displayed in the Sponsor's table, Table 38 of the ISS. There are two seizure related adverse event terms in this table, "complex partial seizures" and "convulsion". The only group meeting the criterion under the term "complex partial seizures" is the ESL 1200 mg (3/410=0.7%). 0.5% of both the placebo and ESL 400 mg groups (2/426 placebo and 1/196 ESL 400 mg) discontinued study medication secondary to "convulsion". Disposition information in Table 4 of the ISS indicates that one placebo subject (0.2%) compared to two ESL 400 mg subjects (1%) , 0/415 ESL 800 mg, and 1/410 (0.2%) of the ESL 1200 mg group had "exacerbation of seizures" as the primary reason for withdrawal. Exacerbation of seizures required an increase in seizure frequency of more than 100% compared with baseline frequency.

  In study 201, the table of study discontinuations indicates a subject on placebo discontinued early due to status epilepticus. The disposition figure (figure 2 in the study report for study 201), indicates that 2/46 subjects in the twice daily ESL group and 1 of 47 placebo subjects discontinued secondary to "exacerbation of seizures". "Exacerbation of seizures" was defined as an increase seizure frequency of more than 50% or appearance of new seizure type.

  In study 202 (pediatric study, uncontrolled), two subjects discontinued prematurely due to seizures increased.

- Absence or other new seizure types- The Sponsor's tables in the ISS (Table 7.7.1.5.1 and 7.7.3.5.1) indicate there were no adverse events of absence in the controlled epilepsy study pool. In the combined controlled and uncontrolled phase 3 epilepsy study pool, there was one subject with "petit mal" epilepsy on open-label ESL treatment (subject 301-123-90376). In study 201, the sponsor's table 7.7.7.5.1 reports there were no subjects with absence epilepsy events. In the pediatric study, study 202, no subject experienced an absence event though two subjects experienced EEG findings consistent with generalized seizure disorders (of which absence is one). These EEG findings were spike and wave and continuous spike and wave which is suggestive of possible status (202-000-00114 and 202-000-00201). Both of these subjects were hospitalized due to worsening seizures and both received EEG in the hospital. Study drug was reduced and then

stopped in both cases with recovery clinically though there are not reported follow-up EEGs.

The Sponsor states there were no reports of atonic or new onset primarily generalized seizure types (ISS, p. 227/465). This statement appears to reference the all studies pool and not be limited to the epilepsy studies.

The Sponsor reports that one subject (304-807-80705) experienced a treatment-emergent adverse event of myoclonus during titration while taking ESL 800 mg (randomized to 1200 mg) but that this was not specified as a myoclonic seizure.

Non-epilepsy:

- The sponsor reports there was an "absence" of seizure-related serious adverse events in non-epilepsy populations (p 7/465 ISS) and that new onset seizures were not seen in the non-epilepsy studies (p.9/465).
- The sponsor reports that the emergence of absence seizures or other generalized seizures was not reported. In the "All Studies" pool, one subject in study 301 open-label (301-123-90376) experienced an absence epilepsy on ESL. One subject in 304 (304-807-80705) experienced a treatment emergent adverse event of myoclonus in titration while on ESL 800 mg but randomized to ESL 1200 mg. The sponsor reports this was not specified as a myoclonic seizure.

**Reviewer:**

Any event of seizure:

Due to GCP issues with study 303, this data are shown last in the tables if at all.

I used several approaches for this evaluation based on differing search strategies, of ADEVENTX.xpt in the submission dated 2-11-13. One was based on both HLGT terms (neurologic NEC, CNS, and of seizures including subtypes) and on fragments of words (such as 'conv', 'stat', 'epil', 'seiz' 'fit' and 'shak'). AETERMS for non-seizure related events, such as status migraine were eliminated from the results. I also performed the search without using the HLGT terms. There were a few minor variations in the subject numbers in part due to some discrepancy in picking out AETERMS and perhaps as the injuries were apparently were not always recoded also to a seizure term.

For any event of seizure in the controlled phase of a phase 3 study, overall, more placebo subjects appear to have reported adverse events of this nature. The 400 mg ESL group was second in reporting (6.1%). More subjects reported events of seizure in maintenance.

**Table 33 Seizure Events Study 304**

| | placebo subjects/total safety (%) | 400 mg subjects/total safety | 800 mg subjects/total safety | 1200 mg subjects/total safety |
|---|---|---|---|---|
| **study 301** | 4/ 102 | 8/100 | 3/98 | 5/102 |
| **study 302** | 7/100 | 4 / 96 | 2 / 101 | 3/ 98 |
| **study 304** | 18/224 | NA | 14/216 | 11/210 |
| | 29/426 (6.8%) | 12/195* (6.1%) | 19/415 (4.58%) | 19/410 (4.63%) |
| **study 303** | 5/87 | NA | 2/85 | 0/80 |

This clinical reviewer, adeventx.xpt, 2-11-13 submission to NDA, word fragment search, AETERM contains 'seiz', 'conv', 'fit', 'epi', 'shak'. For safety population numbers per study-Tables 12-10 CSR 303, Synopsis of CSR 301 and CSR 302. Other safety populations numbers in Dr. Doi's review show placebo n of 426, and ESL 400 mg n=196, 800 mg =415, and 1200 mg= 410.

79 unique subjects (301,302, 304)

| Titration | Maintenance | Taper |
|---|---|---|
| 31subjects | 42 subjects | 7 or 8 subjects |

some subjects had seizures in more than one phase

Worsening of seizures in phase 3 controlled studies 301, 302, 304:

Events with adverse event terms in the dataset ADEVENTX.xpt indicating a worsening seizure frequency or intensity or perceived increase or worsening were included in this search.

Thirty-nine subjects experienced events consistent with seizure worsening based on adverse event terms. In the controlled pool, based on my analysis of the dataset, somewhat more ESL 400 mg subjects experienced "worsening of seizures' (4%) followed by placebo (3.5% or 3.8%) and ESL 800 mg (3.45%).

**Table 34 Worsening Seizures**

| | placebo subjects/total | 400 mg subjects/total | 800 mg subjects/total | 1200 mg subjects/total |
|---|---|---|---|---|
| **study 301** | 3 / 102 | 5/ 100 | 1/ 98 | 3/ 102 |
| **study 302** | 4 /100 | 3 / 96 | 0 / 101 | 3 / 98 |
| **study 304** | 9* / 224 | NA | 4 / 216 | 4/ 210 |
| | 16 /426 (3.76%) 15/426=(3.52%) | 8 /196 (4.08%) | 5 /415 (3.45%) | 10 / 410 (2.44%) |

*includes subject 304-653-65307-"myocloniform jerks in whole body exacerbation"

safety populations used for denominator. The results from a broad search for fragments of words (seizure, convulsion, fit, epi, cluster, status, shaking) were then evaluated for terms suggesting worsening seizures. Specifically, terms of 'status epilepticus' cluster' 'prolonged seizure' or 'seizure prolong' were not selected in the final unless the term indicated this was worse or increased.

By time period in a controlled phase 3 epilepsy study (exclusive of study 303), 15 subjects had seizure worsening in titration, 20 subjects experienced worsening of seizures in maintenance, and 4 in tapering (note: in this pool, only study 301 had a tapering phase pool).

- 'worsening seizures' in titration- 15 total: 9 placebo subjects, 3 ESL 400 mg subjects, and 3 ESL 1200 mg subjects
- 'worsening seizures' in maintenance – 20 total: 7 placebo subjects, 3 ESL 400 mg, 4 ESL 800 mg, and 6 ESL 1200 mg
- 'worsening seizures' in taper-off- 2 subjects in ESL 400 mg, 1 ESL 800 mg, and 1 in ESL 1200 mg

Any seizure death in controlled studies:
ADEVENTx.xpt

- placebo-301-194-90132 unwitnessed death, found dead
- 304-009-00901 –reported as a status- randomized to 800 mg ESL

Status Epilepticus (SE): Controlled phase 3

The search was based on adverse event terms strongly suggestive of status epilepticus or that included the word "status" plus a seizure term. This included complex partial status epilepticus.

In the studies 301, 302, and 304, controlled phase- 6 subjects: 3 in titration, and 3 in maintenance. All except one subject was on placebo. A subject in study 304 was on ESL.

- Titration-302-336-80777-"seizures lasting 25 and 40 mins., respectively (status epilepticus)" (placebo)
- Titration 304-301-30107- patient had GTC seizures in series-(placebo)
- Titration 304-441-44101-SE (placebo)
- STUDY 303--303-706-70181 (placebo)
- Maintenance-304-751-75103 (placebo) Complex partial status epilepticus
- Maintenance 304-441-44101 (SE) placebo
- Maintenance 304-009-00901 (SE) subject died (800 mg ESL)

In epilepsy study 201, there is one status epilepticus (201-005-09043-placebo).

Cluster:

- 4 subjects: 2 in 301, 1 each in 302 and 304
- 301 -1 ESL 400 mg in taper, 1 ESL 800 mg in titration
- 302-1 placebo in titration
- 304- 1 ESL 800 mg in maintenance

Absence or onset of a new seizure type-(all epilepsy studies)

In the dataset, there is an AETERM of "new type of seizure-generalized tonic-clonic" (201-019-09123).

In study 202 (pediatric), there were two findings on EEG consistent with generalized seizure disorders. These are discussed above in the section based on the Sponsor's presentations.

Non-fatal Serious Adverse Events of Seizure
I performed this analysis several times. There is some discrepancy of a few subjects based partly on events that may have been picked up in an audit or review or in dataset manipulation or interpretation differences. There is also discrepancy between the numbers in my analysis and in Dr. Doi's (Table 61 of Dr. Dois' NDA safety review). I used the variables AESER and IFPRTSAE for seriousness determination. The second variable, per the define file, is from the 2012 data review for CIOMS/SAE without CIOMS only, "is the potential adverse event part of an existing serious adverse event diagnosis". This may explain some of the discrepancy.

The discrepancies in my analyses did not alter that more events were in the 800 mg group (and in the ESL 400 mg group, but this is not proposed for marketing) than in the placebo group . Dr. Doi's analysis was performed using AESER variable for seriousness. Dr. Doi's analysis of the phase 3 epilepsy controlled pools indicates that there were more serious adverse events of seizure in the pooled ESL groups when compared to placebo (0.5% compared to 1.4%).

I do not display these by the number of events as some events appear to be duplicated possibly due to having a different source in the dataset (such as CIOMS or database but have the same start date for the event).

- 18 to 20 subjects with 24 ± events–events are provided but some injuries are listed more than once (AESER=y and IFPRTSAE=y).
- By phase for these 19
  - Titration only- 9 subjects: 3 placebo subjects, 5 subjects at ESL 800, 1 subject ESL 1200 mg
  - Maintenance -6 subjects; 1placebo subject, 1 ESL 400 mg subject, 4 ESL 800 mg subjects,

- Taper- 3 subjects- all 400 mg

**SAES**

**Table 35 Seizures as Serious Adverse Events**

| **safety pop total n** | **Placebo 426** | **400 mg 196** | **800 mg 415** | **1200 mg 410** |
|---|---|---|---|---|
| **301 subjects** | 0 or 1 | 3 | 1 | 0 |
| **302 subjects** | 1 | 1 | 1 | 0 |
| **304 subjects** | 3 | NA | 7 or 8 | 1 |
| **total subjects** | 4 or 5 (0.9 or 1.2%) | 4 (2%) | 9 or 10 (2.17 or 2.4%) | 1 (0.2) |
| | 0.9% or 1.2% | total ESL= 1.37% to 1.47% | | |

Source: ADEVENTX.xpt, reviewer use, includes
301-194-90132=placebo AETERM "possibly following a seizure"

Discontinuations secondary to seizure event 301-302 and 304:

A few more subjects discontinued in titration compared to maintenance (10 versus 8). There of the subjects were from studies 301-302 and the rest were from study 304.

- 20 events in 18 subjects. By period in the study, 10 subjects with 12 events in titration and 8 subjects with 8 events in maintenance
- Study 301- 0 placebo, 0 400 mg, 0 800 mg, 1subject (1event) 1200 mg
- Study 302-0 placebo, 1 400 mg, 0 800 mg, 1 subject (1 event) in 1200 mg
- Study 304- 8 placebo (9 events), 2* in the 800 mg (3 events), and 5 in the 1200 mg (5 events).
- Of note, the reasons in the dataset (variable PRIMERSN) for discontinuation are not all adverse events or lack of efficacy: 1 each for administrative (1200 mg ESL with AETERM of seizure number increase), lack of efficacy (1200 mg ESL with AETERM increase of seizure frequency by 100% or more during the treatment periods compared to baseline period), and protocol violation; 2 each for compliance (placebo with AETERM of increase in number of seizures or increase in severity of seizures) and other (both 800 mg subjects with one being the subject who died from status and the other with an AETERM of secondary generalized seizures), 3 for withdrew consent (1 placebo and 2 ESL 1200 mg-all with AETERMS indicating seizures), 7 for adverse events (4 placebo and 3 at 1200 mg), and one for exacerbation of seizures (1 ESL 400 mg).

## Other Epilepsy studies 201 and 202:

**Study 201-**
This study was conducted by Bial and was a phase 2 study, placebo-controlled study in refractory partial seizures when added to ongoing therapy. 144 subjects were randomized to receive increasing daily doses of ESL 400 mg, 800 mg, and 1200 mg once or twice daily, orally or placebo. The Sponsor conclude that once daily doses seemed to show an increased effect when compared to the same total dose divided into twice daily dosing. The safety presentations were generally based on once daily, twice daily, or placebo grouping in the study report.

- 1 SAE with seizure term-exacerbation of seizures in subject 201-006-09068
- 3 discontinuations secondary to a seizure AE term-one is placebo with status epilepticus 201-005-09043
- a new type of seizure (generalized tonic clonic) was noted as AETERM for subject 019-09123
- 40 subjects with 44 events. 37 of these subjects had exacerbations of seizures, one had an increase in the number of seizures, and one had new type of seizure, and one was status epilepticus.
    - ●11 subjects (12 events) placebo
    - ●3 subjects (3 events) ESL 400 mg
    - ●24 subjects (27 events) ESL 800 mg
    - ●2 subjects with 2 events ESL 1200 mg

**Study 202**: This study does not provide controlled data. There were 3 subjects with 4 events that had explicit terms indicating seizure worsening or increasing numbers of worsening. The subjects were on ESL 800 mg, ESL 400 mg, and ESL 75 mg. One of three seizure subjects discontinued. This was a subject (202-000-00114) who was hospitalized with worsening seizures and an EEG showed generalized spike wave (as AETERM). There was an additional EEG finding of in another subject of continuous spike and wave (202-000-00201).

## Non-epilepsy studies:

Six subjects had 6 events called seizure activity or possibly suggestive of seizure though it appears there is one adverse event of treatment-emergent seizure (based on the adverse event terms) and this was a subject with a history of epilepsy (106-000-00003). This subject was in pharmacokinetic study that was evaluating the effect of ESL on the pharmacokinetics of phenytoin. The event occurred while on phenytoin and ESL. No action was taken and the event resolved.

One subject in a migraine study (209-131-90554) was hospitalized for status migraine and apparently underwent EEG. The EEG was read as “irregular alpha eeg with inclusion of epilepsy- typical potentials bilateral temporo-occipital”. This subject was assigned to ESL 800 mg. The narrative does not indicate a clinical seizure event. One other non-epilepsy subject had an AETERM that included a seizure term but this

appears to have been in or before screening (210-582-582012) and the subject discontinued.

No terms of status epilepticus were seen in the phase 1 studies.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

### 7.4.2 Laboratory Findings

### 7.4.3 Vital Signs

### 7.4.4 Electrocardiograms (ECGs)

### 7.4.5 Special Safety Studies/Clinical Trials

### 7.4.6 Immunogenicity

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

### 7.5.2 Time Dependency for Adverse Events

7.5.3 Drug-Demographic Interactions

7.5.4 Drug-Disease Interactions

7.5.5 Drug-Drug Interactions

### 7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

7.6.3 Pediatrics and Assessment of Effects on Growth

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Review of withdrawal and dependence was performed by Controlled Substance, Dr. Alicja Lerner.

### 7.7 Additional Submissions / Safety Issues

## 8 Postmarket Experience

Review by Dr. Mary Doi.

# 9 Appendices

## 9.1 Literature Review/References

## 9.2 Labeling Recommendations

## 9.3 Advisory Committee Meeting

Not Applicable

# Appendix:

1. email J. Senior to T. Podruchny
2. 2010 Audit findings, Sponsor' s Tables 1 and 2
3. Sample Table 42 from study 301

### 1. EMAIL- DILI related

---Original Message-----
From: Senior, John R
Sent: Saturday, March 30, 2013 4:38 PM
To: Podruchny, Teresa; Hershkowitz, Norman
Cc: Kelley, Laurie; Sun, Su-Lin
Subject: RE: Eslicabazine consultation - candidate for eDISH

Theresa,

As we await the data from the sponsor let me send ahead my impression of the two cases you highlighted. More accurate diagnosis of severity and cause of the findings reported in the two cases is just not possible. The "narratives" are not true medical narratives at all, but simply data dumps of the case reports. After the years have passed there is probably no additional diagnostic information that can be unearthed. We are left with one fairly serious and probably eslicarbazepine-induced liver injury (lacking any alternative information - valproate and pancreatitis are not credible), and one milder cases in which the likelihood is weaker, only at a level of "possible" because they did not find out or report what may really have been going on.

I shall follow with more commentary after we receive and review the data requested. By the way, other than your contact with me, I never even received a request for consultation, which must have gotten lost in the shuffle between ect managers, and I find nothing in DARRTS NDA 022416. The IND number (b) (4) appears to be a mistake, and refers to a research IND for (b) (4) The only IND for eslicarbazepine is (b) (4) and no consult request there either.

John Senior

2. **2010 Audit findings - complete-response.pdf**
**Sponsor's Tables 1 and 2**

**Table 1: Summary Tabulation of Audit Findings for Study 2093-301**

| Study 2093-301 Deficiency Category | Number of Subjects Impacted | | |
|---|---|---|---|
| | 2008 | 2010 | Per Total Audited |
| 1. Eligibility Issues: | | | |
| Confirmed issues involving seizure frequency/type | | | |
| a. Seizure-free periods exceeding 21 days | 0 | 4 | 4/383 |
| b. < 4 seizures in one of the 4-week qualifying periods | 2 | 2 | 4/383 |
| c. Disqualifying seizure types | 0 | 2 | 2/383 |
| Auditors could not confirm eligibility re seizure frequency | 1 | 25 | 26/383 |
| Confirmed issues involving stable AED use | | | |
| a. Taking >2 AEDs (prior to protocol amendment) | 1 | 1 | 2/383 |
| b. Taking disqualifying medication | 0 | 1 | 1/383 |
| c. Dosage not stable prior to randomization | 2 | 5 | 7/383 |
| Auditors could not confirm eligibility re stable AED use | 2 | 7 | 9/383 |
| Other eligibility issues noted during audits | | | |
| a. Delayed receipt and/or review of laboratory tests | 2 | 10 | 12/383 |
| b. Incomplete information on contraception methods | 0 | 11 | 11/383 |
| c. Disqualifying medical history or conditions | 0 | 11 | 11/383 |
| d. Previous exposure to eslicarbazepine acetate | 1 | 0 | 1/383 |
| e. Subject underage | 1 | 0 | 1/383 |
| 2. Adverse Event Reporting | 8 | 57 | 65/383 |
| 3. Informed Consent | 0 | 0 | 0/383 |
| 4. Drug Accountability | 9 | 11 | 20/383 |
| 5. Randomization | 0 | 6 | 6/383 |

**Table 2: Summary Tabulation of Audit Findings for Study 2093-302**

| Study 2093-302 Deficiency Category | Number of Subjects Impacted | | |
|---|---|---|---|
| | 2008 | 2010 | Per Total Audited |
| 1. Eligibility Issues: | | | |
| Confirmed issues involving seizure frequency/type | | | |
| a. Seizure-free periods exceeding 21 days | 1 | 8 | 9/386 |
| b. < 4 seizures in one of the 4-week qualifying periods | 11 | 28 | 39/386 |
| c. Disqualifying seizure types | 2 | 1 | 3/386 |
| d. No seizures during the qualifying period | 0 | 1 | 1/386 |
| Auditors could not confirm eligibility re seizure frequency | 3 | 12 | 15/386 |
| Confirmed issues involving stable AED use | | | |
| a. Taking >2 AEDs (prior to protocol amendment) | 5 | 9 | 14/386 |
| b. Taking disqualifying medication | 0 | 3 | 3/386 |
| c. Dosage not stable prior to randomization | 4 | 19 | 23/386 |
| Auditors could not confirm eligibility re stable AED use | 4 | 8 | 12/386 |
| Other eligibility issues noted during audits | | | |
| a. Delayed receipt and/or review of laboratory tests | 7 | 21 | 28/386 |
| b. Incomplete information on contraception methods | 3 | 6 | 9/386 |
| c. Disqualifying medical history or conditions | 2 | 8 | 10/386 |
| d. Previous exposure to eslicarbazepine acetate | 0 | 1 | 1/386 |
| e. Subject underage | 0 | 0 | 0/386 |
| 2. Adverse Event Reporting | 22 | 91 | 113/386 |
| 3. Informed Consent | 0 | 0 | 0/386 |
| 4. Drug Accountability | 1 | 20 | 21/386 |
| 5. Randomization | 0 | 26 | 26/386 |

## *3. TABLE 42 for study 301 standardized seizure frequency by seizure type ITT*

Table 42: Number of seizures (standardised to a "frequency per 4 weeks") by seizure type (ITT population)

Simple partial seizures

| Treatment | Period | N | % | n | Mean | SD | Median | Inter. Range | Min | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| ESL 1200 mg | Baseline per. | 45 | (45.9%) | 383 | 8.5 | 10.96 | 4.9 | 6 | 0 | 61 |
| | Titration per. | 35 | (35.7%) | 336 | 9.6 | 9.70 | 6.5 | 10 | 2 | 42 |
| | 12-wk maint per. | 42 | (42.9%) | 226 | 5.4 | 7.45 | 2.0 | 6 | 0 | 33 |
| | Titration + 12-wk maint per. | 47 | (48.0%) | 267 | 5.7 | 7.29 | 2.4 | 8 | 0 | 32 |
| | Tap-off per. | 25 | (25.5%) | 223 | 8.9 | 8.21 | 7.0 | 8 | 1 | 34 |
| ESL 800 mg | Baseline per. | 43 | (43.9%) | 367 | 8.5 | 11.88 | 4.5 | 9 | 0 | 68 |
| | Titration per. | 32 | (32.7%) | 320 | 10.0 | 8.27 | 6.5 | 10 | 2 | 31 |
| | 12-wk maint per. | 41 | (41.8%) | 248 | 6.1 | 9.92 | 3.4 | 4 | 0 | 59 |
| | Titration + 12-wk maint per. | 47 | (48.0%) | 314 | 6.7 | 9.46 | 3.4 | 5 | 0 | 54 |
| | Tap-off per. | 32 | (32.7%) | 238 | 7.4 | 10.41 | 4.0 | 5 | 1 | 56 |
| ESL 400 mg | Baseline per. | 42 | (42.4%) | 406 | 9.7 | 10.72 | 6.0 | 9 | 1 | 50 |
| | Titration per. | 33 | (33.3%) | 391 | 11.8 | 12.20 | 8.2 | 10 | 2 | 56 |
| | 12-wk maint per. | 42 | (42.4%) | 346 | 8.2 | 11.50 | 4.2 | 9 | 0 | 47 |
| | Titration + 12-wk maint per. | 44 | (44.4%) | 362 | 8.2 | 11.12 | 4.3 | 9 | 0 | 47 |
| | Tap-off per. | 31 | (31.3%) | 353 | 11.4 | 15.26 | 5.0 | 12 | 1 | 66 |
| Placebo | Baseline per. | 45 | (44.1%) | 450 | 10.0 | 11.80 | 5.6 | 5 | 1 | 63 |
| | Titration per. | 37 | (36.3%) | 436 | 11.8 | 13.55 | 8.0 | 10 | 2 | 82 |
| | 12-wk maint per. | 45 | (44.1%) | 381 | 8.5 | 12.30 | 5.3 | 6 | 0 | 76 |
| | Titration + 12-wk maint per. | 47 | (46.1%) | 443 | 9.4 | 15.12 | 5.8 | 7 | 0 | 82 |
| | Tap-off per. | 30 | (29.4%) | 235 | 7.8 | 5.83 | 5.7 | 6 | 1 | 25 |

Note: N (%) = number (%) of patients experienced respective seizure at respective period, n = number of respective seizures
(Continued)

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/s/

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TERESA A PODRUCHNY
10/10/2013

NORMAN HERSHKOWITZ
10/11/2013
Please see CDTL review for a somehat differing opinion.

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

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**NDA:** 22416
**Drug:** Eslicarbazepine acetate (Trade Name to be determined)
**Route:** Oral
**Indication:** Adjunctive therapy of partial-onset seizures
**Sponsor:** Sunovion Pharmaceuticals, Inc.
**Review Date:** September 16, 2013
**Reviewer:** Sally Usdin Yasuda, Safety Team Leader
Neurology Drug Products

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# 1 Background

Eslicarbazepine acetate (ESL) is an antiepileptic drug (AED) that is structurally similar to the AEDs carbamazepine (Tegretol, Carbatrol, and Equetro) and oxcarbazepine (Trileptal). ESL is primarily metabolized to the active metabolite eslicarbazepine; minor metabolites are (R)-licarbazepine and oxcarbazepine.[1] The apparent half-life of eslicarbazepine is approximately 10-20 hours. The Sponsor is seeking approval for adjunctive therapy of partial-onset seizures. The proposed starting is 400 mg once daily for one week, and increased at increments of 400 mg at approximately weekly intervals to a maximum recommended dosage of 1200 mg once daily, although the proposed recommended maintenance dose is 800 mg once daily. The Sponsor proposes that for some patients, therapy may be initiated at 800 mg once daily if the need for seizure control outweighs a potentially increased risk of adverse reactions during initiation. ESL metabolites are excreted primarily renally, unchanged or as glucuronide conjugates. ESL is available as Zebinix® in the European Union and other foreign countries. The Sponsor estimates 12,279 patient-years of post-marketing exposure from marketing authorization on April 21, 2009 through October 21, 2012.

NDA 022416 was originally submitted on March 29, 2009 by Sepracor, Inc. Sepracor received a Complete Response letter on April 30, 2010 due to significant deficiencies in the conduct and documentation of the studies, and in the structure of the application, including deficiencies in the accuracy, reliability, and presentation of the data. The NDA was resubmitted on August 31, 2012 by Sunovion, Inc., but the Division did not consider this resubmission to constitute a complete response because of persistent deficiencies in the structure of the application, including deficiencies in the accuracy, reliability, and presentation of the data, adverse event datasets that did not contain a comprehensive collection of all of the adverse events that were recorded in various other documents (e.g. narratives, CRFs) in the submission, and narratives in the resubmission that did not provide the same supportive information as narratives from the original NDA. An Incomplete Response letter was sent to the Sponsor on November 2, 2012. Following extensive communications regarding the deficiencies, the NDA was resubmitted on February 10, 2013 by Sunovion, Inc.

[1] Oxcarbazepine given as Trileptal is also metabolized to eslicarbazepine and (R)-licarbazepine.

This memorandum summarizes the primary concerns from the safety review, conducted by Dr. Mary Doi, of the resubmission of February 10, 2013.

# 2 Summary of Findings from the Safety Review

## 2.1 Data Quality Issues

As Dr. Doi notes, the resubmitted application was accepted for review because the specific issues that were previously identified had been corrected. However, despite substantial efforts to identify and address the deficiencies noted in the Complete Response and Incomplete Response letters, the February 10, 2013 submission of the NDA still contained substantial deficiencies and discrepancies that were not identified prior to filing but were identified by Dr. Doi during the review process. These are identified in section 3.1 of Dr. Doi's review with additional specific deficiencies noted throughout her review. As Dr. Doi summarizes in Section 1.2 of her review, these included laboratory data missing from the ISS datasets that required 2 resubmissions to correct, many discrepancies, programming errors, coding omissions, key information missing from the narratives (including a death that was included in a previous version of the narratives), and narratives of subjects with adverse events of special interest missing from the ISS. As Dr. Doi notes, in response to the Division's multiple information requests to address these deficiencies, the Sponsor submitted multiple safety amendments that corrected and/or explained these deficiencies. I believe that the deficiencies and discrepancies identified by Dr. Doi during her review would have been filing issues if identified prior to filing the submission. However, due to Dr. Doi's extensive investigation, these issues have been addressed. Despite Dr. Doi's extensive investigation of such deficiencies, I agree with her that the potential for additional unidentified deficiencies cannot be ruled out due to difficulties in identifying missing or incorrect data, as would be the situation in any case. I believe, as Dr. Doi has demonstrated, that the submission along with the amendments responding to Dr. Doi's many and important information requests allowed for a review of the safety of ESL.

## 2.2 Integrated Review of Safety

The current submission summarizes safety data for 4225 ESL-exposed subjects from 53 clinical trials in healthy volunteers (n=847), subjects with partial onset seizures (n=1554), and subjects with nonepilepsy indications (n=1832) of bipolar disorder, neuropathic pain, migraine, and fibromyalgia[2]. The nonepilepsy studies included doses of < 600 mg/day to ≥1600 mg/day. The primary focus of Dr. Doi's review is the Phase 3 Epilepsy Controlled Pool that is pooled safety data from the three Phase 3 double-blind (DB) clinical trials (Study 301 Part 1, 302 Part 1, and 304 Part 1) in subjects with partial-onset seizures that evaluated doses of 400 to 1200 mg/day. The pooling excludes epilepsy Study 303 because of GCP deficiencies identified in the previous review cycle, although Dr. Doi considers the safety data from that study.[3] According to Dr. Doi's review, 586

[2] Eight subjects who were counted twice because they were enrolled in more than 1 ESL study are not included in the total number.

[3] Of note, there were several adverse event datasets available for review. ADEVENTX included audit findings of potential events, review events, and signs and symptoms but excluded events that had been crossed out by the investigators in the case report forms. ADAE had not been subject to audit. Dr. Doi

subjects were exposed to ESL in the Phase 3 epilepsy studies for at least 6 months, and 462 for at least 12 months. Other Pools analyzed are:

- Phase 3 Epilepsy Uncontrolled Pool
- Phase 3 Epilepsy Controlled and Uncontrolled Pool
- Nonepilepsy Controlled Pool (includes 2 Phase 2 Bipolar studies, 1 Phase 2 postherpetic neuralgia Study, a Phase 2 Migraine Study, and a Phase 2 Fibromyalgia Study)[4]
- Bipolar Controlled and Uncontrolled Pool
- Phase 1 Pool
- All Studies Pool.

The Sponsor has met the ICH guidelines for exposure (1500 total, 300 for 6 months, and 100 for 1 year at clinically relevant doses). All of the patients in the Nonepilepsy DB pool and the majority of patients in the Phase 3 Epilepsy Controlled Pool were ≥18 years old (only 20 in the ESL group were < 18 y.o. in the Phase 3 Epilepsy Controlled Pool).

### 2.2.1 Deaths

According to Dr. Doi's review, there were 11 post-randomization deaths in the Epilepsy Phase 2/3 studies; 8 of those occurred in the open label extension (OLE). In the Epilepsy Phase 2/3 controlled studies there were 3 deaths, 2 in placebo and 1 in ESL. In these studies, the mortality rate was lower in the ESL group (0.08%, 1/1313) than in the placebo group (0.36%, 2/560). One ESL death was classified as probably/possible SUDEP by the sponsor; Dr. Doi notes that this death may have been secondary to status epilepticus. The incidence rate of SUDEP in this epilepsy population is 0.76 per 1000 subject years, compared to 3.5-9.3 per 1000 person years in subjects with refractory epilepsy as reported in the literature. Dr. Doi notes an additional case coded to SUDEP in ongoing studies, and she notes a total of 5 cases of possible SUDEP in the postmarketing dataset (0.41 per 1000 patient years). In Nonepilepsy studies overall there were a total of 6 ESL deaths (0.33% or 9.72 per 1000 patient years) and 1 placebo death. In the Nonepilepsy DB studies, there were 4 deaths in the ESL group and 1 in the placebo group; the mortality rate in this pool was similar in the ESL group (0.23%, 4/1755) and in the placebo group (0.2%, 1/507). Reported causes of death were brain oedema (thought due to seizure)/arteriosclerosis, drowning (3; 1 of which was off ESL x 3 weeks) /asphyxia, arteriosclerosis coronary artery (in a patient with cardiovascular risk factors), status epilepticus, and astrocytoma (in a patient with recurrence of previous malignancy) in the Epilepsy studies, and suicide (2; one in a subject with a history of bipolar disorder and the other 73 days after the last dose of ESL), prostate cancer, bronchopneumonia, lung neoplasm malignant, gastric cancer/septic shock/tracheobronchitis in the nonepilepsy studies. In Phase 1 studies there was 1 ESL death (due to coronary artery occlusion in a patient with cardiovascular risk factors). There were 13 deaths in ongoing studies; I agree these were unlikely due to ESL as they either occurred off ESL for ≥ 18

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primarily used the ADEVENTX dataset; the Sponsor used primarily the ADAE and ADAE_AU datasets in the original ISS supplementing the tables in the NDA resubmission after the incomplete response letter with analyses using the ADEVENTX and ADEVENTS datasets.

[4] Study 206 was performed in diabetic peripheral neuropathy patients and was not included in the Nonepilepsy Controlled Pool (due to a different risk factor profile in this group of patients), but has been included in a pool of all nonepilepsy double blind studies called the Nonepilepsy DB Pool.

days or were due to accidental trauma or in subjects with other significant risk factors or due to single events. Overall, there is not a cluster of cases due to any one cause. I agree with Dr. Doi that it is difficult to draw conclusions about the causal role of ESL in these deaths.

2.2.2 Serious Adverse Events

Dr. Doi notes that there are differences in the SAE analysis using different AE datasets. She has primarily relied on the ADEVENTX dataset[5] and in that dataset serious adverse events (SAEs) in the Phase 3 Epilepsy Controlled Pool occurred more frequently in ESL patients (5.3% overall) than in placebo patients (2.8%). She notes an inverse dose response for ESL (7.1% for 400 mg, 7% for 800 mg, and 2.7% for 1200 mg) but acknowledges the small number of SAEs contributing to these events. In the Phase 3 Epilepsy Controlled Pool the following SAEs occurred most frequently (≥3 subjects (0.3%) and > placebo): nausea, vomiting, partial seizures, ataxia, diplopia, and vertigo and gait disturbance, and drug toxicity, all occurring at approximately ≤ 1%. In the Phase 3 Epilepsy Uncontrolled and Controlled Pool, 8.8% of subjects had SAEs; the SAEs with the highest frequency in this pool were partial seizures (1.6%) and vertigo, fall, vomiting, convulsion, ataxia, nausea, diplopia, status epilepticus, gait disturbance, drug toxicity, psychotic disorder, head injury that all occurred at 0.4% to 0.8%. In the Nonepilepsy DB Pool the following SAEs occurred most frequently: vomiting, dyspnea, abdominal pain, cardiac failure, pyrexia, nausea, unevaluable event, and hyponatremia, all occurring at 0.2% vs 0 for placebo. In the Nonepilepsy Uncontrolled and Controlled Pool, the most frequent SAEs were mania, vomiting, nausea, pyrexia, unevaluable event, vertigo, dyspnoea, and cardiac failure, all at 0.3% to 0.4%).

In the Phase 1 pool there were 6 ESL subjects (0.7%) with SAEs and no placebo subjects. The SAEs were in 1 subject each: cardiac failure, tonsillitis, hepatic encephalopathy in a subject in the hepatic impairment study, pregnancy, Stevens-Johnson syndrome, and hypertension.

In the entire development program, there was 1 ESL case each of SAEs coded to: acute renal failure, acute respiratory failure, hyperthermia, ventricular arrhythmia, pancytopenia, septic shock, hepatic encephalopathy, blindness, Stevens Johnson syndrome, and toxic skin eruption. There were 6 ESL cases with SAEs of loss of consciousness and 2 cases of syncope. There were no ESL patients with SAEs of acute pancreatitis, acute hepatic failure (or hepatic failure), agranulocytosis, anaphylaxis, aplastic anemia, rhabdomyolysis, toxic epidermal necrolysis, torsades de pointes, ventricular fibrillation, or ventricular tachycardia.

Dr. Doi notes that SAEs in ongoing trials are consistent with those reported in clinical trials. Other SAEs in ongoing trials include angioedema, DRESS, acute respiratory failure, acute renal failure/ failure/renal failure, suicidal ideation/attempt, pregnancy/abortion spontaneous, cardiac arrest, cardiogenic shock, ventricular tachycardia, and pancreatitis. Similarly, Dr. Doi notes that overall, the postmarketing SAE reports are consistent with those reporting in the clinical trials. The most commonly

[5] The ADEVENTX dataset had more SAEs than did the ADAE dataset.

reported were hyponatremia, seizures, neurologic effects (dizziness, ataxia, vertigo, aphaseia, diplopia, altered state of consciousness, somnolence), and rash. There were 2 cases of spontaneous abortion, and there was 1 case each of the following: hepatorenal syndrome, cardiac arrest, circulatory collapse, pancytopenia, Stevens-Johnson syndrome, and angioedema.

Details of specific SAEs are discussed in the relevant sections of Dr. Doi's review and this memo.

2.2.3 Dropouts and Other Significant Adverse Events

AEs were the primary reason for discontinuation of study drug in the Phase 3 Epilepsy Controlled Pool and accounted for discontinuation of approximately 14% overall in ESL subjects (approximately 6% for 400 mg, 10% for 800 mg, and 21% for 1200 mg) and 3% of placebo subjects. After stratifying by study, Dr. Doi reports that subjects randomized to the 1200 mg dose group (Studies 301 and 302) withdrew due to AEs > 12x more frequently than placebo subjects. Approximately one third of all withdrawals occurred during the first 2 weeks (titration period). In the Phase 3 Epilepsy Uncontrolled and Controlled Pool, approximately 37% of subjects withdrew, most commonly for adverse events (approximately 15%). Similarly, in the Nonepilepsy DB Pool, a higher percentage of ESL subjects (24%) discontinued compared to placebo subjects (17%), and this was driven by discontinuations due to AEs in 14% of ESL subjects compared to 6% of placebo subjects. A dose response for discontinuations due to AEs was observed in this pool as well. In Phase 1 studies, the most common reason for discontinuation for ESL treated subjects was due to AEs (5.4%), approximately the same rate as for placebo subjects.

The most common AEs leading to discontinuation among ESL subjects in the Phase 3 Epilepsy Controlled Pool were dizziness, nausea, vomiting, ataxia, diplopia, and somnolence, accounting for discontinuations in 2-6% of ESL subjects and < 1% of placebo subjects. AEs leading to discontinuation in the Epilepsy Controlled and Uncontrolled Pool were similar to those in the Controlled Pool. The most common AEs leading to discontinuation among ESL subjects in the Nonepilepsy DB Pool were nausea, vomiting, dizziness, accounting for discontinuations in approximately 2% of ESL subjects and ≤1% in placebo. Dr. Doi notes that in the Phase 1 Study Pool, the preferred terms (PTs) leading to discontinuation were consistent with those in the other trials, although there was 1 ESL subject who discontinued due to hepatic encephalopathy in the hepatic impairment study. There was 1 ESL case each in the entire development program of the following AEs leading to discontinuation: acute renal failure, acute respiratory failure, hyperthermia, hepatic encephalopathy, pancreatitis, and toxic skin eruption, and 2 ESL cases of syncope and loss of consciousness. No ESL subjects discontinued due to acute hepatic failure, agranulocytosis, anaphylaxis, aplastic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson syndrome, Toxic epidermal necrolysis, torsades de pointes, ventricular fibrillation, or ventricular tachyarrhythmia or tachycardia. Discontinuations in the ongoing trials are consistent with those reported for the clinical trials.

### 2.2.4 Significant Adverse Events

*Drug-Induced Liver Injury* - Dr. Doi finds that in the Phase 3 Epilepsy DB pool and in the Nonepilepsy DB pool, the incidence of transaminase elevations was slightly higher for subjects receiving ESL than placebo as shown below, from Dr. Doi's review.

**Table 47. Liver Test Outliers**

| | Phase 3 Epilepsy DB | | Nonepilepsy DB Pool^ | |
|---|---|---|---|---|
| **Test/Cutoff threshold** | **Placebo** n=426 | **ESL** n=1021 | **Placebo** n=506 | **ESL** n=1752 |
| ALT | | | | |
| ALT >3xULN | 1 (0.2) | 3 (0.3) | 3 (0.6) | 16 (0.9) |
| ALT >5xULN | 1 (0.2) | 0 | 0 | 7 (0.4) |
| ALT >10xULN | 0 | 0 | 0 | 2 (0.1) |
| ALT >20xULN | 0 | 0 | 0 | 1 (<0.1)* |
| AST | | | | |
| AST >3xULN | 1 (0.2) | 1 (<0.1) | 1 (0.2) | 10 (0.6) |
| AST >5xULN | 0 | 1 (<0.1) | 0 | 4 (0.2) |
| AST >10xULN | 0 | 0 | 0 | 3 (0.2) |
| AST >20xULN | 0 | 0 | 0 | 2 (0.1) |

In the All Studies Pool (including 303) there were ESL subjects who developed transaminase elevations > 3X ULN without bilirubin elevations which led to discontinuation of ESL and resolution of elevations within 15 days, and there were other elevations that occurred in the OLE studies with a latency of > 1 year, or others that improved while remaining on ESL. In the Nonepilepsy DB pool, only ESL subjects (n=3, 0.2%) and no placebo subjects had concurrent elevations of transaminases > 3XULN and bilirubin > 2X ULN; no patients in the Epilepsy Controlled pool met these criteria. One ESL subject in the Nonepilepsy DB pool (203-337-203058) had laboratory values that met the criteria for Hy's Law: transaminase elevations > 3X ULN associated with total bilirubin > 2XULN and alkaline phosphatase < 2X ULN.[6] An additional subject in Study 206 (206-563-563010) was identified by Dr. Doi as meeting Hy's lab criteria. Dr. Doi notes that the Sponsor did not report any cases of severe Drug Induced Liver Injury (DILI). The Hy's law cases and implications will be further discussed below.

In the Phase 3 Epilepsy Controlled Pool, there were no SAEs in the SOC hepatobiliary disorders or SOC Investigations (HLT liver function analysis). One ESL subject (with slightly elevated ALT at baseline and developed AST elevation < 2XULN) discontinued due to "ALT increased". A slightly higher percentage of ESL subjects compared to placebo (0.8%) vs 0.2%) had TEAEs in the HLT liver function analyses and in the SMQ Hepatic disorders (1.3% vs 0.5%). In the Nonepilepsy DB pool, a similar percentage of ESL subjects (0.7%) and placebo subjects (0.6%) developed TEAEs in the SOC Hepatobiliary disorders, but more ESL subjects (4.2%) than placebo (1.4%) developed TEAES in the HLT liver function analysis. One subject in this pool had an SAE with PTs biliary dilatation, cholangitis, cholestasis, and jaundice in the setting of newly diagnosed gastric cancer and discontinued; I agree with Dr. Doi that this is unlikely related to ESL. Two other ESL subjects in this pool discontinued due to liver-related

[6] There were additional subjects who had ALT or AST > 3x baseline and total bilirubin > 2X baseline and ALP < 2X baseline, but these do not meet Hy's law criteria.

SAEs, one discussed under DRESS and one with slightly elevated ALT at baseline and developed a mild increase in AST < 2X ULN and ALT <2X ULN. In the Phase 2 studies there were fewer ESL subjects than placebo subjects (3.1% vs 4.3%) with liver function TEAEs and there were no liver-related SAEs or TEAEs leading to discontinuation. In the Phase 1 Pool, there was 1 ESL subject (in the hepatic impairment study) with an SAE coded to hepatic encephalopathy[7]. In ongoing studies 1 ESL subject developed an SAE of cholelithiasis obstructive. In the postmarketing database, there were few events (9 events, 0.00073 per patient year) of hepatic disorders or hepatotoxicity; there was 1 acute pancreatitis that lacked details and there was one case of hepatorenal syndrome[8].

Two Hy's law cases were identified by Dr. Doi. Subject 203-337-203058 had a history of chronic pancreatitis and hypertension, as well as a history of transaminitis that may have been association with a helminth infection 14 years prior to this event, and developed vomiting (severe) and diarrhea on Study day 4. Two days later ESL was discontinued. Baseline liver enzymes were within normal limits (WNL). On the day of discontinuation ALT was 37X ULN, AST > 30X ULN and total bilirubin > 2X ULN. ALP was 2.5X ULN. INR was within normal range. Serum ESL concentration was 13,400 ng/ml; according to communication received by Dr. Doi from the Office of Clinical Pharmacology on 8/30/133, this not an outlier in terms of concentration but the level was drawn 36 hours after the dose and the patient had vomiting so that the maximum concentration is unknown. Dr. Doi notes no other potentially clinically significant (PCS) values for lab, vital or ECG parameters. Eight days after ESL discontinuation AST, total bilirubin and ALP returned to normal; ALT decreased to 1.7 X ULN. All labs were within normal limits 1 month later. A thorough investigation for alternative etiologies was not performed by the investigator at the time of the event. I agree with Dr. Doi that ESL-induced liver injury in this subject cannot be ruled out. Subject 206-563-563010 with a history of hepatic steatosis, diabetes, and hypertension, with ALP 1.8X ULN at baseline, developed elevated liver tests on Day 36 of ESL (AST 25X ULN, ALT 10X ULN, T bili 3.6X ULN, ALP 2.8X ULN but 1.6X baseline). ESL concentration was more than 2X higher than the mean of all patients in this study. No symptoms were reported. ESL was continued. Although there was a decrease in LFTs and most lab values that Dr. Doi believes may be a result of sample dilution with normal saline, liver tests remained elevated two months later (1 day after ESL discontinuation). The subject had been hospitalized 5 months prior to the study due to "jaundice associated with decompensation of chronic alcoholic liver lesion", and there was another hospitalization for jaundice 21 days after the subject completed the study. The subject was reportedly taking concomitant paracetamol during the study. A thorough

[7] Subject 111-000-0009 had a history of liver disease/portal hypertension and hepatic encephalopathy experienced hepatic encephalopathy on study Day 5 of ESL 800 mg. Resolved after ESL discontinuation and treatment with lactulose. Confounded by recent excessive dietary intake of protein.

[8] Subject BIAL 00494 with a history of diabetes, multi-infarct dementia, and cardiac failure developed rash and fever after an unknown number of days on ESL (dose 1200 mg). Labs included elevated WBC, ALT and AST 2X ULN, ALP 5.5X ULN, and T bili 5.9X ULN with normal creatinine. All medications including ESL were discontinued. Subject as treated with IV steroids and diuretics and subject recovered with unspecified sequelae after 10 days. I agree with Dr. Doi that this is unlikely to represent hepatorenal syndrome with normal renal function, and that it may represent DRESS, although the timing relative to ESL initiation is unknown and therefore the role of ESL is not clear.

investigation of alternative etiologies for liver disease was not be performed by the investigator. Dr. Doi notes that pre-existing liver disease does not rule out the possibility of additional liver injury. She notes that this case does not technically meet Hy's Law criteria because the alkaline phosphatase was < 2X baseline instead of < 2X ULN. This case seems unlikely to be a Hy's law case associated with ESL, but I agree that a contribution of ESL in this case cannot be ruled out.

I agree that there was a slightly higher incidence of ALT/AST > 3x ULN in ESL treated subjects than placebo, but few ESL subjects with more marked peak ALT/AST elevations. There is a Hy's law case for which a role for ESL cannot be ruled out; conservatively Dr. Doi considers 2 Hy's law cases. Conservatively Dr. Doi concludes that the risk is 2/4225 subjects (in the All Studies Pool) or 4.7 per 10,000 subjects, and that the theoretical risk of severe DILI is 10% of that or 0.47 per 10,000 patients (based on the estimate from the "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation". Dr. Doi notes that this is less than the frequency of severe DILI for most drugs withdrawn from the market (according to the "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation", "most of the drugs withdrawn from the market for hepatotoxicity have caused death or transplantation at frequencies in the range of ≤1 per 10,000"), and I note that the ESL cases did not result in death or transplantation. With 12,279 patient years of exposure worldwide through 10/21/12 there have not been any postmarketing cases of severe DILI reported by the sponsor. I agree with Dr. Doi that information regarding drug-induced liver injury should be included in the Warnings and Precautions section of ESL labeling, that cases of severe DILI should be reported in an expedited manner, and that the Sponsor should perform and submit annual analyses of DILI. Dr. Doi notes that carbamazepine is labeled for liver injury in the Warnings sections.

*Skin and Immune System Disorders*
Serious skin reactions - Dr. Doi finds that ESL use is associated with an increased occurrence of rash and discontinuations due to rash compared with placebo use. The rates were low (the TEAE of rash was reported in 1.9% of ESL subjects and 0.9% of placebo subjects in the Phase 3 controlled pool and the rates were lower in the Nonepilepsy pool). In the Phase 1 pool 1.5% of ESLI subjects vs 0 placebo subjects discontinued for subcutaneous tissue disorders AEs (and these were primarily rash). Dr. Doi identified one ESL subject (119-000-0004) with an SAE of possible Stevens Johnson Syndrome (SJS) vs Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) that included mucosal ulceration and skin exfoliation, but SJS not confirmed by biopsy or dermatologist; with lymphadenopathy, fever, and elevation of AST and ALT beginning 10 days after starting ESL and 18 days after starting lamotrigine (which has a boxed warning for SJS/TEN). Although confounded by lamotrigine, the role of ESL cannot be ruled out. There were additional cases of serious rash-related AEs with mucocutaneous involvement and skin exfoliation/detachment, but no dermatologist or biopsy confirmed cases of SJS in the database. Dr. Doi notes that serious skin reactions are included in the prescribing information for carbamazepine and oxcarbazepine in Warnings or Warnings and Precautions, I agree with her recommendation to include similar Warnings in the ESL label. I also agree with her recommendation for a postmarketing requirement to study possible risk factors including the association of

HLA alleles with severe cutaneous reactions, with guidance from the Office of Clinical Pharmacology/Genomics.

Anaphylactic reaction/Angioedema – Dr. Doi notes that there were no AEs coded to the PTs anaphylactic reaction or angioedema in the completed clinical trials. There were events of hypersensitivity-related terms (e.g. hypersensitivity, eye swelling, pharyngeal oedema, tongue oedema) that occurred in < 0.5% in ESL and less ( or none) in placebo in the Phase 3 Epilepsy Controlled Pool and the Nonepilepsy DB Pool. Onset of hypersensitivity reactions was typically within 1 month of ESL initiation and resolved generally in < 1 week after ESL discontinuation. None reported associated respiratory signs and symptoms. There were 3 postmarketing SAEs of hypersensitivity, including 1 case with urticaria, itching, dyspnea, and circulatory problems in the first hour after taking ESL that resolved after ESL was discontinued (in a patient with a history of rash on oxcarbazepine), pharyngospasm on Day 17 of ESL that resolved after discontinuation, and 1 case with rash, Quincke's edema with tongue edema "quickly after treatment with ESL" for which the resolution is unknown. I agree with Dr. Doi that this should be included in Warnings/Precautions.

DRESS – Dr. Doi reports that there are 2 ESL subjects (114-000-00008, 301-111-90341,) meeting RegiSCAR criteria for DRESS occurring within approximately 1 week to 1 month of beginning ESL and with positive dechallenge. In a 3rd case (301-174-90414) the event resolved while the patient continued on ESL. In ongoing studies there were 2 subjects with SAEs meeting the criteria of DRESS and there have been 3 additional cases meeting the criteria reported since the data cutoff date, confounded by concomitant use of antibiotics or by prior history of multiple environmental allergies. I agree with Dr. Doi that there are cases of DRESS associated with ESL use and I agree with her recommendation that information regarding DRESS be included in the Warnings/Precautions section of ESL labeling with language similar to that for other AEDs.

*Nervous System Disorders* – Dr. Doi finds that a higher number of ESL subjects experienced TEAEs in the SOC Nervous System Disorders than placebo subjects in both the Phase 3 Epilepsy controlled Pool (48.3% vs 31.2%) and in the Nonepilepsy DB Pool (22.8% vs 13.4%). Discontinuation due to these TEAEs occurred at least 4x more frequently in ESL than in placebo subjects in both pools. Nervous System SAEs occurred twice as often in ESL subjects vs placebo in both pools. Preferred terms (PTs) under the HLGT Neurological disorders accounted for most of the SAEs and Discontinuations in both pools. In the Phase 2 Study 201 there was 1 ESL subject with the SAE ischemic stroke (in a patient with a recent history of carotid artery thrombosis and taking oral contraceptives). There were no SAEs in the Phase 1 studies in the SOC Nervous System Disorders, and in ongoing studies the SAEs that occurred were consistent with those observed in the Epilepsy Controlled and Nonepilepsy DB pools. PTs related to Dizziness/Gait disturbance occurred more frequently in ESL than placebo in the Phase 3 Epilepsy controlled pool and with a dose response and included *dizziness* (22% ESL total vs 9% for placebo), *ataxia* (5% ESL total vs 2% placebo), *vertigo* (4% ESL total vs 0.5% for placebo), *balance disorder* (3% ESL total vs 0.5% placebo), and

*gait disturbance* (2% ESL total vs 0.5% placebo). These occurred to a greater extent in the titration period than in the maintenance period. In the Phase 3 Epilepsy controlled pool, subjects ≥60 y.o. were at higher risk for developing TEAEs in this group from ESL vs placebo than adults < 60 y.o. A dose response relationship was also observed for PTs related to Somnolence and fatigue in the Phase 3 Epilepsy controlled pool, particularly for *somnolence* (14% ESL total vs 8% placebo), *fatigue* (5% ESL total vs 4% placebo), and *asthenia* (3% for ESL total vs 2% for placebo). A dose response relationship was observed for PTs related to Cognitive dysfunction that occurred in 6% of ESL subjects in the Phase 3 Epilepsy Controlled Pool vs 1% of placebo subjects. The most frequent PTs in this group were *dysarthria, memory impairment, disturbance in attention, amnesia, confusional state, and aphasia*, that each occurred in approximately 1% and greater than placebo. A dose response relationship was observed for PTs related to Eye Disorders that occurred in 16% of ESL subjects vs 6% of placebo subjects in the Phase 3 Epilepsy Controlled Pool and in 3% of ESL subjects vs 1% of placebo subjects in the Nonepilepsy DB pool. The only PTs that occurred in > 2% ESL were *diplopia* (10% for ESL vs 2% for placebo) and *vision blurred* (5% for ESL vs 1% for Placebo) in the Phase 3 Epilepsy Controlled Pool. In that pool, subjects ≥60 y.o. had a higher relative risk for ESL vs placebo for developing TEAEs in this SOC than did adults < 60 y.o., although I note that there were very few subjects > 60 years old, and approximately half of those were 60-65 years old, so little can be said regarding the risk in "elderly". Dr. Doi evaluated Falls and Injuries and notes that while the incidence of AEs coded to the PT fall was low and only slighty higher in ESL subjects vs placebo (2% vs 1% in the Phase 3 Epilepsy DB pool; 0.4% vs 0.2% in the Nonepilepsy DB pool) , and SAEs in this category were similar for ESL and placebo, fall PTs leading to DC occurred in 0.5% for ESL (n=5) vs none in the placebo group in the Epilepsy Phase 3 DB pool (and only 1 report for ESL in the Nonepilepsy pool). Dr. Doi reported that there were more falls, fractures, and injuries that occurred without seizure events in ESL subjects than placebo, but this analysis is based on very small numbers of falls, fractures, and head injuries not related to seizures (3, 5, and 4, respectively for ESL and fewer for placebo). Subjects ≥60 y.o. had a higher relative risk for ESL vs placebo for the PT Fall than did adults < 60 y.o., although this analysis is also limited by small numbers of subjects. I agree with Dr. Doi that there is reasonable evidence of a causal relationship between ESL use and dizziness/gait disturbance, somnolence/fatigue, cognitive dysfunction, visual changes in particular, as well as falls, that are clinically significant AEs and could potentially be mitigated with appropriate use of the drug and possibly closer monitoring during the titration period, and I agree that these AEs should be included in Warnings/Precautions in the label.

*Psychiatric Disorders* – Slightly more ESL subjects experienced TEAEs in the SOC Psychiatric Disorders than placebo subjects in both the Phase 3 Epilepsy Controlled Pool (11% vs 10%) and the Nonepilepsy DB Pool (5% vs 4%). In the Nonepilepsy pool, the greater differences were seen in the bipolar studies and the fibromyalgia study. Discontinuations due to these TEAEs occurred slightly more often in the Epilepsy pool for ESL vs Placebo (2% vs 1%), and related SAEs occurred at similar rates for ESL and placebo in both pools. Dr. Doi finds greater differences (ESL > placebo) in the bipolar, fibromyalgia, and migraine studies driven by differences in insomnia, anxiety, and logorrhea for the bipolar studies and by anxiety in the fibromyalgia and migraine studies.

Using psychiatric-related SMQs Dr. Doi finds similar or lower incidence for ESL compared to placebo in both pools (Epilepsy Controlled and Nonepilepsy DB). In the Phase 3 Epilepsy Controlled Pool, the Psychiatric-related TEAEs >2% and > placebo were *irritability* (2% vs 0.5% placebo), *insomnia* (2% vs 1% for placebo) and *nervousness, confusional state, apathy, and agitation* (all approximately 1% and > placebo). The median time to event was 22 days for ESL vs 26 days for placebo and the median duration was longer for ESL than placebo (27 days vs 13 days). Generally, the Psychiatric AE were reported in only 1 subject each for ESL (0 for placebo) in the Epilepsy Controlled Pool and in the Nonepilepsy DB Pool. Similarly, AEs leading to discontinuations for ESL subjects each occurred in only 1 subject each (except for irritability (3), bradyphrenia (2), depression (4), and insomnia (3). There were no psychiatric-related SAEs in the Phase 2 Study 201, Study 303, or the Phase 1 Study Pool. In ongoing studies there were few SAEs, generally limited to 1 or 2 patients each including depression (2), suicidal ideation (2), and suicide attempt (1), and in the postmarketing database the psychiatric SAEs were limited to 1 subject each but also included completed suicide, suicidal ideation, suicide attempt, depression, anger, and aggression. Dr. Doi has analyzed suicidality, identified by the Sponsor as an AE of special interest and evaluated by the Sponsor using TEAEs as well as C-SSRS scores (assessed prospectively in several studies including 304) and using C-CASA scores assessed retrospectively in all studies (with broader C-CASA categories than used in the suicidality assessment that is the basis for the class labeling). TEAEs in the Depression and Suicidality group were slightly greater in the ESL subjects (7-8%) than in placebo (6%) in the Phase 3 Epilepsy controlled pool; the most frequently reported event was depression, but, except for the ESL 400 mg group (3%) it was not greater than placebo (2%). Using C-CASA, events were seen only in ESL (0.7%) and not placebo. Using C-SSRS events were similar in ESL (2% overall) and Placebo (3%). In the Nonepilepsy controlled pool, the incidence of Depression and Suicidality events was similar in ESL subjects and in placebo (2.6% vs 1.5%); Dr. Doi notes the most frequently reported event in this category was disturbance in attention. Of the 7 ESL subjects identified by the Sponsor using C-CASA, Dr. Doi considers that only 3 of them met the criteria for suicidality events used in the class labeling for AEDs (C-CASA categories 1-4). In that case, for the Phase 3 Epilepsy Controlled Pool, the incidence of suicidal thoughts or behavior (3/1021 or 2.9/1000) was slightly lower than in the meta-analysis for epilepsy patients (3.4/1000 in the class labeling). The nonepilepsy pool had an incidence of 2.3/1000, similar to the meta-analysis in class labeling of "other" and psychiatric indications (1.8-8.5 per 1000). The median time to these TEAEs was 17-22 days in both groups. Overall Dr. Doi identifies 8 ESL subjects with suicidality (2 completed suicides) in the ADEVENTX database: 1 with a history of bipolar disorder, 3 occurring 73-200 days after discontinuing ESL, 3 in patients with a prior history of depression or bipolar disorder. Dr. Doi notes that major psychiatric disorders and schizophrenia with acute psychosis episode (within 2 years) or suicide attempt were exclusion criteria in the epilepsy studies, and therefore the results may not represent the effects of ESL in the general population. I recommend that the class labeling language regarding suicidality is appropriate for eslicarbazepine.

*Endocrine Disorders* – A similar percentage of ESL and Placebo subjects experienced TEAEs in this SOC in both the Phase 3 Epilepsy Controlled Pool (1.3% vs 0.9%) and the Nonepilepsy DB pool (0.6% vs 0.6%). There were no SAEs in this SOC. There was 1 ESL subject who discontinued on Day 99 due to the PT hypothyroidism (in a patient with baseline and Day 58 Thyroid function tests (TFTs) WNL and no abnormal findings suggestive of clinical hypothyroidism; events were ongoing at the time of the report). Dr. Doi finds that ESL use is associated with dose-dependent decreases in T3 and T4 values, along with concurrent increases in TSH, and signs and symptoms of hypothyroidism. The following table, extracted from Dr. Doi's review, shows concurrent thyroid function tests in the Phase 3 Epilepsy controlled pool where, of subjects with a high TSH, ESL subjects had a higher incidence than placebo of low free T4 or T3 values.[9]

**Table 89. Concurrent Thyroid Function Tests, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=426 | n=196 | n=415 | n=410 | n=1021 |
| Thyrotropin >ULN and | n=20 | n=0 | n=18 | n=15 | n=53 |
| Free T3 <LLN | 2 (10) | 0 | 4 (22) | 5 (33) | 9 (17) |
| Free T4 <LLN | 5 (25) | 0 | 8 (44) | 10 (67) | 18 (34) |
| Total T3 <LLN | 2 (10) | 0 | 0 | 1 (6.7) | 1 (1.9) |
| Total T4 <LLN | 1 (5.0) | 0 | 0 | 0 | 0 |
| | | | | | |
| Thyrotropin <LLN and | n=2 | n=0 | n=2 | n=0 | n=4 |
| Free T3 >ULN | 1 (50) | 0 | 0 | 0 | 0 |

Smaller differences were seen in the Nonepilepsy controlled pool (I note that levothyroxine was among the most common concomitant medications in this pool, according to p. 45 of Dr. Doi's review). Dr. Doi notes that hypothyroidism can be associated with hyponatremia, hypercholesterolemia, hypertriglyceridemia and increased CPK, and in Table 90 (p. 138 of her review) she shows this to be the case for subjects with PCS values of low free T4, in more ESL subjects than in placebo subjects. Although the Sponsor concluded that subjects with abnormal TFTs were generally not symptomatic, Dr. Doi notes that the TEAE alopecia was reported in 0.6% of ESL subjects (27/4334), 8 of whom also had free T4 or free T3 < LLN. In the Phase 3 Epilepsy Controlled Pool, out of the 10 ESL subjects with the TEAE of alopecia, 4 ESL subjects (40%) had either low free T4 or T3 levels; out of the 3 placebo subjects with the TEAE of alopecia, all had free T4 ≥ LLN and 1 subject had free T3 levels < LLN but not in the PCS range. (She also notes larger differences between ESL and placebo for vertigo, diplopia, dizziness, and fall in subjects with low T4 vs subjects with normal T4; these symptoms are not typically associated with hypothyroidism and are common AEs for ESL). I agree with Dr. Doi that ESL use is associated with signs and to some extent symptoms of hypothyroidism and I agree with her recommendation to add this information in the Warnings and Precautions section of labeling.

### 2.2.5 Submission Specific Primary Safety Concerns

*Cardiac Disorders* – Dr. Doi finds that differences between ESL and placebo subjects in cardiac-related TEAEs in the Cardiac Disorders SOC were small in both the Phase 3 Epilepsy Controlled Pool (approximately 2% in each group) and the Nonepilepsy DB Pool (approximately 3% for ESL vs 2% for placebo) and difficult to attribute to ESL in

[9] Dr. Doi notes that in the Phase 3 Epilepsy Controlled Pool, TSH values were measured only in Study 304, and were drawn at baseline and at the end of the study along with T3 and T4. She notes that typically changes in TSH lag changes in T3/T4 by 4 weeks, and therefore additional measurements of TSH after study completion may have provided more complete information.

light of baseline differences in prior cardiac history and cardiac risk factors in the Nonepilepsy population (discussed in section 7.2.1.2 of Dr. Doi's review). Similarly, there were isolated serious cardiac events including syncope in the database, but these were confounded by the presence of risk factors.

Dr. Doi has reviewed ECG data from ECGs performed during the epilepsy, nonepilepsy, and Phase 1 trials, and the FDA Interdisciplinary Review Team (IRT) has reviewed the through QT Study 116. Based on those reviews, there is no evidence of QT prolongation with ESL. Dr. Doi discusses, however, that because there were small numbers of PCS ECG values in the Nonepilepsy Controlled Pool, it is difficult to make any conclusions about ECG values in that pool. Dr. Doi notes several concerns with the ECG datasets, summarized in the footnote below, that represent another example of quality issues requiring resolution during the review period, and that identified prior to filing, I believe would have been filing issues.[10] In Study 201, more ESL subjects than placebo (2.1% vs 0) had heart rate < 50 bpm and > 20% decrease from baseline. In each pool, and in Phase 2 Study 201, ESL subjects had an increase in PR interval more frequently than placebo subjects. In the Phase 3 Epilepsy Controlled Pool, Dr. Doi notes small differences (< 1%) between ESL and placebo subjects in incidences of increased PR interval (mean change of 2ms vs 0.6 ms), also seen in the Nonepilepsy Controlled Pool (7.2 ms vs 0.5 ms). There was a slightly higher frequency in ESL subjects vs placebo in the Epilepsy Phase 3 Controlled Pool of conduction abnormalities (13% vs 11%) and for Rhythm abnormalities (25% vs 24%), also seen in the Nonepilepsy DB Pool. Dr. Doi's evaluation of ESL subjects who developed PCS changes in QT and PR intervals did not identify concerning clinical events. She notes that information regarding AV block is included in the carbamazepine labeling. I agree that information regarding PR prolongation should be included in the prescribing information for ESL.

*Gastrointestinal Disorders* – A higher number of ESL subjects experienced TEAEs in this SOC than placebo subjects in both the Phase 3 Epilepsy Controlled Pool (25% vs 16) and the Nonepilepsy DB Pool (21% vs 15%). The TEAEs were driven by the PTs nausea and vomiting, for which a dose response relationship was observed for the combined terms in the Phase 3 Epilepsy Controlled Pool (6% for placebo, 11% for ESL 400 mg, 13% for 800 mg, and 19% for 1200 mg). There were SAEs as well as discontinuations in this SOC that occurred more frequently for ESL subjects than placebo in both pools. The median time to events in the ESL groups was 5 days for 1200 mg and 10.5 days for 800

[10] Only approximately three fourths of the ESL subjects had at least 1 post-dose ECG assessment in the Phase 3 Epilepsy Controlled Pool. The Sponsor states that some ECGs were not included in the analysis because they were considered uninterpretable in part due to a sometimes 4 year period between study completion and review of the ECGs by the central ECG overread, and faded tracings, poor quality of photocopies, leads not labeled, missing grids, paper speed, or voltage. In Study 304, ECGS were provided by some sites only as pdf files of ECG tracings. Dr. Doi notes that she considered 6 ECGs, considered uninterpretable by the Sponsor, that she felt were adequate enough to evaluate the ECG parameters. The Sponsor concluded that the number of uninterpretable ECGs is minimal and would not alter the overall assessment, and considered it not feasible to reevaluate ECGS deemed uninterpretable by the cardiac safety vendor (b) (4). Finally, when Dr. Doi asked the sponsor for an explanation of discrepancies in the number of subjects with ECG measurements in the Nonepilepsy Controlled Pool, the Sponsor reported a "programming error" that led to misclassification. The Sponsor provided corrected information.

mg, and 49 days for 400 mg vs 14.5 days for placebo, and the median duration of events (4-9 days) was similar to placebo (4 days). Out of a total of 15 subjects in both pools with SAEs of nausea and vomiting, Dr. Doi notes that the majority of events occurred during episodes of vertigo/dizziness, ataxia (n=8) usually during the first 2 weeks of ESL, or during hyponatremia (n=2). One subject developed acute on chronic renal failure as a result of severe nausea and vomiting. As severe events of nausea and vomiting appear to be related to episodes of vertigo/dizziness or ataxia, it does not need to be described separately.

*Other Organ Systems* - These are discussed on pages 149-151 of Dr. Doi's review. I agree with Dr. Doi that ESL does not appear be to be associated with renal, respiratory, or pancreatic disorders, or infectious diseases in the database. There was 1 each ESL subject in the database coded to Sjogren's syndrome, vasculitis/vasculitis cerebral (confounded by a history of positive anti-nuclear antibodies), and leukocytoclastic vasculitis/purpura, but no signal otherwise in the database for such immune system disorders.

### 2.2.6 Common Adverse Events

Dr. Doi shows a dose-response relationship for TEAEs for the Phase 3 Epilepsy Controlled Pool (placebo 58%, 400 mg 67%, 800 mg 71%, and 1200 mg 78% using the ADEVENTX dataset) as well as for the individual studies in this dataset. Most of the AEs were considered mild to moderate in severity. In the Phase 3 Epilepsy Controlled Pool, Dr. Doi shows on p. 159 of her review the AEs occurring most commonly (≥2%) and more frequently than placebo in any dose group. The most common and with the largest risk difference vs placebo were dizziness (22% overall vs 9% in placebo), somnolence (14% overall vs 8% in placebo, headache (13% overall vs 9% in placebo), and nausea (12% overall vs 5% in placebo, and diplopia (10% overall vs 2% in placebo), as well as vertigo (4% overall vs < 1% for placebo), vision blurred(5% overall vs 1% for placebo), vomiting (7% overall vs 3% for placebo), and ataxia(5% overall and 2% for placebo). The TEAEs in the Phase 3 Epilepsy Uncontrolled and Controlled Pool were similar to the controlled trials, but with more AEs in the SOC infections and Infestations including nasopharyngitis, influenza, and upper respiratory infection. In 201, the findings were similar, with TEAEs in ≥2 ESL subjects and greater than placebo in the SOCs of Ear and labyrinth disorders (including vertigo and ear buzzing), gastrointestinal disorders (including diarrhea, dry mouth, dyspepsia, nausea, and vomiting) and Nervous system disorders ( including concentration impaired, dizziness, headache incoordination, and somnolence), as well as hair loss, and hypertension. In Study 202, the more frequently reported TEAEs were upper respiratory tract infections and somnolence, and Dr. Doi notes that aggressive behavior, aggression aggravated, and psychomotor agitation were seen in 1 ESL subject each in the 7-11 y.o. group. In the Nonepilepsy DB Pool, incidence of developing TEAEs was higher for ESL than placebo. In that pool, the TEAEs with the largest risk difference were dizziness, somnolence, headache, and disturbance in attention, with a greater risk difference than in the epilepsy pool particularly for GGT increased and pruritus. In the Phase 1 pool, there was a greater incidence of TEAEs for ESL (69%) vs placebo (42%), and the SOCs with the highest incidence of TEAEs included nervous system disorders and gastrointestinal disorders.

Dr. Doi notes that 14 ESL subjects had the PT "unevaluable event"; these events do not support a particular signal.

### 2.2.7 Laboratory findings

The laboratory findings of concern to Dr. Doi are hematology, thyroid function tests (discussed in Section 7.3.4 of her review and in Section 2.2.4 of my memo), and hyponatremia and hypochloremia.

*Hematology* – Dr. Doi notes that missing values in WBC differentials in the bipolar studies (missing due to a variety of reasons ) preclude a comprehensive assessment of hematologic AEs such as neutropenia, lymphopenia, and eosinophilia, but that the percentage of subjects with missing values is low compared to the overall number of subjects (<5%). In the Phase 3 Epilepsy Controlled Pool, there were few subjects with PCS hematology values at consecutive visits. The incidences of clinically significant post-dose laboratory values were small and overall slightly higher in ESL than placebo subjects. There were hematology related SAEs in 6 ESL subjects vs placebo in the Phase 3 Epilepsy Controlled Study including 3 anemia, 3 leukopenia/lymphopenia, 2 thrombocytopenia, and 1 developing polycythemia, as well as 3 in the Nonepilepsy DB pool (vs 0 in placebo), 11 additional events in the OLE and Phase 1 and 2 studies, 4 of which were cytopenias, and 7 events in the postmarketing database including 3 thrombocytopenia events, 2 bycytopenia and other isolated events. There were no events coded to aplastic anemia or agranulocytosis. There were 2 cases coded to pancytopenia (1 in a patient in whom events resolved while continuing ESL and 1 with an underlying history of anemia in a patient during an episode of infection). ESL use was associated with higher frequency of decreases in RBC compared to placebo in both the Epilepsy Phase 3 Controlled Pool and the Nonepilepsy DB pool, in hemoglobin in the Phase 3 Epilepsy Pool, and in hematocrit primarily in the Nonepilepsy DB pool, as shown below as extracted from Dr. Doi's review.

**Table 109. Shifts from Normal for Hematology Parameters**

| Parameter | Phase 3 Epilepsy Controlled Pool | | | | Nonepilepsy Controlled Pool^ | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| | n | # shift (%) | n | #shift (%) | n | # shift (%) | n | #shift (%) |
| RBC low | 366 | 19 (5.2) | 878 | 57 (6.5) | 365 | 2 (0.5) | 1146 | 22 (1.9) |
| Hematocrit low | 382 | 6 (1.6) | 914 | 22 (2.4)* | 348 | 17 (4.9) | 1085 | 79 (7.3) |
| Hemoglobin low | 389 | 7 (1.8) | 906 | 28 (3.1)* | 328 | 31 (9.5) | 1024 | 86 (8.4) |

Though SAEs and TEAEs were related to hematologic parameters were rare, Dr. Doi recommends postmarketing surveillance for effects of ESL exposure on hematologic parameters, particularly erythrocytes. Of note, Tegretol has a boxed warning for aplastic anemia and agranulocytosis and Trileptal has information in the Warnings and Precautions section regarding hematologic events (rare postmarketing reports of pancytopenia, agranulocytosis, and leukopenia).

*Chemistry:* Changes in thyroid function tests and hepatobiliary parameters were discussed in Sections 7.3.4 of Dr. Doi's review and in Section 2.2.4 of my memo. Additional changes of concern, described below, are in sodium and chloride.

Bicarbonate values and magnesium values were only collected in some Phase 1 studies, and according to Dr. Doi the results did not show clinically meaningful differences in those values. However, those parameters were not collected in Phase 3 studies.

Dr. Doi identified quality issues with the chemistry parameters bilirubin, cholesterol, and glucose values. In response to an information request to clarify the discrepancies, the Sponsor reported that there had been incomplete integration of the data due to a programming error that omitted a portion of the data, and the Sponsor then reported multiple additional instances of this problem. This error was corrected. This is described in detail on p. 171-172 of Dr. Doi's review.

In the Phase 3 Epilepsy Controlled Pool, a higher percentage of ESL subjects than placebo developed hyponatremia (19% vs 6% for sodium ≤ 135 meq/L), and severe hyponatremia (sodium values ≤ 125 meq/L) occurred only in ESL subjects (1.1%). A higher percentage of ESL subjects than placebo subjects experienced decreases in sodium values > 10 meq/L (5.1% vs 0.7%) and consecutive low sodium values (1.4% vs 0), with a dose response relationship observed. Similar results were observed in the Nonepilepsy DB Pool. Hyponatremia SAEs and discontinuations occurred only in ESL subjects in both controlled pools. Dr. Doi notes that associated adverse events included somnolence, nausea, vomiting, disorientation, confusion, fall, vertigo, ataxia, diplopia, coordination abnormal, gait disturbance, dizziness and balance disorder. She also notes that concurrent hypochloremia was present in the subjects. She identified that the sodium values reported in the narratives that were collected during hospitalizations (some ≤ 125 meq/L) were not included in the integrated lab dataset, and that therefore the integrated lab dataset may underestimate the incidence of hyponatremia events, including severe hyponatremia. Many events occurred in patients who were also taking carbamazepine. Additional subjects with hyponatremia or blood sodium decreased were reported for ongoing studies and in the postmarketing database (including 8 cases with a concomitant seizure event). Dr. Doi finds that subjects with hyponatremia had a greater relative risk (RR) of TEAEs particularly in the SOCs Nervous System Disorders (RR 2.68 vs placebo) and Eye Disorders (RR 6.32 vs placebo) compared with subjects without hyponatremia where the relative risks were was approximately 1.8 and 2.6, respectively. Dr. Doi reports that hyponatremia developed as early as Study Day 3 and that normalization of serum sodium generally occurred within a few days after ESL dose reduction or discontinuation. Hypochloremia was also observed in the database, and Dr. Doi shows that the majority of ESL subjects (but not placebo subjects) who had chloride values ≤ 90 meq/L also had sodium values ≤ 130 meq/L. I agree with Dr. Doi that there is reasonable evidence of a causal relationship between ESL use and hyponatremia (and hypochloremia) that have resulted in severe, life-threatening complications. I agree that because of the serious nature of ESL-associated hyponatremia and the possibility of mitigating the risk, that hyponatremia be included in the Warnings/Precautions in the ESL label. Because of the association of metabolic alkalosis with these electrolyte abnormalities, and the absence of bicarbonate values in Phase 2 or 3 studies, I also agree with Dr. Doi that a postmarketing requirement should be considered to further characterize whether there is an association between ESL use and acid-base abnormalities.

Dr. Doi has reviewed CPK test outlier results for the Phase 3 Epilepsy Controlled Pool and finds a higher percentage of ESL subjects than placebo developed extremely high CPK values. Increases to 3-5X ULN were observed in 1.5% of ESL and 0.2% of Placebo; increases > 5 X ULN were observed in 0.6% of ESL and 0.2% of placebo. A dose response relationship was not observed for increases 3-5X ULN, and although a dose response appeared to be present for > 5X ULN, this was based on very few subjects (6 in the ESL group: 3 for 800 mg and 3 for 1200 mg). There were no AEs coded to the PT rhabdomyolysis in the completed clinical trials or reported by the Sponsor for ongoing studies or in the postmarketing database.

Based on Dr. Doi's review, ESL does not appear to affect lipids to a significant extent, with some shifts from normal to borderline but without a dose-response relationship observed. Changes in other chemistry parameters were similar in ESL and placebo. ESL does not appear to be associated with changes in urinalysis parameters that were measured (RBC, WBC, bacteria casts, crystals, epithelial cells, yeast/fungi, and pH and specific gravity in specific studies).

2.2.8 Vital Signs

Temperature was not included in vital sign determinations in the ISS. There are no trends observed in changes in systolic and diastolic blood pressure. The number of subjects with orthostatic measurements precludes the ability to make any conclusions about the effect of ESL on orthostatic changes in vital signs. I agree with Dr. Doi no conclusions can be made regarding an adverse effect of ESL on weight loss based on the small risk differences (≤ 1%) for ESL vs placebo.

2.2.9 Other findings and considerations

*Dose- and Time-Dependency for AEs* – Dr. Doi notes that there was a dose response observed for safety issues, as previously noted, but she highlights the difficulties in interpreting dose response in trials where titration to the targeted dose occurs, as any AE occurring during titration may have occurred at a dose lower than the final target dose for a subject. She notes that the highest relative risk of AEs occurred during the titration period but that rates higher than placebo continued to occur during the maintenance period. Dose initiation at ESL 800 mg in the Phase 3 Epilepsy Controlled Pool was associated with a much higher incidence of TEAEs vs dose initiation at ESL 400 mg. I agree with Dr. Doi that based on this, ESL should be initiated at the 400 mg dose and titrated to the appropriate final dose to minimize incidence of TEAEs.

*Drug Demographic Interactions:* Dr. Doi analyzed the relative risk of TEAEs by Demographics in the Phase 3 Epilepsy controlled pool. I agree with her that due to small numbers and overlapping confidence intervals it is difficult to draw conclusions regarding age, gender, race, region, or BMI for the development of AEs with ESL use vs placebo. I also note that the Phase 3 Epilepsy group labeled "elderly" is ≥ 60 y.o. and only included 58 subjects of whom 43 (63%) were ≤ 65 y.o., and this does not truly reflect an elderly population. Dr. Doi notes that in an ongoing elderly epilepsy study 401, the Sponsor reported that 46% of subjects discontinued prematurely, a rate much

higher than either of the controlled pools (up to 17.5%). The most frequent TEAEs included dizziness, somnolence, bronchitis, and hyponatremia. I agree with Dr. Doi that elderly patients are more likely to have an estimated creatinine clearance of < 50 ml/min, in the range of moderate renal impairment, and may require dose adjustment.

In the Phase 3 Epilepsy Controlled Pool, most of the ESL group was treated at baseline with 2 AEDs (69%). I agree with Dr. Doi that with overlapping confidence intervals, it is difficult to draw conclusions regarding concomitant AEDs as a risk factor for development of AEs with ESL vs placebo.

2.2.0 Additional Safety Evaluations
*Human Carcinogenicity*: In the All Studies Pool (including Study 303), there were 13 cases of malignant neoplasms. Dr. Doi notes that most (62%) were either diagnosed early in the study (Day 1 in 1 subject) or in subjects with related symptoms or a cancer diagnosis prior to ESL exposure (7) and that the remaining cases did not establish a pattern of types of neoplasms with only single cases of each, except for 2 cases of different types of lymphoma. There are disparate cancers in the ongoing studies, and no postmarketing reports of neoplasm. I agree it is difficult to establish a causal role of ESL in carcinogenicity.

*Human Reproduction and Pregnancy Data:* Dr. Doi notes that the Sponsor reported no fetal malformations in mice, rats, or rabbits, although maternal toxicity and secondary fetal toxicity was seen with increase post-implantation loss along with lower offspring survival, developmental delays, delayed ossification, and reduced fetal weight.

The Sponsor reported a total of 8 pregnancies (all ESL exposed) in the entire safety database resulting in 4 healthy births and 4 induced abortions. Dr. Doi identified additional pregnancies listed in the PSURs that the Sponsor submitted with the NDA (3 that occurred before the cut-off date for the ISS) and there was an additional pregnancy not included in the Sponsor's list because the subject was described under deaths (likely due to seizures 6 weeks after ESL discontinuation). These additional cases accounted for 4 healthy births, 1 spontaneous abortion, and the maternal death. There were 6 additional pregnancies in the ongoing studies and 4 in the postmarketing data resulting in 1 infant with multiple congenital anomalies with genetic testing revealing chromosomal abnormality whose mother had taken ESL for < 4 weeks (with last menstrual period 1 month prior) and who was also taking lamotrigine and lorazepam; 3 spontaneous abortions; 2 healthy births; 1 induced abortion; and 3 outcome unknown as of 7/1/13. I agree with Dr. Doi that with a small number of pregnancies, the assessment of the causal relationship between ESL exposure and spontaneous abortions is difficult.

*Overdose, Drug Abuse Potential, Withdrawal, and Rebound:* Dr. Doi notes that there were 5 cases of overdose in the All Studies Pool; 4 were accidental and 1 was intentional. In only 1 case was the dose reported and it was 800 mg/day instead of 400 mg. Dr. Doi found 8 subjects in the dataset with the PT drug toxicity and 4 ESL subjects with the PT poisoning. The symptoms appear to be extensions of the effects observed in the AE experience. The largest intentionally administered dose of ESL was 3600 mg in a Phase

1 Study, and resulted in a high incidence of dizziness, nausea, headache, vomiting leading to discontinuation, and fatigue. There was an IND safety report from an ongoing study with an accidental overdose with events that may have represented a seizure that could have been temporally related to the overdose of 2400 gm or 3200 mg. In postmarketing reports, the Sponsor reported 35 cases of overdose (later reported as 24 cases), with the highest reported dose of 3200 mg with no adverse outcome reported. One subject reportedly was a completed suicide by overdose (dose unknown).

2.2.10 Postmarket Experience

As previously noted, ESL was granted marketing authorization by the European Commission on April 21, 2009 and is approved in 36 countries. It is estimated that there have been 12, 279 patient-years of exposure. There have been 373 uniquely identified postmarketing safety reports containing 720 individual adverse even. SOCs with the most AEs were nervous system disorders (particularly dizziness and seizures), metabolism and nutrition disorders (98/107 were hyponatremia), skin and subcutaneous tissue disorders (15/95 were rash), injury, poisoning, and procedural complications (30 medication error and 24 overdose), general disorders and administration site conditions (20/59 were fatigue), and investigations (27/55 were blood sodium decreased). The postmarketing spontaneous reports did not reveal new safety concerns.

2.2.11 Labeling and Post-Marketing Risk Management Plan

Recommendations for labeling will be found in the draft document in the e-room.

I agree with Dr. Doi's recommendation for a postmarketing requirement to evaluate the association between ESL use and acid-base abnormalities in light of the hyponatremia and hypochloremia that have been observed and the lack of bicarbonate measurements in the Phase 3 trials.

I also agree with Dr. Doi's recommendation for a postmarketing requirement to evaluate genetic risk factors for developing severe cutaneous adverse reactions, specifically the association with the presence of HLA alleles. Identifying predictive risk factors for sever cutaneous adverse reactions is especially important as those risk factors become identified for other AEDs and options without those risks in a specific patient are necessary. I recommend consulting with the Office of Clinical Pharmacology Genomics group for guidance in this area.

I agree with Dr. Doi's recommendation for expedited reporting of any cases of severe DILI along with annual analyses and reports of DILI. The Sponsor should be given explicit guidelines for follow-up of any such reports.

I agree with Dr. Doi's recommendation for postmarketing surveillance for anemia. There were small hematologic changes and few related TEAEs and SAEs, but there is information in the Warnings and Precautions sections of Tegretol and Trileptal labeling related to this issue. Postmarketing surveillance would include quarterly reporting of anemia events. The quarterly reporting should include a cumulative analysis of these events.

## 3 Conclusions

Many significant quality issues were identified in this NDA after submission. Dr. Doi spent a great deal of review effort identifying and ensuring that these quality issues were addressed, allowing for her review of the NDA. Dr. Doi has not identified any safety issues in her review of the safety data that would prevent approval of ESL with appropriate labeling. Recommendations for postmarketing evaluation of specific safety signals are outlined in section 2.1.11, above.

Because of the significant quality issues in the submission, and the effort required during the review period to correct these issues, I recommend that prior to any future submission, the sponsor consult with a third party to ensure the quality of the review. The Sponsor should be reminded, prior to submission of any supplement to this NDA, of the types of quality issues that have been identified in this submission and should be reminded that we do not expect to see such issues in any future submission.

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SALLY U YASUDA
09/16/2013

# CLINICAL SAFETY REVIEW

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 022-416 |
| Priority or Standard | Resubmission |
| Submit Date(s) | February 10, 2013 |
| Received Date(s) | February 11, 2013 |
| PDUFA Goal Date | November 8, 2013 (extended by major amendment) |
| Division / Office | Division of Neurology Products<br>Office of New Drugs |
| Reviewer Name(s) | Mary Doi, M.D., M.S. |
| Review Completion Date | September 6, 2013 |
| Established Name | Eslicarbazepine acetate |
| (Proposed) Trade Name | To be determined |
| Therapeutic Class | Anticonvulsant |
| Applicant | Sunovion Pharmaceuticals Inc. |
| Formulation(s) | Oral tablet |
| Dosing Regimen | 400 mg – 1200 mg daily |
| Indication(s) | Adjunctive therapy in the treatment of partial-onset seizures |
| Intended Population(s) | 18 years of age and above |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

This is the safety review of NDA 022-416 (eslicarbazepine acetate) as of August 1, 2013. The efficacy of eslicarbazepine acetate in the adjunctive therapy of partial-onset is being reviewed by Dr. Teresa Podruchny. Final recommendations on approval of this application will be provided by Drs. Podruchny (primary reviewer) and Hershkowitz (CDTL).

## 1.2 Risk Benefit Assessment

There are many FDA-approved medications for partial-onset seizures with or without secondary generalization, but none of these treatments are completely efficacious in all patients. In addition, the adverse reactions (hepatic, hematologic, dermatologic, teratogenic, etc.) of these approved treatments can limit their use. For these reasons, additional treatments are needed for partial-onset seizures.

An important consideration in the evaluation of eslicarbazepine acetate (ESL) is that there were extensive deficiencies in the structure of this resubmitted application, including deficiencies in the accuracy, reliability, and presentation of the data. In addition to laboratory data missing from the ISS datasets, there were many discrepancies, programming errors, coding omissions, key information missing from the narratives, and narratives of subjects with adverse events of special interest missing from the ISS that were identified by the Division. In response to the Division's information requests, the Sponsor submitted a multitude of safety amendments that corrected and/or explained these deficiencies.

Several safety issues have been identified in this application with evidence of a dose response. However, based on my review of the Sponsor's submission along with all of the safety amendments, I did not identify any safety issues that would preclude approval. The safety of eslicarbazepine acetate appears to be acceptable once safety concerns are mitigated by the strategies outlined below. The proposed maintenance dose of 800 mg to 1200 mg per day (with treatment initiation with a dose of 400 mg/day) in patients aged 18 years and older is acceptable from a safety point of view.

I recommend that the following information be incorporated into the prescribing information for eslicarbazepine acetate:

- Indications and Usage: Adult patients (≥18 years old)
- Warnings and Precautions for the following serious adverse reactions:
  - Drug-Induced Liver Injury

  - Serious Dermatologic Reactions
  - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
  - Anaphylaxis and Angioedema
  - Hyponatremia and Hypochloremia
  - Neurologic Events
    - Dizziness/Gait Disturbance
    - Somnolence/Fatigue
    - Cognitive dysfunction
    - Visual changes
    - Fall/Injuries
  - Thyroid Function Test Changes
  - PR prolongation
  - Suicidal Behavior and Ideation (required by the Division for all antiepileptic drugs)
  - Withdrawal of Antiepileptic Drugs (see Dr. Podruchny's review for further details)
- Dosage and Administration:
  - Dose adjustment in patients with moderate and severe renal impairment (per Clinical Pharmacology recommendations)
- Medication Guide because of the Suicidality warning required by the Division for all antiepileptic medications

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

## 1.4 Recommendations for Postmarket Requirements and Commitments

The following safety issues should be further studied as Postmarketing Requirements:
- Genetic risk factors for developing severe cutaneous adverse reactions, specifically the association with the presence of HLA alleles (e.g., HLA-B*1502, HLA-A*3101)
- Association between ESL use and acid-base abnormalities

For the safety issue of drug-induced liver injury, I recommend expedited reporting of any cases of severe DILI along with annual analyses and reports of DILI.

Additionally, postmarketing surveillance is recommended for anemia.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

The chemical name of eslicarbazepine acetate (ESL) is (S)-10-Acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide. It is a member of the family of dibenz[b,f]azepine antiepileptic drugs which includes the approved drugs carbamazepine (first-generation) and oxcarbazepine (second-generation). Eslicarbazepine acetate shares with carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitution but is structurally different at the 10,11 position. Eslicarbazepine acetate is primarily metabolized to eslicarbazepine which is the active metabolite. Oxcarbazepine is also metabolized to eslicarbazepine (also called (S)-licarbazepine) and (R)-licarbazepine.

Eslicarbazepine acetate and its metabolites block voltage-gated sodium and T-type calcium channels. The precise mechanism by which eslicarbazepine acetate exerts its antiepileptic effects has not yet been fully established.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are many currently available drugs approved for the adjunctive therapy of partial-onset seizures. Please see the list provided in the efficacy review performed by Dr. Podruchny.

## 2.3 Availability of Proposed Active Ingredient in the United States

ESL, carbamazepine, and oxcarbazepine are structurally similar. ESL and oxcarbazepine have the same active metabolite, eslicarbazepine, although oxcarbazepine is also metabolized to R-licarbazepine. Oxcarbazepine is available in the US as Trileptal® and carbamazepine is available as Tegretol®, Carbatrol®, and Equetro®; both are available also as generic drugs.

## 2.4 Important Safety Issues With Consideration to Related Drugs

The prescribing information for Tegretol® includes the following information (in the last approved labeling dated 3/06/13):

- Boxed Warning:
  - Serious Dermatologic Reactions and HLA-B*1502 Allele
  - Aplastic Anemia and Agranulocytosis
- Warnings section:
  - Hypersensitivity Reactions and HLA-A*3101 Allele

  - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multiorgan hypersensitivity
  - Suicidal Behavior and Ideation
  - General: mild anticholinergic activity (intraocular pressure)
    - activation of latent psychosis (relationship to tricyclic compounds)
    - avoided in patients with hepatic porphyria
    - withdrawn gradually to minimize increased seizure frequency
- Precautions section:
  - General:
    - Use with caution in patients with a mixed seizure disorder due to increased frequency of generalized convulsions
    - AV heart block (second and third degree block)
    - Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure
  - Laboratory Tests:
    - Hyponatremia
    - Thyroid function test decreases
    - Recommended testing for: HLA-B*1502 genotyping, blood counts, liver tests, eye examinations, urinalysis, BUN, blood levels

The prescribing information for Trileptal® includes the following information in the Warnings and Precautions section (of the last approved labeling dated 2/08/13):

- Hyponatremia
- Anaphylactic Reactions and Angioedema
- Patients with a past history of Hypersensitivity Reaction to Carbamazepine
- Serious Dermatologic Reactions
- Suicidal Behavior and Ideation
- Withdrawal of AEDs
- Cognitive/Neuropsychiatric Adverse Events (cognitive symptoms, somnolence/fatigue, and coordination abnormalities)
- Multi-Organ Hypersensitivity
- Hematologic Events (rare postmarketing reports of pancytopenia, agranulocytosis, leukopenia)
- Seizure control during pregnancy
- Laboratory tests (decreases in serum sodium levels and $T_4$)

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

For detailed presubmission regulatory activities related to this submission, the reader is referred to Dr. Podruchny's clinical review of efficacy.

Briefly, the original IND for ESL (IND 67466) for the treatment of refractory partial-onset epilepsy was opened on November 2006. On March 29, 2009, Sepracor Inc. submitted

a New Drug Application (NDA 022-416) for ESL to the FDA for the proposed indication of adjunctive treatment of patients with refractory partial-onset epilepsy. Sepracor Inc. received a Complete Response (CR) letter on April 30, 2010 from the Division due to "significant and serious deficiencies in [the] application and/or data [that] ma[d]e it impossible to reach any definitive conclusions about the safety and effectiveness of eslicarbazepine acetate." The clinical deficiencies fell into 2 general categories: 1) deficiencies in the conduct and documentation of the studies, based on inspections of several study sites, and 2) deficiencies in the structure of the application, including deficiencies in the accuracy, reliability, and presentation of the data.

The NDA application was resubmitted on August 31, 2012 by Sunovion Inc. in response to the Division's Complete Response letter. However, the Division did not consider this resubmission to constitute a complete response to the CR letter and an Acknowledge Incomplete Response letter was sent to Sunovion Inc. on November 2, 2012 along with multiple teleconferences and email communications to provide additional clarifications requested by the Sponsor. Based on a preliminary review of the August 2012 submission, there were persistent deficiencies in the structure of the application, including deficiencies in the accuracy, reliability, and presentation of the data. Mainly, the adverse event datasets were insufficient and did not contain a comprehensive collection of all of the adverse events that were recorded in various other documents in the submission (e.g., narratives, CRFs). Examples of adverse events that were missing from the datasets included signs and symptoms that were subsumed under "umbrella" terms or "diagnoses" (e.g., nausea and gait disturbance subsumed under vertigo), verbatim terms that included falls but were not coded to falls, and adverse events suggestive of causality (e.g., fall, seizure, accident) were missing in subjects who sustained fractures. There was also an example of a subject with an event that was identified as meeting criteria for a serious adverse event (in the narrative), Stevens-Johnson syndrome, but was not designated as a serious event in the dataset. Furthermore, narratives from the original NDA and the resubmission did not provide the same supportive information. Additionally, there were numerous other issues regarding the presentation of the safety data.

The NDA application was resubmitted on February 10, 2013 by Sunovion Inc. The original PDUFA goal date of August 10, 2013 was extended to November 8, 2013 by a major amendment.

## 2.6 Other Relevant Background Information

For additional background information and presubmission regulatory activities, the reader is referred to Dr. Podruchny's clinical review of efficacy.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

For detailed information on submission quality and integrity, the reader is referred to Dr. Podruchny's clinical review of efficacy (particularly in regard to the initial submission of this NDA in 2009). General information regarding the quality and integrity of the clinical safety portion of the most recent submission of this NDA (February 10, 2013) is included below. Additional information regarding specific deficiencies and discrepancies are noted in appropriate sections throughout this review.

The resubmitted application (2/10/13) was accepted for review because the specific issues that were previously noted as deficiencies and detailed in the Acknowledge Incomplete Response letter (11/2/12) were corrected by the Sponsor. However, during the review process, numerous additional deficiencies and discrepancies were identified in this application requiring clarification by the Sponsor.

There were a total of 23 Safety Information Amendments submitted by the Sponsor (a total of over 5000 pages) in response to the Division's safety team's 14 information requests that included approximately 65 separate questions/items. Some examples of the information requests are listed below:

- narratives, case report forms, postmarketing reports, and additional follow up information for key subjects (including serious adverse events and deaths) which were required to characterize important adverse events
- patient-time exposure data
- dose-dependency data for adverse events for the pooled groups that included open-label extension trials
- clarifications on the many discrepancies in the enumeration of subjects in the ISS
- pregnancies not reported in the ISS by the Sponsor but included in the most recent PSUR
- ECG data not reported in the ISS for approximately ¼ of the ESL subjects in the Phase 3 Epilepsy controlled studies
- additional analyses for laboratory/vital sign/ECG measurements and for the ongoing studies (described further in sections of this review)

This application's most significant deficiency was the occurrence of both missing and incorrect data in the integrated analysis datasets. The analysis laboratory datasets had to be resubmitted twice by the Sponsor due to missing or incorrect laboratory data along with the resubmission of the following analysis datasets: medical history (ADMH), physical examination (ADPE), vital sign (ADVS), and adverse events of special interest (ADSI, ADIEVNT, ADSIEVTX). The following paragraphs provide more detailed information regarding these events.

After missing laboratory values were initially identified by the reviewer (e.g., 40% of ESL subjects lacked total bilirubin, glucose, and total cholesterol values in the Phase 3 Epilepsy Controlled Pool), an information request was sent to the Sponsor to "[i]dentify and list (by study) any other laboratory, vital, or ECG values that are missing from the ISS analysis datasets. Submit new updated analysis datasets and analyses that include these missing values." In the Sponsor's Safety Information Amendment dated 5/20/13, the Sponsor confirmed that "[i]ncomplete integration of the data regarding glucose, bilirubin and cholesterol occurred due to a programming error that did not identify differences in the nomenclature for these tests (e.g. bilirubin versus total bilirubin) and therefore omitted a portion of the data [from Study 304] in the raw datasets from the integrated dataset…Following a systematic review of the programming for laboratory parameters, we also noted similar instances of incomplete integration had occurred for the following: Total protein, absolute counts of WBC differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) from study 304, GGT values from study 301 Part 4, and urine microscopy parameters (bacteria, casts, crystals, epithelial cells, RBC, WBC) in studies 101, 102 and 130…We confirm that the no vital signs or ECG values are missing from the ISS analysis datasets…No other laboratory values are missing from the ISS analysis datasets."

However, subsequent to the 5/20/13 amendment, additional missing laboratory values were identified by the reviewer for a subject in the Phase 1 Study 114. In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 6/22/13 that included the following information: "While researching the response for this question which was submitted June 14, 2013 (NDA Sq.0098), it was discovered that an incorrect subject identification variable was used during the ISS data integration process of the raw data for labs, vital signs, medical history, and physical exams for the subjects in study 2093-114. Table 1 maps how the subjects' data for study 2093-114 were misaligned in the integrated datasets ADLAB, ADMH, ADPE, and ADVS. For example, lab data for subject 2093114-000-00008 was misassigned to subject 2093114-000-00005. Thus, all data are present in the integrated datasets, but for the indicated datasets, they are identified with the incorrect subject identifier."

*Comment: These corrected datasets provided important information for a subject with a potential case of a significant adverse event (DRESS). Furthermore, a few additional subjects were identified to have had special interest events of hyponatremia and drug-induced liver injury.*

The Sponsor included the following comments in this Safety Information Amendment dated 6/22/13: "The scope, size, and complexity of data integration for this submission – spanning more than 50 studies and study parts, utilizing dozens of differing dataset structures from a variety of CROs – has been a significant challenge. We have therefore made every attempt to thoroughly research and explain any and all errors as they come

to light, and provide revised analyses, tables, and datasets, as appropriate, in an attempt to facilitate the Division's understanding of these situations and their impact on the overall submission."

It is important to note that additional missing laboratory data was identified by the reviewer in the revised laboratory datasets that were submitted on 6/22/13. WBC differentials in some of the nonepilepsy studies that were reported as percentages in the CRFs instead of absolute counts were not integrated and, therefore, missing from the analysis datasets. In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 8/1/13 and explained that they "elected to exclude the WBC differentials for these studies from the integrated dataset" and confirmed that the missing WBC differentials were limited to the 3 bipolar studies (studies 203, 204, and 205). The Sponsor justified their decision to exclude these values from the integrated dataset due to "challenges in accurate interpretation of WBC differential data from these studies" and "analysis of medical risk in context of other data." The Sponsor gave multiple examples of highly variable results between sites, within sites and within multiple reports for an individual subject. Furthermore, the Sponsor stated that the missing WBC differential data constitutes data from approximately 30 subjects, "which is small in comparison to the data available for 1294 ESL treated subjects from nonepilepsy studies and 1021 ESL treated subjects from epilepsy studies."

*Comment: However, using the Sponsor's ADLAB integrated laboratory dataset, I identified that while all of the ESL subjects had WBC counts measured, approximately only one-fourth of ESL subjects (25.0-30.4%) had WBC differentials reported (in absolute values for basophils, eosinophils, lymphocytes, monocytes, and neutrophils). Therefore, 70-75% of the ESL subjects in the bipolar studies (more than 100 subjects) were missing WBC differentials rather than 30 subjects (as reported by the Sponsor above). However, the percentage of subjects with missing WBC differentials remains low compared to the overall number of ESL-treated subjects (<5%).*

Furthermore, in addition to the laboratory data missing from the integrated laboratory datasets and many programming errors, there were many examples of preferred terms missing from the adverse events datasets (coding omissions) and even an example of information missing from the narrative (information regarding a death that was included in the original NDA but not the resubmission, subject 302-395-80794 described further in Sections 7.3.1 and 7.6.1).

Therefore, there were persistent deficiencies in the structure of this resubmitted application, including deficiencies in the accuracy, reliability, and presentation of the data. The magnitude and extent of the deficiencies in the analysis datasets (in addition to the many other discrepancies and deficiencies) are very concerning and worrisome. It is definitively known that data from 6 studies (12% of all of the studies) were incorrectly integrated into the ISS datasets. Even though the deficiencies were

identified by the Division and corrected for this review, the potential for additional unidentified deficiencies cannot be ruled out because of the difficulty in identifying missing or incorrect data.

### 3.2 Compliance with Good Clinical Practices

For detailed information on compliance with good clinical practices, the reader is referred to Dr. Podruchny's clinical review of efficacy.

### 3.3 Financial Disclosures

For detailed information on financial disclosures, the reader is referred to Dr. Podruchny's clinical review of efficacy.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The reader is referred to the Chemistry, Manufacturing and Controls (CMC) review.

### 4.2 Clinical Microbiology

Not applicable.

### 4.3 Preclinical Pharmacology/Toxicology

The executive summary of Dr. Toscano's 2009 Pharmacology/Toxicology review of the initial NDA submission included the following information:

"With the exception of the deficiency discussed in Section 1.1.2 of this review, NDA 22416 contains an adequate, non-clinical assessment of the pharmacology and toxicology of eslicarbazepine acetate (BIA 2-093). Although eslicarbazepine acetate has been demonstrated by the Sponsor to be both a teratogen (cleft and irregular ridging of the palate, exencephaly, increased number of vertebrae) and a carcinogen (hepatocellular carcinoma) in nonclinical studies, the overall nonclinical toxicity profile of eslicarbazepine acetate is consistent with other FDA-approved antiepileptics. With this in mind, it is the opinion of the Reviewer that there are no non-clinical safety signals that would preclude the approval of eslicarbazepine acetate for treatment of partial-onset seizures in adults with epilepsy. However, as a condition of approval, it is the Reviewer's recommendation that the Sponsor should complete, as a post marketing requirement (PMR), a study investigating the mutagenic and clastogenic potential of the

main human metabolite, eslicarbazepine, in both the in vitro mouse lymphoma mutation assay and the in vitro cytogenetic assay in Chinese Hamster Ovary (CHO) cells."

The reader is referred to Dr. Toscano's review of the resubmission for updated information.

## 4.4 Clinical Pharmacology

For details on the Clinical Pharmacology of ESL, the reader is referred to the Clinical Pharmacology review. The following information has been excerpted from the applicant's overview of clinical pharmacology in the clinical overview and from the proposed Prescribing Information.

The proposed maintenance dose is 800 mg to 1200 mg per day, given as a single daily dose in patients aged 18 years and older. The sponsor proposes treatment initiation with a dose of 400 mg/day, increasing in increments of 400 mg/day at weekly intervals. For some patients, therapy may be initiated at 800 mg once daily.

### 4.4.1 Mechanism of Action

Please see Section 2.1 of this review.

### 4.4.2 Pharmacodynamics

The Sponsor reports that ESL demonstrates anticonvulsant effects in animal seizure models with protection against electrically induced seizures and against kindled seizures in the maximum electroshock test in mice. The reader is referred to Pharmacology/Toxicology review by Dr. Toscano for further details.

### 4.4.3 Pharmacokinetics

The following information was included in the overall summary of clinical pharmacology and biopharmaceutics section from the Clinical Pharmacology Review for the 2009 NDA submission by Dr. Veneeta Tandon. Please refer to the Clinical Pharmacology review for the resubmission for additional details and updates.

The pharmacokinetics of eslicarbazepine are linear and dose-proportional, in both healthy subjects and patients, in the dose range of 400 to 1200 mg/day.

Absorption

- Eslicarbazepine acetate (ESL) is a prodrug of eslicarbazepine. Following oral administration, plasma concentrations of the prodrug usually remain at undetectable levels. It rapidly forms the major active metabolite (S)-licarbazepine or

eslicarbazepine. The pharmacokinetics is mainly described in terms of this active species, which represents ~95% of overall plasma exposure.

- Peak plasma concentrations ($C_{max}$) of eslicarbazepine are attained 1-4 hours post-dose.
- Steady-state plasma concentrations attained after 4 to 5 days of once-daily dosing.
- Bioavailability is assumed to be high because the amount of metabolites recovered in urine corresponded to more than 90% of ESL dose.
- Food has no effect on ESL or eslicarbazepine pharmacokinetics.

Distribution

- The binding of eslicarbazepine to plasma proteins is relatively low (<40%) and independent of concentration.
- Tissue distribution of eslicarbazepine is extensive as evidenced by a high apparent volume of distribution ($V_d/F$).

Metabolism

- Eslicarbazepine acetate is rapidly and extensively metabolized to its major active metabolite eslicarbazepine by hydrolytic first-pass metabolism in the presence of hydrolase. Eslicarbazepine corresponded to approximately 91% of the sum of all circulating drug entities (using $AUC_{0-24}$ as a measure of systemic exposure) and to approximately 95% of the sum of the active compounds (ESL, eslicarbazepine, (R)-licarbazepine and oxcarbazepine).
- Minor metabolites in plasma are (R)-licarbazepine (4%) and oxcarbazepine (<1%), which are known to be pharmacologically active. Other metabolites that are pharmacologically inactive include the glucuronic acid conjugates of ESL, eslicarbazepine, (R)-licarbazepine and oxcarbazepine. Altogether, the plasma drug glucuronides (ESL-GLU, eslicarbazepine-GLU, (R)-licarbazepine-GLU, and oxcarbazepine-GLU) corresponded to only approximately 3% of total systemic drug exposure in healthy subjects.

Elimination

- ESL metabolites are eliminated from the systemic circulation, primarily by renal excretion, in the unchanged and glucuronide conjugate forms (two thirds (67%) in the unchanged form and one third (33%) after conjugation with glucuronic acid). In total, eslicarbazepine unchanged and its glucuronide form corresponds to 92% of total drug material excreted in urine.
- In healthy subjects, the renal clearance of eslicarbazepine (approximately 20 mL/min) is substantially lower than glomerular filtration rate (80-120 mL/min), suggesting that renal tubular reabsorption occurs.
- The apparent half-life of eslicarbazepine was 10-20 hrs and 13-20 hrs for healthy subjects and epileptic adult patients, respectively.

# 5 Sources of Clinical Data

NDA 022-416 was resubmitted on February 11, 2013. During the review cycle, a large number of FDA informational requests were required due to the application's many deficiencies and inconsistencies (described in more detail in Section 3.1 above). The Sponsor responded diligently to these informational requests. The dates of the Safety Information Amendments are listed below. Unless otherwise noted, this review covers information submitted to NDA 022-416 up to August 16, 2013.

Safety Information Amendments were submitted by the Sponsor on the following dates in 2013:

February 20, 25, 27
March 4, 8, 11, 21, 27, 28
April 8, 19
May 7, 20
June 5, 10, 11, 17, 21, 22, 27
July 1
August 1, 16

The integrated summary of safety (ISS) for ESL includes data from 53 completed studies: 11 studies performed in the primary indication of epilepsy, 9 studies performed in other non-epilepsy indications (bipolar disorder, neuropathic pain, migraine, and fibromyalgia), and 33 Phase 1 studies.

## 5.1 Tables of Studies/Clinical Trials

The tables in Appendix 1 list all of the completed studies in the epilepsy population (11) and non-epilepsy population (9) along with the Phase 1 studies (33), and ongoing studies (18).

## 5.2 Review Strategy

This review focuses on the safety of oral ESL in the epilepsy population, non-epilepsy population (bipolar disorder, neuropathic pain, migraine, and fibromyalgia), and clinical pharmacology studies. Safety will be presented for deaths, serious AEs, discontinuations due to AEs, AEs of interest, common AEs, laboratory and ECG evaluations, and vital signs. The efficacy of oral ESL as adjunctive therapy in the treatment of partial-onset seizures was evaluated by Dr. Podruchny.

## 5.3 Discussion of Individual Studies/Clinical Trials

The detailed characteristics of the studies are presented in the tables in Appendix 1 of this review. A summary of the 53 completed studies is provided below. Thirty-six

studies were included in the original NDA review and 17 new studies are included in this NDA resubmission, including one new Phase 3 epilepsy double-blind study (Study 304).

The epilepsy development program included the following 11 studies (see Table 1):

- Four double-blind (DB) Phase 3 studies:
    - 301 Part 1
    - 302 Part 1
    - 303 Part 1
    - 304 Part 1
- Five open-label extension (OLE) studies for long-term safety and efficacy data:
    - 301 Parts 2, 3, 4
    - 302 Part 2
    - 303 Part 2
- Two Phase 2 studies: 201 (adult) and 202 (pediatric)

*Comment: In ISS Table 7.1, I noted for Study 303 that "patients completing Part 2 could participate in a further study extension by continuing until marketing authorization was obtained or clinical development was discontinued." However, Study 303 Part 3 was not listed as either a completed or ongoing study by the Sponsor. In the Safety Information Amendment dated 3/28/13, the Sponsor confirmed that subjects completing Part 2 could continue to receive eslicarbazepine acetate under the local regulations governing compassionate use. However, the Sponsor stated that the receipt of ESL under the compassionate use regulations was not considered part of Study 303, and this data was not included in the ISS.*

The following 9 studies evaluated ESL for other indications:

- Bipolar disorder:
    - 2 double-blind studies (203 and 204)
    - 1 OLE study (205)
- Neuropathic pain (diabetic or postherpetic neuropathy):
    - 2 double-blind studies (206 Part 1, 207 Part 1)
    - 2 OLE studies (206 Part 2, 207 Part 2)
- Migraine headache: 1 double-blind study (209)
- Fibromyalgia: 1 double-blind study (210)

The following 33 Phase 1 studies evaluated ESL:

- Bioavailability and bioequivalence:
    - Studies 103, 104, 109, 110, 115, 117, 122, 130, 155
- PK and initial tolerability: Studies 101, 102, 113, 116, 118, 127
- Effects of intrinsic factors on PK: Studies 105, 111, 112
- Effects of extrinsic factors on PK:
    - Studies 106, 107, 108, 114, 119, 120, 121, 124, 125, 126, 128, 129, 150
- PK and PD: Studies 123, 153

*Comment: Of note, in response to the CSS Division's information request dated 5/21/13, the Sponsor submitted a Safety Information Amendment on 6/10/13 that stated that "upon review of ISS [tables], we noted an error in which Study 106 is listed as evaluating a healthy normal population. In fact, this study enrolled subjects with epilepsy and should have been noted in ISS [tables] to have been included in the epilepsy population."*

Other studies (labeled as ongoing by the Sponsor):
- Adult epilepsy OLE study: 304 Part 2, 304 Part 3, 302 Part 3
- Elderly study: 401
- Pediatric studies: 208 (Parts 1, 2), 305 (Parts 1, 2, 3, 4)
- Monotherapy studies: 311, 045, 046, 050
- Neuropathy studies: 307 (Parts 1, 2), 308 (Parts 1, 2)

**Table 1. Overview of Epilepsy Studies**

| Study #<br>Study Objectives | # Subjects enrolled (completed) | Treatment Groups / Dose / Duration |
|---|---|---|
| **Phase 2 Adjunctive Studies in Refractory Partial Epilepsy Patients** | | |
| BIA-2093-201<br>PK Safety & Efficacy | Total=143 (110)<br>ESL QD=50<br>ESL BID=46<br>Placebo=47 | Total 12 weeks with 1 week tapering off :<br>ESL QD: 400 mg, ↑ by 400 mg every 4 weeks to 1200 mg<br>ESL BID: 200 mg bid, ↑ by 200 mg bid q4 wks to 600 mg bid |
| BIA-2093-202<br>PK Safety & Efficacy<br>Children & adolescents<br>Single Center | Total=31 (26)<br>2-6 yo=12 (9)<br>7-11 yo=8 (7)<br>12-17 yo=11 (10) | Total 12 weeks:<br>Group 1=ESL suspension and Groups 2 & 3=ESL tablets<br>Start 5 mg/kg/day QD, doubling dose every 4 weeks to 30 mg/kg/day QD or 1800 mg/day QD whichever is less |
| **Phase 3 Adult Double-Blind Placebo Controlled Adjunctive Studies, Refractory Partial Epilepsy** | | |
| BIA-2093-301 Part 1<br>Safety and Efficacy<br>Drug-drug interaction<br>Health-related QOL & depressive symptoms | Total=402 (330)<br>ESL 400 mg=100<br>ESL 800 mg=98<br>ESL 1200mg=102<br>Placebo=102 | Total 26 weeks:<br>8 week single-blind placebo baseline<br>2 week titration<br>12 week maintenance<br>4 week tapering off |
| BIA-2093-302 Part 1<br>Safety & Tolerability<br>Maintenance of therapeutic effects of ESL<br>Drug-drug interaction<br>Health-related QOL & depressive symptoms | Total=395 (325)<br>ESL 400 mg=96<br>ESL 800 mg=101<br>ESL 1200mg=98<br>Placebo=100 | Total 22 weeks:<br>8 week baseline<br>2 week titration<br>12 week maintenance |
| BIA-2093-303 Part 1<br>Safety & Tolerability<br>Maintenance of therapeutic effects of ESL<br>Drug-drug interaction<br>Health-related QOL & depressive symptoms | Total=253 (197)<br>ESL 800 mg=85<br>ESL 1200mg=80<br>Placebo=88 | Total 26 weeks:<br>8 week single-blind placebo baseline<br>2 week titration<br>12 week maintenance<br>4 week tapering off |
| BIA-2093-304 Part 1<br>Safety & Efficacy of ESL in patients treated with 1-2 AEDs | Total=653 (504)<br>ESL 800 mg=216<br>ESL 1200mg=211<br>Placebo=226 | Total 22 weeks:<br>8 week baseline<br>2 week titration<br>12 week maintenance |

| | | |
|---|---|---|
| **Phase 3 Adult Open-Label Uncontrolled Studies, Refractory Partial Epilepsy** | | |
| BIA-2093-301 Part 2<br>Open label extension to 301 Part 1 | Total=314 (239) | Total 52 weeks:<br>Starting dose=800 mg QD with up or down titration at 400 mg intervals between ESL 400 mg to 1200 mg QD |
| BIA-2093-301 Part 3<br>Open label extension to 301 Part 2 | Total=95 (81) | Total 52 weeks:<br>ESL 400 mg to 1200 mg QD |
| BIA-2093-301 Part 4<br>Open label extension to 301 Part 3 | Total=71 (49) | Total=unlimited weeks<br>ESL 400 mg to 1200 mg QD |
| BIA-2093-302 Part 2<br>Open label extension to 302 Part 1 | Total=325 (223) | Total 52 weeks:<br>Starting dose=800 mg QD with up or down titration at 400 mg intervals between ESL 400 mg to 1200 mg QD |
| BIA-2093-303 Part 2<br>Open label extension to 303 Part 1 | Total=194 (150) | Total 52 weeks:<br>Starting dose=800 mg QD with up or down titration at 400 mg intervals between ESL 400 mg to 1200 mg QD |
| **Adult Epilepsy Ongoing Studies, Open-Label Extension Studies** | | |
| BIA-2093-302 Part 3<br>To continue subjects until ESL was marketed | Total=20 enrolled<br>Ongoing | Total=unlimited weeks<br>ESL 400 mg to 1200 mg QD |
| BIA-2093-304 Part 2<br>Open label extension to 304 Part 1 | Total=495 (46)<br>Ongoing | Total 52 weeks:<br>ESL 400 mg to 1600 mg QD |
| BIA-2093-304 Part 3<br>Open label extension to 304 Part 2 | Total=2 enrolled<br>Ongoing | Total 104 weeks:<br>ESL 400 mg to 1600 mg QD |

Source: ISS Appendix 7.1 Table 1

# 6 Review of Efficacy

The reader is referred to Dr. Teresa Podruchny's review of efficacy.

# 7 Review of Safety

## ***Safety Summary***

The ESL NDA submission summarizes the safety data of 4225 ESL-exposed subjects from 53 completed trials conducted in Phase 1 volunteers (n=847), subjects with partial-onset seizures (n=1554), and in subjects with nonepilepsy indications (n=1832) such as bipolar disorder, neuropathic pain, migraine, and fibromyalgia.

The Sponsor reported a total of 16 deaths in ESL-exposed subjects in the completed epilepsy studies (n=9), nonepilepsy studies (n=6), and Phase 1 studies (n=1). When all of the controlled studies were pooled together, there was a slightly lower mortality rate in the ESL-treated subjects (0.15%) than in placebo subjects (0.23%). The deaths were either related to seizures, confounded by significant comorbidities or underlying risk factors, or were due to disparate events to preclude any definitive conclusions regarding the causal role of ESL. The incidence rate of sudden, unexplained death in epilepsy (SUDEP) cases in the completed epilepsy trials was lower than historical rates reported in the literature.

The Sponsor proposed a Warnings and Precautions statement for the ESL prescribing information for the following adverse reactions:

- Suicidal Behavior and Ideation (as required by the Division for all antiepileptic drugs)
- Hypersensitivity Reactions
  - Serious Dermatologic Reactions
  - Drug Reaction with Eosinophilia and Systemic Symptoms
- Hyponatremia
- Neurologic Adverse Events (dizziness, coordination, balance disorders, gait disturbance, somnolence, and sedation)
- Withdrawal of Antiepileptic Drugs

I have identified several areas of safety concerns with ESL in this review. I agree with the Sponsor's list of adverse reactions listed above. Additionally, I recommend that the following adverse reactions also be added to the prescribing information for ESL. There was reasonable evidence of a causal association between ESL and these adverse reactions. Furthermore, all of these safety issues resulted in serious (or otherwise clinically significant), life-threatening outcomes.

- Drug-Induced Liver Injury
- Anaphylaxis and Angioedema
- Neurologic events
  - Dizziness/Gait Disturbance
  - Somnolence/Fatigue
  - Cognitive dysfunction
  - Visual changes
  - Falls/Injuries
- Thyroid Function Test Changes
- PR Prolongation

Additionally, there were other adverse events of concern. I recommend a postmarketing requirement to further investigate the potential safety issues of acid-base abnormalities and genetic risk factors for developing severe cutaneous adverse reactions. For the potential safety issue of anemia, I recommend close monitoring in the postmarketing period.

Finally, there was no definitive evidence of any ESL-related cases of agranulocytosis, aplastic anemia, or rhabdomyolysis. An association between ESL use and malignant neoplasms or congenital malformations was not identified in this database. A formal QT study did not find evidence of QT prolongation in subjects exposed to ESL.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In their ISS, the Sponsor summarized safety data from 53 completed clinical trials. The safety data from these trials were divided into the following categories: Phase I trials (n=33), Epilepsy studies (2 Phase II, 4 Phase III DB studies, 5 Phase III OLE studies), and Nonepilepsy studies (3 bipolar, 4 neuropathy, 1 migraine, 1 fibromyalgia). These trials are described in Section 5.1 of this review and listed in Table 1 of the ISS Appendix 7.1 (and in Appendix 1 of this review).

The focus of this safety review is pooled data from the three Phase 3 double-blind clinical trials performed in subjects with partial-onset seizures (Study 301 Part 1, 302 Part 1, and 304 Part 1 excluding Study 303 due to GCP deficiencies identified during the previous review cycle). These studies were randomized, double-blind, placebo-controlled, parallel-group studies that evaluated the efficacy and safety of ESL given as adjunctive therapy in subjects with refractory partial seizures aged 18 years and older (16 years and older in Study 304). The following table summarizes the differences among these three Phase 3 controlled trials in ESL doses and dosing regimens.

**Table 2. Dosing Regimens, Epilepsy Phase 3 Studies**

| Study | Randomized Treatment Group (mg) | Titration Dose (mg), Week 1 / Week 2 | Maintenance Dose (mg), Weeks 1-12 | Tapering-off Dose [a] (mg), Week 1 /Week 2 /Weeks 3-4 |
|---|---|---|---|---|
| BIA-2093-301 | 400 | 400 / 400 | 400 | 400 / 400 / Placebo |
| | 800 | 400 / 800 | 800 | 800 / 400 / Placebo |
| | 1200 | 400 / 800 | 1200 | 800 / 400 / Placebo |
| BIA-2093-302 | 400 | 400 / 400 | 400 | No Taper |
| | 800 | 800 / 800 | 800 | No Taper |
| | 1200 | 800 / 800 | 1200 | No Taper |
| BIA-2093-304 | 800 | 400 / 400 | 800 | 400 / 400 / No Dose |
| | 1200 | 600 / 600 | 1200 | 600 / 600 /No Dose |
| | | 800 / 800 [b] | 1200 | 800 / 800 / No Dose [c] |
| | | | | 800 / 400 / No Dose [d] |

[a] In study BIA-2093-301, all subjects tapered regardless of continuation into Part 2; in study BIA-2093-302, subjects abruptly withdrew if they did not continue on into Part 2; in study BIA-2093-304, subjects tapered if they did not continue into Part 2.
[b] In study BIA-2093-304, subjects who were randomized to receive 1200 mg of eslicarbazepine acetate after the enactment of Amendment 1 (dated 27 Apr 2009) were to be titrated to 800 mg during both Week 1 and Week 2 of the Titration Period. Prior to this amendment, subjects were to be titrated to 600 mg during both Week 1 and Week 2 of the Titration Period.
[c] In study BIA-2093-304, subjects who were randomized to receive 1200 mg of eslicarbazepine acetate and were tapered after the enactment of Amendment 1 (dated 27 Apr 2009) were tapered to 800 mg during both Week 1 and Week 2 of the Tapering-off period. Prior to this amendment, subjects were to be tapered to 600 mg during both Week 1 and Week 2 of the Tapering Period.
[d] In study BIA-2093-304, subjects randomized to receive 1200 mg of ESL and were tapered after Amendment 5 (dated 28 Jul 2011) were tapered to 800 mg during Week 1 of the Tapering-off period and 400 mg during Week 2 of the Tapering-off period.
Source: ISS DARP Table 2

*Comment: While Study 303 had significant GCP deficiencies and could not be used as a pivotal study, I analyzed and presented the significant safety findings from this study in this review.*

The key inclusion and exclusion criteria for the Phase 3 DB studies are listed below (Source: Clinical Study Reports Section 9.3 for Studies 301, 302, and 304).

**Key Inclusion Criteria**
At Visit 1 (screening):
- Written informed consent signed by subject.
- Aged **16 years or older** (≥ 18 years old for Study 301 and 302).
- Females of **nonchildbearing potential** or of childbearing potential with negative β-hCG tests prior to treatment & remain abstinent or use ≥1 method of contraception.
- Diagnosis of **simple or complex partial seizures** +/- secondary generalization at least 12 months prior to screening.
- At least **4 partial-onset seizures** (including subtypes of simple partial, complex partial, and partial seizures evolving to secondarily generalized) within past 28 days.
- Currently treated with **1 or 2 AEDs** (up to 3 AEDs in Study 302) in a stable dose regimen for ≥ 1 month (VNS [vagal nerve stimulator] was a concomitant AED prior to Amendment No. 3).
- For subjects on **vigabatrin**: vigabatrin needed to be taken for ≥ 1 year with no visual field deficits.
- Device for **VNS** was to be implanted ≥ 6 months before screening; parameters had to be stable for ≥ 1 month prior to screening.
- Excepting epilepsy, subject was judged to be in **general good health** based on medical history, physical examination findings, and clinical laboratory test results.

Additional inclusion criteria at Visit 2 (randomization visit):
- **At least 8 partial-onset seizures** during baseline and ≥ 3 partial-onset seizures in each 4-wk period of the 8-wk baseline period and no seizure-free interval >28 days.
- **Diaries satisfactorily completed** by the subject or his/her caregiver.
- Satisfactorily complied with the study requirements during the baseline period (including **no changes in concomitant AED therapy** in the baseline period).

**Key Exclusion Criteria**
At Visit 1 (screening):
- **Pregnant** or nursing.
- **Questionable capability** to complete the trial.
- Only **simple partial seizures with no motor symptomatology**.
- Primarily **generalized seizures**.
- Known **progressive neurological disorders**.

- History of **status epilepticus** or **cluster seizures** within the 3 months prior to screening.
- Seizures of **non-epileptic origin** or of **psychogenic origin**.
- Known exposure to **ESL from previous study**.
- Currently treated with **oxcarbazepine** (or felbamate in Study 301 and 302)
- Using **benzodiazepines** (≥2 times per week), except when used chronically as AED.
- Currently treated with **VNS**, but implanted < 6 months before screening
- History of **abuse of alcohol, drugs or medications** within the last 2 years.
- Major **psychiatric disorders**.
- **Schizophrenia** with acute psychosis episode (within 2 years) or **suicide** attempt.
- Known **hypersensitivity** to carboxamide derivatives.
- **Uncontrolled cardiac, renal, hepatic, endocrine, gastrointestinal, metabolic, hematological or oncology disorder**.
- Second or third-degree **atrioventricular blockade** not corrected with a pacemaker.
- Relevant **clinical laboratory abnormalities** (e.g., sodium < 130 mmol/L, ALT or AST > 2 XULN, WBC count < 3,000 cells/mm3) or for subjects of Asian ancestry, **positive HLA-B*1502** test.
- Estimated **creatinine clearance < 60 mL/min** (< 50 mL/min in Study 301 and 302).

Additional exclusion criteria at Visit 2 (randomization visit):
- **Inadequate compliance** to concomitant AEDs during the 8-week baseline period.
- Inadequate completion of the **study diary**.
- Any other condition or circumstance that, in the opinion of the Investigator, may have compromised the **subject's ability to comply** with the study protocol.

*Comment: The inclusion and exclusion criteria may limit the generalizability of the safety data, as subjects with some of the excluded conditions would likely receive ESL in clinical practice (e.g., patients needed to be in "general good health" without an "uncontrolled" cardiac, renal, hepatic, endocrine, gastrointestinal, metabolic, hematological or oncology disorder, or any major psychiatric disorders).*

*Of note, the exclusion criteria in some of the nonepilepsy studies were less restrictive. In Studies 203/204 and 206/207, subjects were excluded only if they had severe renal impairment with creatinine clearance values <30 mL/min (or "any other uncontrolled clinically relevant disorder" in 203/204 or "any clinically significant concomitant condition that might influence the assessments or conduct of the study" in 206/207). In Studies 209 and 210, subjects were excluded if they had a "severe hepatic, renal, respiratory, haematological, or immunologic illness, unstable cardiovascular disease, or any other medical or psychiatric condition that, in the judgment of the investigator, made the subject inappropriate for entry into this study."*

Data Cutoff Dates
At the time of the NDA submission, except for the ongoing studies, the 53 ESL clinical trials were finished and the safety data was complete. For the ongoing studies, the Sponsor identified January 31, 2012 as the ISS cutoff date for the majority of the safety data and December 19, 2012 as the cutoff date for the listings of SAEs and discontinuations due to AEs (to correspond to the IND 67,466 annual report cutoff date). Additionally, the cutoff date of October 21, 2012 was used for postmarketing data (coincident with the most recent Periodic Safety Update Report issued by Bial-Portela, the marketing authorization holder for eslicarbazepine acetate, Zebinix®, in the European Union and other foreign countries).

### 7.1.2 Categorization of Adverse Events

The Sponsor defined the safety population as subjects who received at least one dose of study drug (ESL or placebo).

An adverse event (AE) was defined as any "undesirable change in the function, structure, or chemistry of the body occurring to a subject during the clinical study, whether or not considered related to the study drug" (Study 304 CSR Section 9.5.4.3). An adverse event could include symptoms, signs, or clinically relevant laboratory abnormalities occurring during the study (including any worsening of a pre-existing condition). Each adverse event was characterized with reference to intensity, date of occurrence, duration, frequency, treatment, outcome, serious/non-serious, and drug-related/not-related. Adverse events were ascertained at each visit by direct inquiry by the Investigator about the subject's well-being since the last visit. Any adverse events reported at all scheduled and unscheduled visits (including telephone calls) were recorded.

Treatment-emergent adverse events (TEAEs) were defined as AEs that either began on or after the date of the first dose of study medication (or the date of randomization if the date of the first dose is missing) and up to 30 days after the date of the last dose of study medication (ISS Data Analysis and Reporting Plan [DARP]). It is reported in the Sponsor's DARP that if the start time of the AE is unknown but the date is on or after that of the date of first dose of study medication, the AE will be considered treatment emergent. Furthermore, AEs with missing or incomplete onset dates will be considered to be treatment-emergent unless it can be determined that the event began before the treatment period (i.e., the end date is prior to the date of first dose).

Attributable risk (or incidence difference or placebo-adjusted incidence) was defined by the Sponsor as the percent of subjects in a select ESL dose group minus the percent of subjects in the placebo group.

The adverse event verbatim terms from the 53 trials were originally coded using different versions of the Medical Dictionary for Regulatory Activities (MedDRA). To

allow pooling of the adverse event data, the Sponsor recoded all of the adverse events from the individual Clinical Study Reports (CSRs) to MedDRA Version 13.1.

*Comment: After reviewing the analysis AE dataset (ADEVENTX) to assess the coding of the verbatim terms to the MedDRA preferred terms, the coding process overall seemed appropriate and allowed for reliable estimates of AE risks. However, there were instances where the MedDRA coding process resulted in splitting likely related AEs into separate SOCs leading to an underestimation of the true incidence for a particular event or syndrome. For example, the MedDRA PT, gait disturbance, was coded only under the primary SOC of General disorders, administration site conditions which provided less precise information than the secondary SOC of Nervous system disorders. Other preferred terms that described similar symptoms were also coded to other primary SOCs instead of grouped together within the SOC Nervous system disorders. Confusional state and disorientation were coded to the SOC Psychiatric disorders whereas the PTs mental impairment and cognitive disorder were coded to SOC Nervous system disorders. Vertigo was coded to the SOC Ear/labyrinth disorders (whereas ataxia and dizziness were coded to SOC Nervous system disorders). Therefore, in order to account for the splitting of the preferred terms into different system organ classes, additional analyses were performed by the reviewer (in Section 7.3) to group these preferred terms across SOCs to provide more accurate estimates of adverse event syndromes.*

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data in the Epilepsy population were pooled into 3 different groups (Phase 3 Epilepsy Controlled Study Pool, Phase 3 Epilepsy Uncontrolled Study Pool, Combined Phase 3 Epilepsy Controlled and Uncontrolled Study Pool). Safety data in the Nonepilepsy studies were pooled into 3 different groups (Nonepilepsy Controlled Study Pool, Bipolar Controlled and Uncontrolled Study Pool, Migraine/Fibromyalgia Controlled Study Pool). Safety data in the Phase 1 studies were all pooled together into the Phase 1 Study Pool. An All Studies Pool combined data from all of the studies (except for 303). The following table summarizes the integrated analysis pools.

### Table 3. Overview of Integrated Analysis Pools

| Phase/ Study ID (Indication) | Phase III Epilepsy Controlled Study Pool[a,b] | Phase III Epilepsy Uncontrolled Study Pool[a,b] | Combined Phase III Epilepsy Controlled and Uncontrolled Study Pool[a,b] | Non-Epilepsy Controlled Study Pool | Bipolar Controlled Uncontrolled Study Pool | Migraine/ Fibromyalgia Controlled Study Pool | Phase I Study Pool[c] | All Studies Pool[a] |
|---|---|---|---|---|---|---|---|---|
| **Completed Phase III Studies** | | | | | | | | |
| 2093-301 Part 1 (Epilepsy) | YES | - | YES | - | - | - | - | Y |
| 2093-301 Parts 2,3,4 (Epilepsy) | - | YES | YES | - | - | - | - | Y |
| 2093-302 Part 1 (Epilepsy) | YES | - | YES | - | - | - | - | Y |
| 2093-302 Part 2 (Epilepsy) | - | YES | YES | - | - | - | - | Y |
| 2093-303 Part 1 (Epilepsy) | - | - | - | - | - | - | - | |
| 2093-303 Part 2 (Epilepsy) | - | - | - | - | - | - | - | |
| 2093-304 Part 1 (Epilepsy) | YES | - | YES | - | - | - | - | Y |
| **Completed Phase II Studies** | | | | | | | | |
| 2093-201 (Epilepsy) | - | - | - | - | - | - | - | Y |
| 2093-202 (Pediatric epilepsy) | - | - | - | - | - | - | - | Y |
| 2093-203 (Bipolar disorder) | - | - | - | YES | Y | - | - | Y |
| 2093-204 (Bipolar disorder) | - | - | - | YES | Y | - | - | Y |
| 2093-205 (Bipolar disorder) | - | - | - | - | Y | - | - | Y |
| 2093-206 Part 1 (PDN) | - | - | - | - | - | - | - | Y |
| 2093-206 Part 2 (PDN) | - | - | - | - | - | - | - | Y |
| 2093-207 Part 1 (PHN) | - | - | - | YES | - | - | - | Y |
| 2093-207 Part 2 (PHN) | - | - | - | - | - | - | - | Y |
| 2093-209 (Migraine headaches) | - | - | - | YES | - | Y | - | Y |
| 2093-210 (Fibromyalgia) | - | - | - | YES | - | Y | - | Y |
| **Completed Phase I Studies** | - | - | - | - | - | - | Y | Y |
| **Ongoing Studies** | - | - | - | - | - | - | - | - |

PDN: painful diabetic neuropathy; PHN: postherpetic neuralgia
[a] Key ISS tables repeated with the inclusion of Study 2093-303.
[b] Key ISS tables repeated for data collected at Sites 301-174 and 301-175 only.
[c] Key ISS tables repeated for Hepatic/Renal Impaired/Healthy Subjects (Studies 111 & 112).
Source: ISS Table 1

The following tables summarize the number of subjects (in the safety population) from each study in the controlled pooled groups by dose group. In the Phase 3 Epilepsy Controlled Pool, the lowest dose group was evaluated only in Studies 301 and 302 (and not in Study 304). Even though the higher dose groups (800 mg and 1200 mg) were evaluated in all 3 studies, more than half of these subjects were from Study 304.

### Table 4. Number of Subjects by Study and Randomized Dose Group, Phase 3 Epilepsy Controlled Pool

| Study | Placebo | ESL (randomized dose groups) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| 301 Part 1 | 102 | 100 | 98 | 102 | 300 |
| 302 Part 1 | 100 | 96 | 101 | 98 | 295 |
| 304 Part 1 | 224 | | 216 | 210 | 426 |
| TOTAL | 426 | 196 | 415 | 410 | 1021 |

Source: ISS Table 1.2 and respective CSRs

The Nonepilepsy Controlled Pool included safety data from 5 double-blind studies (2 bipolar, 1 neuropathy, 1 migraine, and 1 fibromyalgia). The following table summarizes the number of subjects by study and by mean daily dose group in the Nonepilepsy Controlled Pool.

**Table 5. Number of Subjects by Study and Mean Daily Dose Group, Nonepilepsy Controlled Pool (excludes Study 206)**

| | | ESL (mean daily dose groups) | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Placebo** | <600 mg | 600-<1000 mg | 1000-<1400 mg | ≥1400 mg | Total |
| 203 | 40 | 6 | 34 | 37 | 44 | 121 |
| 204 | 11 | 0 | 9 | 9 | 9 | 27 |
| 207 Part 1 | 93 | 126 | 215 | 88 | 46 | 475 |
| 209 | 136 | 18 | 166 | 90 | 0 | 274 |
| 210 | 131 | 153 | 147 | 97 | 0 | 397 |
| TOTAL | 411 | 303 | 571 | 321 | 99 | 1294 |

Source: ISS Table 1.2 and created by the reviewer using JReview (ADSL: DOSCATC) for studies 203, 204, 207, 209, 210

*Comment: One additional nonepilepsy DB study, Study 206 Part 1, was performed in diabetic peripheral neuropathy patients. This study was not included in this Nonepilepsy Controlled Pool based on recommendations by the Division during the first review cycle (in order to isolate these diabetic patients with a different risk factor profile for adverse events). I will perform additional analyses pooling all 6 of the nonepilepsy double-blind studies together and name this pooled group, the Nonepilepsy Double-blind Pool. I will also primarily use the randomized dose groups (rather than mean daily dose groups) to tabulate the data for the Nonepilepsy Double-blind Pool. The following table summarizes the subjects in this pool by study and randomized dose group. Notably, after examining the data between the 2 tables (above and below), there is a higher number of subjects in the lowest mean daily dose group than in the lowest randomized dose group. This suggests that some subjects in the higher randomized dose groups did not reach the targeted dose and remained at lower doses.*

**Table 6. Number of Subjects by Study and Randomized Dose Group, Nonepilepsy Double-blind Pool (includes Study 206)**

| | | ESL (randomized dose groups) | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Placebo** | <600 mg | 600-<1000 mg | 1000-<1400 mg | ≥1400 mg | Total |
| 203 | 40 | 0 | 121 | 0 | 0 | 121 (6.9%) |
| 204 | 11 | 0 | 8 | 9 | 10 | 27 (1.5%) |
| 206 Part 1 | 96 | 0 | 181 | 180 | 100 | 461 (26.3%) |
| 207 Part 1 | 93 | 0 | 188 | 197 | 90 | 475 (27.1%) |
| 209 | 136 | 0 | 135 | 139 | 0 | 274 (15.6%) |
| 210 | 131 | 130 | 135 | 132 | 0 | 397 (22.6%) |
| TOTAL | 507 | 130 | 768 | 657 | 200 | 1755 (100%) |

Source: ISS Table 1.2, respective CSRs, and JReview (ADSL: TRTP1) for studies 203, 204, 206, 207, 209, 210

*Comment: The majority (53.3%) of the total ESL group in this pooled group was enrolled in the 2 neuropathy trials (Study 206 and 207). The bipolar trials (Study 203 and 204) contributed only a small minority of the subjects (8.4%) in this pooled group. The fibromyalgia study 210 contributed 22.6% of the ESL subjects (and 16.4% of the ESL subjects in the higher dose groups) while the migraine study 209 contributed 15.6% of the ESL subjects in this pooled group.*

After stratifying by the specific dose groups rather than the dose range (see following table), the number of patients in each respective dose category (<600mg, 600-<1000 mg, 1000-<1400 mg, and ≥1400 mg) was driven by the same dose groups (400 mg, 800 mg, and 1200 mg) that were used for the Phase 3 Epilepsy Controlled Pool. Therefore, these dose categories for the nonepilepsy controlled studies adequately reflect the dose groups used for the epilepsy controlled studies. Furthermore, the majority (77.1%) of the ESL subjects in this Nonepilepsy Double-blind Pool was assigned to the 800 mg and 1200 mg dose groups (along with 11.3% assigned to even higher dose groups). The following table summarizes the number of subjects from each nonepilepsy controlled study by the specific dose group (randomized).

**Table 7. Number of Subjects by Study and Randomized Dose, Nonepilepsy Double-blind Pool (includes Study 206)**

| | | ESL (randomized dose) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Study** | **Placebo** | 400 mg | 600 mg | 800 mg | 1200 mg | 1600 mg | 1800 mg | Total |
| 203 | 40 | 0 | 64 | 57 | 0 | 0 | 0 | 121 |
| 204 | 11 | 0 | 8 | 0 | 9 | 0 | 10 | 27 |
| 206 Part 1 | 96 | 0 | 0 | 181 | 180 | 100 | 0 | 461 |
| 207 Part 1 | 93 | 0 | 0 | 188 | 197 | 90 | 0 | 475 |
| 209 | 136 | 0 | 0 | 135 | 139 | 0 | 0 | 274 |
| 210 | 131 | 130 | 0 | 135 | 132 | 0 | 0 | 397 |
| TOTAL | 507 | 130 | 72 | 696 | 657 | 190 | 10 | 1755 |

Source: ISS Table 1.2, respective CSRs, and JReview (ADSL: TRTP1) for studies 203, 204, 206, 207, 209, 210

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### 7.2.1.1 Exposure

Overall Exposure
The exposure to ESL in the entire eslicarbazepine acetate drug development program meets the minimum ICH guidance recommendations (minimum 1500 total, 300 subjects for 6 months and 100 for one year at clinically relevant doses). As of the cutoff date for

the ISS, the Sponsor reports that a total of 3993 subjects had received at least one dose of ESL (excluding Study 303). A total of 902 subjects and 686 subjects were exposed for greater than 6 months and 1 year, respectively (excluding Study 303). All of the long-term safety data (>6 months of exposure) was collected from the open-label extension studies. The following table summarizes the number of unique subjects who were exposed to ESL in the epilepsy, nonepilepsy, and Phase 1 studies.

**Table 8. ESL Exposure by Duration and Study Pool (Unique Subjects)**

| Exposure to ESL | TOTAL* | Epilepsy | | | Nonepilepsy | | Phase 1 |
|---|---|---|---|---|---|---|---|
| | | Phase 3 DB Pool | Phase 3 (DB+OLE) | Phase 2 (201+202) | DB Pool (+206) | All (DB+OLE) | |
| ≥ 1 dose | **3993** | 1021 | 1195 | 127 | 1755 | 1832 | 847 |
| ≥ 6 months | 902 | 0 | 586 | 0 | 0 | 316 | 0 |
| ≥ 12 months | 686 | 0 | 462 | 0 | 0 | 224 | 0 |
| Subject-years | 1766.1 | 246.3 | 1098.4 | 26.4^ | 316.9 | 617.4 | 22.9 |

Source: ISS Tables 1.1, 6.1.1.1.r1, 6.6.1.1.s1, 6.5.1.1.r1, 6.5.3.1.s1, 6.5.4.1.s1, CSR 201 Table 50, CSR 202 Table 51, and Safety Amendment 3/28/13 Tables 6.5.5.1.r1, 6.5.5.2.r1
*excluding Study 303 with 232 subjects (217.6 subject-years)
^calculated by the reviewer using the CSRs (# subjects x mean duration of treatment)

A total of 1322 subjects received ESL in the Phase 2 and 3 epilepsy studies (excluding Study 303). An additional 1832 subjects received ESL in studies performed for nonepilepsy indications. For the nonepilepsy indications, a total of 316 subjects and 224 subjects were exposed for at least 6 months and one year, respectively. In the Phase 1 studies, a total of 847 subjects received ESL.

*Comment: There were many discrepancies in the enumeration of the subjects exposed to ESL. Requests to clarify these discrepancies were sent to the Sponsor who provided information in multiple Safety Information Amendments.*

*In ISS Table 1.1, there was a discrepancy between the overall number of unique subjects for eslicarbazepine (n=3993) and the number after adding the totals for the eslicarbazepine group for each study phase (n= 3975). In the Safety Information Amendment dated 3/28/13, the Sponsor stated that the reason for the discrepancy is due to bipolar subjects who took placebo in studies 203 and 204 and then entered into study 205 and took ESL; these subjects were not counted within the section total row for the bipolar studies (studies 203, 204 and 205). This accounts for an additional 26 bipolar subjects who received ESL, which brings the number of subjects up from 3975 to 4001. Furthermore, the Sponsor reported that there were a total of 8 subjects (further details below) who were enrolled in more than one ESL study and who appear in more than 1 study grouping, which accounts for the difference between the updated ESL total of 4001 and the 3993 total subjects presented in ISS Table 1.1 (4001-3993=8).*

*In the Safety Information Amendment dated 2/25/13, the Sponsor clarified the discrepancy between the total number of subjects (both placebo and ESL including 303) reported in ISS Table 1.2 with all subjects with courses of therapy (n=5192) and ISS*

*Table 1.1 with "unique" subjects (n=5079). The Sponsor reported that the difference between these 2 numbers was due to a total of 113 duplicate (non-unique) subjects with two different unique subject IDs:*

- *104 subjects who enrolled in OLE Study 205 after completing Study 203 or 204*
- *9 subjects enrolled in more than one study (8 subjects appeared in more than 1 study grouping):*
  - *1 subject in 207 twice (207-381-381002; 207-381-381003)*
  - *1 subject in 301 and 304 (301-211-90220; 304-856-85602)*
  - *1 subject in 302 and 304 (302-385-80424; 304-753-75303)*
  - *2 subjects in 201 & 301(201-011-09116; 301-161-90294) (201-018-09150; 301-175-90470)*
  - *4 subjects in 119 & 121 (121-000-00004; 119-000-00006) (119-000-00001; 121-000-00001) (121-000-00029; 119-000-00032) (119-000-00002; 121-000-00003)*

*Of note, duplicate (non-unique) subjects were identified by the Sponsor by first matching 4 key demographic characteristics (the date of birth, race, gender, and country) and then matching height within 2 centimeters. Subjects who were missing any of these 5 demographic characteristics were considered to be potential unique subjects. The final determination was made by examination of the site records by clinical operations personnel. In the ISS (page 36), the Sponsor reported that due to the "very low incidence of repeat courses of therapy", these duplicate subjects with multiple enrollments were treated in the analyses as independent observations.*

*Finally, the Sponsor reported that the following 6 subjects were excluded from the ISS analysis datasets (but not excluded from the total enumeration of unique subjects):*

- *2 subjects in Phase I Study 108 who received only run-in warfarin (000-00002 & 000-00006)*
- *1 subject in epilepsy Study 302 Part 2 who did not have enough dose information (missing drug return information) to confirm dose of eslicarbazepine (302-301-80640)*
- *3 subjects in epilepsy Study 303 Part 2 who "did not have enough dose information to confirm a dose of eslicarbazepine" (303-608-70140, 303-702-70257, 303-702-70303)*

The following table summarizes the number of unique subjects by treatment group.

**Table 9. Total Number of Subjects by Treatment Group, Controlled Studies**

| Study Pool | Placebo | ESL |
|---|---|---|
| Epilepsy Studies | | |
| Phase 3 (Part 1: 301, 302, 304) | 426 | 1021 |
| Other Phase 3 (303 Part 1) | 87 | 165 |
| Phase 2 Epilepsy (201) | 47 | 96 |
| Nonepilepsy Studies | | |
| Bipolar Studies (203, 204) | 51 | 148 |
| Neuropathic Pain (Part 1: 206, 207) | 189 | 936 |
| Migraine/Fibromyalgia (209, 210) | 267 | 671 |
| Total | 507 | 1755 |
| Total (without Study 206) | 411 | 1294 |
| Phase 1 Studies* | 223 | 847 |
| **Total** | 1290 | 3884 |

Source: ISS Table 1.1
*includes cross-over studies (155 subjects counted in both the placebo and ESL column)

Phase 3 Epilepsy Controlled Pool
The main active treatment phase in the Phase 3 controlled studies was 14 weeks in duration (comprised of a titration period of 2 weeks and a maintenance period of 12 weeks) along a 4 week tapering off period (in Studies 301 and 304). Each of the 3 studies had different titration regimens. During the maintenance period, down-titration of the dose was not permitted, and subjects were to be withdrawn if dose adjustment was required (e.g., due to experiencing intolerable adverse events).

The following table summarizes extent of exposure by randomized dose for the Phase 3 Epilepsy Controlled Pool. Fewer subjects completed the trial in the higher dose groups. Specifically, more than 14 weeks of treatment was received by 54.5% of the subjects in the placebo group and 63.8%, 45.3%, and 40.0% of those in the 400 mg, 800 mg, and 1200 mg/d groups, respectively. Furthermore, the mean duration of exposure was shorter in the 1200 mg group (11.6 weeks) than the lower dose groups (13.0-14.4 weeks) and placebo (14.2 weeks). The 2 week period with the highest frequency of discontinuations for the higher dose groups occurred during the first 2 weeks (the titration period): 6.7% for the 800 mg group and 9.8% for the 1200 mg (compared to 1.9% for the placebo group and 1.5% for the 400 mg dose group).

*Comment: Of note, it is unclear why more than 8% of the placebo subjects continued to receive placebo for longer than 18 weeks (while all 3 of the epilepsy Phase 3 controlled studies were a total of 18 weeks).*

The Sponsor reported that in the Phase 3 Epilepsy Controlled Pool, analysis of compliance showed that 90.2% to 96.4% of subjects had 80% to 120% compliance.

**Table 10. Extent of Exposure, Phase 3 Epilepsy Controlled Pool**

| Extent of Exposure | Placebo n (%) | ESL n (%), Randomized dose group | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| Any exposure, n (%) | 426 | 196 | 415 | 410 | 1021 |
| 1-7 days | 3 (0.7%) | 1 (0.5%) | 18 (4.3%) | 24 (5.9%) | 43 (4.2%) |
| > 1 to 2 weeks | 5 (1.2%) | 2 (1.0%) | 10 (2.4%) | 16 (3.9%) | 28 (2.7%) |
| > 2 to 4 weeks | 12 (2.8%) | 0 | 8 (1.9%) | 26 (6.3%) | 34 (3.3%) |
| > 4 to 6 weeks | 5 (1.2%) | 1 (0.5%) | 7 (1.7%) | 13 (3.2%) | 21 (2.1%) |
| > 6 to 8 weeks | 9 (2.1%) | 5 (2.6%) | 12 (2.9%) | 13 (3.2%) | 30 (2.9%) |
| > 8 to 10 weeks | 4 (0.9%) | 5 (2.6%) | 8 (1.9%) | 21 (5.1%) | 34 (3.3%) |
| > 10 to 12 weeks | 5 (1.2%) | 2 (1.0%) | 4 (1.0%) | 3 (0.7%) | 9 (0.9%) |
| > 12 to 14 weeks | 151 (35%) | 55 (28.1%) | 160 (39%) | 130 (31.7%) | 345 (34%) |
| > 14 to 16 weeks | 137 (32%) | 102 (52%) | 139 (34%) | 131 (32.0%) | 372 (36%) |
| > 16 to 18 weeks | 59 (14%) | 22 (11.2%) | 44 (10.6%) | 25 (6.1%) | 91 (8.9%) |
| > 18 to 20 weeks | 31 (7.3%) | 0 | 1 (0.2%) | 2 (0.5%) | 3 (0.3%) |
| > 20 to <26 weeks | 3 (0.7%) | 0 | 0 | 0 | 0 |
| ≥ 26 to <52 weeks | 2 (0.5%) | 0 | 1 (0.2%) | 0 | 1 (<0.1%) |
| Missing | 0 | 1 (0.5%) | 3 (0.7%) | 6 (1.5%) | 10 (1.0%) |
| | | | | | |
| Duration of exposure (wks) | | | | | |
| n | 426 | 195 | 412 | 404 | 1011 |
| Mean | 14.2 | 14.4 | 13.0 | 11.6 | 12.7 |
| Median | 14.1 | 14.9 | 14.0 | 14.0 | 14.0 |
| Number of subject-years | 116.2 | 53.9 | 102.3 | 90.1 | 246.3 |

Source: ISS Table 6.2.1.1.s1 and Safety Amendment 3/28/13 Table 1

Phase 3 Epilepsy Controlled and Uncontrolled Pool

The protocols of the open-label extension portions (Part 2) of Studies 301 and 302 defined the starting dose of open-label ESL as 800 mg QD, which could be titrated up or down in 400 mg increments between 400 mg and 1200 mg. The mean duration of exposure for the 600-<1000 mg and 1000-<1400 mg dose groups was similar and both approximately one year (50.8 and 50.2 weeks, respectively). For these two dose groups, approximately one-half of the subjects discontinued before 16 weeks of exposure (during the double-blind portion of the trials 49.3% and 45.2%, respectively). However, out of those subjects who continued into the OLE portions of these trials, the majority received ESL for more than 1 year (77.6% and 77.7%, respectively). The following table summarizes extent of exposure by modal dose for the Phase 3 Epilepsy Controlled and Uncontrolled Pool.

**Table 11. Extent of Exposure, Phase 3 Epilepsy Controlled and Uncontrolled Pool**

| Extent of Exposure | ESL n (%), Modal Dose Group | | | | |
|---|---|---|---|---|---|
| | <600 mg | 600-<1000mg | 1000-<1400 mg | ≥1400 mg | Total |
| Any exposure, n (%) | 157 | 642 | 381 | 3 | 1192 |
| 1-7 days | 14 (8.9%) | 31 (4.8%) | 1 (0.3%) | 1 (33.3%) | 47 (4.0%) |
| > 1 to 2 weeks | 12 (7.6%) | 15 (2.3%) | 1 (0.3%) | 0 | 28 (2.4%) |
| > 2 to 4 weeks | 6 (3.8%) | 24 (3.7%) | 5 (1.3%) | 1 (33%) | 36 (3.0%) |
| > 4 to 8 weeks | 12 (7.6%) | 25 (3.9%) | 18 (4.7%) | 1 (33%) | 56 (0.7%) |
| > 8 to 16 weeks | 33 (21%) | 195 (30%) | 163 (43%) | 0 | 391(33%) |
| > 16 to <26 weeks | 11 (7.0%) | 19 (3.0%) | 9 (2.4%) | 0 | 39 (3.3%) |
| ≥ 26 to <52 weeks | 30 (19%) | 60 (9.3%) | 34 (8.9%) | 0 | 124 (11%) |
| ≥ 52 weeks | 39 (25%) | 273 (43%) | 150 (39%) | 0 | 462 (39%) |
| | | | | | |
| Duration of exposure (wks) | | | | | |
| n | 157 | 642 | 381 | 3 | 1183 |
| Mean | 35.6 | 50.8 | 50.2 | 3.1 | 48.4 |
| Median | 16.4 | 34.3 | 18.1 | 4 | 25.0 |
| Number of subject-years | 107.2 | 624.6 | 366.4 | 0.2 | 1098.4 |

Source: ISS Table 6.4.1.1.s1

Phase 2 Epilepsy Studies
In Study 201, 143 subjects received at least one dose of ESL or placebo over a period of 12 weeks. ESL was titrated at 4-week intervals increasing by 400 mg at each interval. After completing the active treatment phase, subjects were given tapering doses of ESL or placebo. Most subjects received a dose of ESL very close to the planned mg dose during the main active treatment phase.

In the pediatric Study 202, 31 subjects received 3 different doses of ESL: 5 mg/kg/day at Weeks 1-4, 15 mg/kg/day at Weeks 5-8, and 30 mg/kg/day (or 1800 mg/day, whichever less) at Weeks 9-12. After the last treatment period or in the event of premature discontinuation, the dose was to be down-titrated over a 2-week period. For all 3 treatment periods, the mean duration of treatment (26.4 to 28.1 days) was close to that determined by the protocol.

Nonepilepsy Studies
The studies included in the nonepilepsy pools differed in duration, doses evaluated, and indication. In the 2 bipolar DB studies, the treatment duration specified by the protocols for both studies was 3 weeks. In the 2 neuropathic pain DB studies (that contributed the largest percentage of subjects in the nonepilepsy pool), the treatment duration specified by the protocols ranged from 12 to 13 weeks. The migraine DB study was 22 weeks while the fibromyalgia DB study was17 weeks. Therefore, in the nonepilepsy controlled pool, the protocol-specified durations of treatment in the 6 studies included in this pool ranged from 3 to 22 weeks.

In the Nonepilepsy Controlled Pool, the mean duration of exposure to ESL overall was 9.1 weeks, with differences across the individual dose groups (longest duration of 10

weeks in the 1000-<1400 mg dose group). The mean and median duration of exposure was lower in the total ESL group (9.1 weeks for both) then the placebo group (10.1 and 12.9 weeks). Also of note, the Sponsor reported that a lower percentage of ESL subjects (91.2%) had 80% to 120% compliance to the study medication than placebo subjects (95.4%). In summary, compared to the epilepsy studies, subjects in the nonepilepsy studies were exposed to similar doses of ESL but with shorter duration of exposure.

**Table 12. Extent of Exposure, Nonepilepsy Controlled Pool (excludes Study 206)**

| | | ESL (Mean Daily Dose Groups) | | | | |
|---|---|---|---|---|---|---|
| | **Placebo** | <600 mg | 600-<1000 | 1000-<1400 | ≥1400 mg | Total |
| Duration of exposure (wks) | | | | | | |
| n | 411 | 301 | 569 | 319 | 96 | 1285 |
| Mean | 10.1 | 8.3 | 9.4 | 10 | 5.6 | 9.1 |
| Median | 12.9 | 9 | 9.1 | 13 | 3.7 | 9.1 |
| Number of subject-years | 79.6 | 47.9 | 102.0 | 63.0 | 10.3 | 223.2 |

Source: ISS Table 6.5.1.1.s1 and Safety Amendment 3/4/13 Table 6.5.1.1.r1

Phase 1 Study Pool
In the Phase 1 Study Pool, the mean daily ESL dose was 1017.3 mg and the mean duration was 9.9 days.

7.2.1.2 Demographics

The Sponsor categorized the demographic characteristics into the following population subgroups: age group (<18 years, ≥18 to <60 years, ≥60 years), sex (male, female), race (Caucasian, Hispanic, Black, Asian, Other), weight (quartiles), and region (North America, Eastern Europe, Western Europe, Latin America, and Rest of the World). Of note, the category of "rest of the world" included the following countries: Australia, South Africa, India, South Korea, and Turkey.

Phase 3 Epilepsy Controlled Pool
The demographic characteristics of the Phase 3 Epilepsy Controlled Pool are summarized in the following table. The subjects were young (mean age 37.5-38.7 years) predominantly white (77.7-95.4%) with mean BMI in the overweight category (≥25 kg/$m^2$). There were only a few subjects in the pediatric (<18 years old) or elderly (≥60 years old) age categories. The demographic characteristics were similar between the placebo group and the higher ESL groups (800 mg and 1200 mg) but not the lowest ESL dose group (400 mg). Of note, the Sponsor reported that for Study 304, Hispanic ethnicity was not consistently collected and may have been underreported.

**Table 13. Baseline Demographics, Phase 3 Epilepsy Controlled Pool**

| | | ESL n (%) | | | |
|---|---|---|---|---|---|
| | **Placebo** n=426 | 400 mg n=196 | 800 mg n=415 | 1200 mg n=410 | Total n=1021 |
| Sex (male) | 212 (49.8%) | 89 (45.4%) | 214 (51.6%) | 201 (49.0%) | 504 (49.4%) |
| Age (mean years) | 37.8 | 37.5 | 38.7 | 37.7 | 38.1 |
| Age Group | | | | | |
| <18 years | 5 (1.2%) | 0 | 4 (1.0%) | 6 (1.5%) | 10 (1.0%) |
| 18-<60 years | 402 (94.6%) | 192 (98.0%) | 390 (94.0%) | 389 (94.9%) | 971 (95.1%) |
| ≥60 years | 18 (4.2%) | 4 (2.0%) | 21 (5.1%) | 15 (3.7%) | 40 (3.9%) |
| Race | | | | | |
| Caucasian | 331 (77.7%) | 187 (95.4%) | 326 (78.6%) | 317 (77.3%) | 830 (81.3%) |
| Black | 14 (3.3%) | 2 (1.0%) | 14 (3.4%) | 17 (4.1%) | 33 (3.2%) |
| Asian | 46 (10.8%) | 2 (1.0%) | 41 (9.9%) | 44 (10.7%) | 87 (8.5%) |
| Hispanic | 7 (1.6%) | 1 (0.5%) | 5 (1.2%) | 6 (1.5%) | 12 (1.2%) |
| Other | 28 (6.6%) | 4 (2.0%) | 29 (7.0%) | 26 (6.3%) | 59 (5.8%) |
| Region | | | | | |
| Eastern Europe | 132 (31.0%) | 95 (48.5%) | 126 (30.4%) | 131 (32.0%) | 352 (34.5%) |
| Latin America | 90 (21.1%) | 53 (27.0%) | 94 (22.7%) | 87 (21.2%) | 234 (22.9%) |
| Western Europe | 58 (13.6%) | 33 (16.8%) | 52 (12.5%) | 59 (14.4%) | 144 (14.1%) |
| North America | 81 (19.0%) | 0 | 78 (18.8%) | 77 (18.8%) | 155 (15.2%) |
| Rest of the World | 65 (15.3%) | 15 (7.7%) | 65 (15.7%) | 56 (13.7%) | 136 (13.3%) |
| BMI Group | | | | | |
| <18 kg/m$^2$ (underwt) | 16 (3.8%) | 6 (3.1%) | 14 (3.4%) | 13 (3.2%) | 33 (3.2%) |
| 18-30 kg/m$^2$ | 333 (78.5%) | 166 (84.7%) | 334 (80.7%) | 316 (77.5%) | 816 (80.2%) |
| >30 kg/m$^2$ (obese) | 75 (17.7%) | 24 (12.2%) | 66 (15.9%) | 79 (19.4%) | 169 (16.6%) |
| BMI (mean kg/m$^2$) | 25.3 | 24.6 | 25.4 | 25.7 | 25.4 |
| Weight (mean kg) | 71.5 | 69.3 | 72.2 | 72.3 | 71.7 |

Source: ISS Table 11

*Comment: When considering the dose-response relationship for adverse events (discussed in subsequent sections of this review), it is important to keep in mind the differences in the demographics among the dose groups. These differences in demographics may change the baseline risk factors for AEs (particularly AEs associated with BMI, age, and race). The highest dose groups (800 mg and 1200 mg from Study 304) also contains the highest percentages of subjects from North America and the Rest of the World, resulting in more minorities (Black, Asian, and Other) with a higher percentage of subjects with BMI in the obese category. Conversely, the lowest dose group (400 mg from Studies 301 and 302) contain the highest percentage of subjects from Eastern Europe and Latin America, resulting in the predominantly a Caucasian cohort (95.4%) with less elderly.*

Nonepilepsy Studies

There were many differences between the demographic characteristics of the subjects enrolled in the epilepsy and nonepilepsy studies. Compared to the Phase 3 Epilepsy Controlled Pool, the nonepilepsy ESL subjects were older (mean age 51.9 years) and predominantly white (99%) females (75%) with higher percentage of BMIs in the obese

category (24%) (ISS Table 13). Almost all of the subjects were from Eastern Europe (63%) or Western Europe (35%) without any subjects from North America. Within the nonepilepsy DB pool, the demographics between the placebo and total ESL groups were similar. However, there were differences among the dose groups, reflecting the demographics in the studies that the dose groups represented. Please see Section 7.1 which includes detailed information regarding the number of subjects in each nonepilepsy study stratified by randomized dose groups. The following table summarizes the demographics of the entire nonepilepsy double-blind pool along with each of the double-blind trials stratified by indication. The following differences in demographics were identified among the studies: a higher percentage of females in the migraine and fibromyalgia studies, older subjects with a higher BMI in the neuropathy studies, subjects from Latin American and rest of the world in the bipolar studies, and subjects from Western Europe in the fibromyalgia study.

**Table 14. Demographics of the Nonepilepsy Double-blind Pool by Study Indication**

| | NonEpi DB Pool | Bipolar 203+204 | Neuropathy 206+207 | Migraine 209 | Fibromyalgia 210 |
|---|---|---|---|---|---|
| Total # of subjects | n=2262 | n=199 | n=1125 | n=410 | n=528 |
| Sex (male) | 677 (30.0%) | 96 (48.2%) | 476 (42.3%) | 64 (15.6%) | 41 (7.8%) |
| Age (mean years) | 54 | 42 | 63 | 41 | 47 |
| Age Group | | | | | |
| <18 years | 0 | 0 | 0 | 0 | 0 |
| 18-<60 years | 1425 (63%) | 178 (89.5%) | 384 (34.1%) | 386 (94.2%) | 477 (90.3%) |
| ≥60 years | 837 (37%) | 21 (10.6%) | 741 (65.9%) | 24 (5.9%) | 51 (9.7%) |
| Race | | | | | |
| Caucasian | 2249 (99%) | 193 (97.0%) | 1124 (99.9%) | 410 (100%) | 522 (98.9%) |
| Black | 4 (0.2%) | 3 (1.5%) | 0 | 0 | 1 (0.2%) |
| Asian | 4 (0.2%) | 1 (0.5%) | 1 (0.1%) | 0 | 2 (0.4%) |
| Hispanic | 2 (0.1%) | 2 (1.0%) | 0 | 0 | 0 |
| Other | 3 (0.1%) | 0 | 0 | 0 | 3 (0.6%) |
| Region | | | | | |
| Eastern Europe | 1559 (69%) | 155 (77.9%) | 933 (82.9%) | 312 (76.1%) | 159 (30.1%) |
| Latin America | 26 (1.2%) | 26 (13.1%) | 0 | 0 | 0 |
| Western Europe | 669 (29.6%) | 10 (5.0%) | 192 (17.1%) | 98 (23.9%) | 369 (69.9%) |
| North America | 0 | 0 | 0 | 0 | 0 |
| Rest of the World | 8 (0.4%) | 8 (4.0%) | 0 | 0 | 0 |
| BMI Group | | | | | |
| <18 kg/$m^2$ (underwt) | 11 (0.5%) | 3 (1.5%) | 3 (0.3%) | 3 (0.7%) | 2 (0.4%) |
| 18-30 kg/$m^2$ | 1567 (69%) | 140 (70.4%) | 678 (60.3%) | 361 (88.1%) | 388 (73.5%) |
| >30 kg/$m^2$ (obese) | 683 (30.2%) | 55 (27.6%) | 444 (39.5%) | 46 (11.2%) | 138 (26.1%) |

Source: ISS Table 13 and created by the reviewer using JReview (ADSL: SEX, AGE, AGEGRP, RACEGRP, REGION, BMIGRP) for studies 203, 204, 206, 207, 209, 210

Phase 1 Study Pool

The Phase 1 subjects were slightly younger (mean age 32.7 years) than the Phase 3 Epilepsy Controlled Pool (38.0 years). The percentage of males (64%) was approximately twice that of females (36%). Most subjects were also white (81%) and

from North America or Western Europe (with different percentages between the total ESL group and placebo: North America 43.6% versus 78.9% and Western Europe 49.7% versus 21.1%, respectively). The mean BMI (24.5 $kg/m^2$) was similar to the epilepsy population (25.4 $kg/m^2$) (ISS Table 3.4.1).

Baseline Disease characteristics
For details about the epilepsy disease characteristics the reader is referred to Dr. Podruchny's review of efficacy.

Baseline and Concomitant AEDs
Subjects enrolled in the Phase 3 Epilepsy Controlled Pool were being treated with 1 or 2 AEDs (or to a maximum of 3 AEDs in Study 302) at stable doses for ≥1 month prior to the first visit. Concomitant use of oxcarbazepine and felbamate were not allowed. Furthermore, no changes in concomitant AED therapy were allowed in the baseline period.

Most of the total ESL group was being treated at baseline with 2 AEDs (68.7%), fewer with only 1 AED (28.2%) and fewest with 3 AEDs (3.0%) (ISS Table 11). A similar pattern was seen in the placebo group. The following table summarizes the concomitant AEDs taken by the subjects by treatment group in the Phase 3 Epilepsy Controlled Pool. The most common concomitant AEDs in the total ESL group were carbamazepine (51.3%, highest in the 400 mg dose group 59.2%), lamotrigine (24.0%), levetiracetam (17.4%, lowest in the 400 mg dose group 11.7%), forms of valproic acid (valproate sodium, 12.4% and valproic acid, 9.1%), topiramate (11.5%), clobazam (9.3%), phenytoin (9.1%), and phenobarbital (9.0%). Differences in percentages of concomitant AED use among the dose groups are likely due to differences in use rates across studies (e.g., Study 304 sites included US and Canada where carbamazepine is less frequently prescribed).

**Table 15. Baseline AEDs, Phase 3 Epilepsy Controlled Pool**

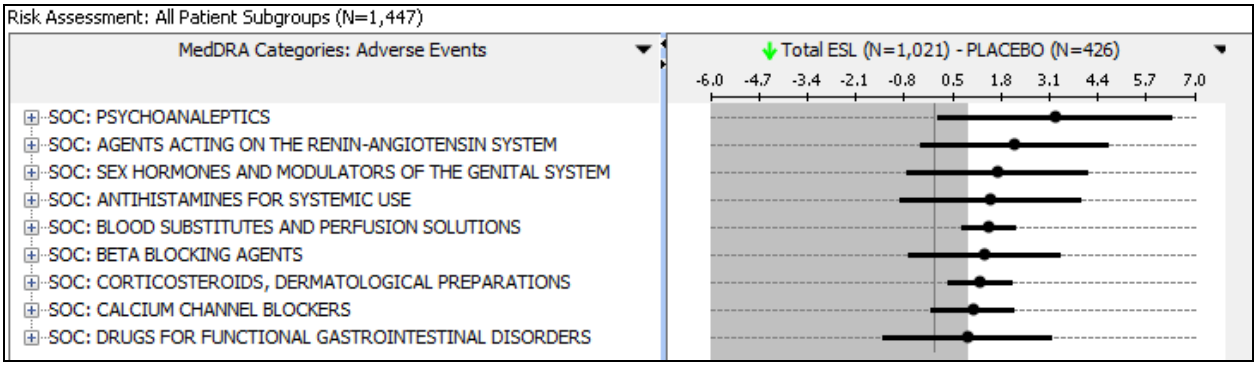
| Standardized Medication Name | PLACEBO | ESL 400 mg | ESL 800 mg | ESL 1200 mg | Total ESL |
|---|---|---|---|---|---|
| CARBAMAZEPINE | 198 (46.48%) | 116 (59.18%) | 204 (49.16%) | 204 (49.76%) | 524 (51.32%) |
| LAMOTRIGINE | 108 (25.35%) | 46 (23.47%) | 94 (22.65%) | 105 (25.61%) | 245 (24.00%) |
| LEVETIRACETAM | 91 (21.36%) | 23 (11.73%) | 80 (19.28%) | 75 (18.29%) | 178 (17.43%) |
| VALPROATE SODIUM | 54 (12.68%) | 26 (13.27%) | 53 (12.77%) | 48 (11.71%) | 127 (12.44%) |
| TOPIRAMATE | 52 (12.21%) | 21 (10.71%) | 48 (11.57%) | 48 (11.71%) | 117 (11.46%) |
| VALPROIC ACID | 41 ( 9.62%) | 16 ( 8.16%) | 42 (10.12%) | 35 ( 8.54%) | 86 ( 8.42%) |
| PHENYTOIN | 42 ( 9.86%) | 14 ( 7.14%) | 34 ( 8.19%) | 44 (10.73%) | 93 ( 9.11%) |
| PHENOBARBITAL | 48 (11.27%) | 15 ( 7.65%) | 39 ( 9.40%) | 32 ( 7.80%) | 92 ( 9.01%) |
| CLOBAZAM | 31 ( 7.28%) | 20 (10.20%) | 48 (11.57%) | 27 ( 6.59%) | 95 ( 9.30%) |
| CLONAZEPAM | 20 ( 4.69%) | 20 (10.20%) | 19 ( 4.58%) | 22 ( 5.37%) | 61 ( 5.97%) |
| LACOSAMIDE | 14 ( 3.29%) | 0 ( 0.00%) | 12 ( 2.89%) | 19 ( 4.63%) | 31 ( 3.04%) |
| ZONISAMIDE | 19 ( 4.46%) | 0 ( 0.00%) | 12 ( 2.89%) | 11 ( 2.68%) | 23 ( 2.25%) |
| GABAPENTIN | 6 ( 1.41%) | 12 ( 6.12%) | 13 ( 3.13%) | 7 ( 1.71%) | 32 ( 3.13%) |
| PREGABALIN | 7 ( 1.64%) | 1 ( 0.51%) | 7 ( 1.69%) | 10 ( 2.44%) | 18 ( 1.76%) |
| VALPROATE SEMISODIUM | 2 ( 0.47%) | 0 ( 0.00%) | 7 ( 1.69%) | 6 ( 1.46%) | 13 ( 1.27%) |
| DIAZEPAM | 1 ( 0.23%) | 1 ( 0.51%) | 6 ( 1.45%) | 3 ( 0.73%) | 10 ( 0.98%) |
| LORAZEPAM | 2 ( 0.47%) | 2 ( 1.02%) | 4 ( 0.96%) | 2 ( 0.49%) | 8 ( 0.78%) |
| TIAGABINE | 1 ( 0.23%) | 0 ( 0.00%) | 2 ( 0.48%) | 6 ( 1.46%) | 8 ( 0.78%) |
| PRIMIDONE | 2 ( 0.47%) | 2 ( 1.02%) | 1 ( 0.24%) | 3 ( 0.73%) | 6 ( 0.59%) |

Source: ISS Table 8.1.2.1 and created by the reviewer using JReview (ADCM2: CMCAT='Anti-epileptic drug', CMPOST=1, CMDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

Concomitant Non-AED Medications and Medical history

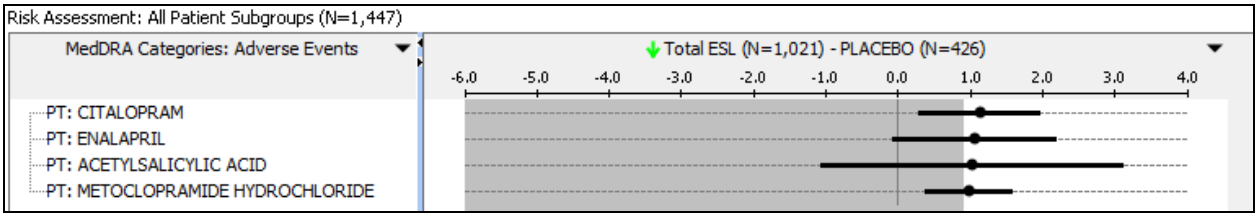
In the Phase 3 Epilepsy Controlled Pool, concomitant non-AED medications were used in similar frequencies in both the placebo (56.8%) and total ESL groups (60.7%) (ISS Table 8.1.1). In any ESL treatment group, the most common (≥5%) concomitant non-AED medications included paracetamol, ibuprofen, and multivitamins (plain). The following forest plots summarize the concomitant non-AED medications (by class and specific drug name) with an incidence of ≥1% above placebo in the total ESL group. Only small differences in concomitant non-AED use were seen between the total ESL group and the placebo group.

**Figure 1. Concomitant Non-AED Medications by Medication Class with ≥1% Difference (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool**




Source: Created by the reviewer using JReview (ADCM2: CMCAT='General Conmed', CMPOST=1, CMCLAS and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

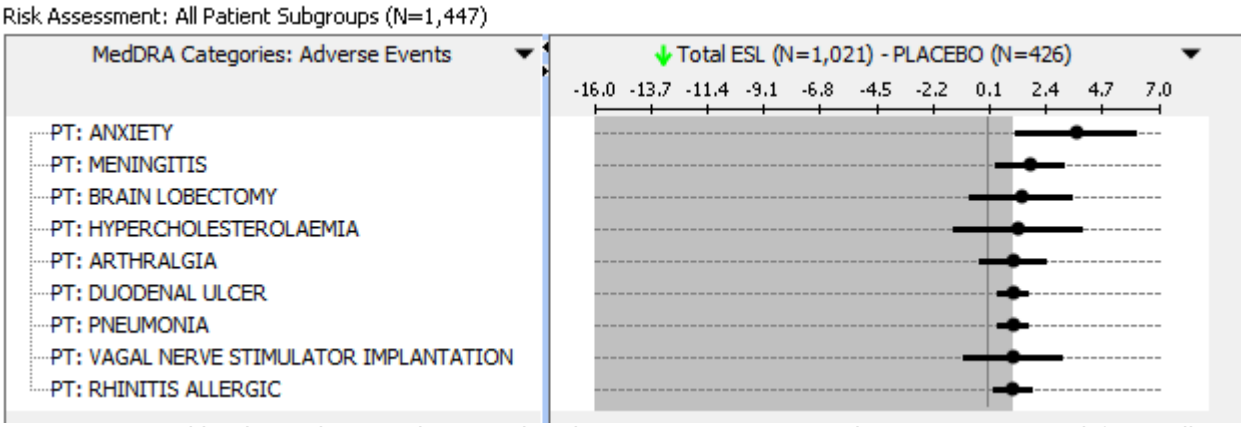
**Figure 2. Concomitant Non-AED Medications by Drug Name with ≥1% Difference (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool**




Source: Created by the reviewer using JReview (ADCM2: CMCAT='General Conmed', CMPOST=1, CMDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

In the Phase 3 Epilepsy Controlled Pool, concomitant diseases were reported by 89.4% of placebo subjects and 89.0% ESL subjects (ISS Table 4.1.1). The most common (≥5%) medical history conditions in any ESL treatment group included seasonal allergy, head injury, hypercholesterolaemia, back pain, headache, migraine, anxiety, depression, insomnia, appendicectomy, brain lobectomy, tubal ligation, vagal nerve stimulator implantation, and hypertension. The following forest plot summarizes the concomitant medical conditions with an incidence of ≥1% above placebo in the total ESL group. More ESL subjects reported a prior history of anxiety than placebo subjects. Only small differences were seen for the other medical conditions.

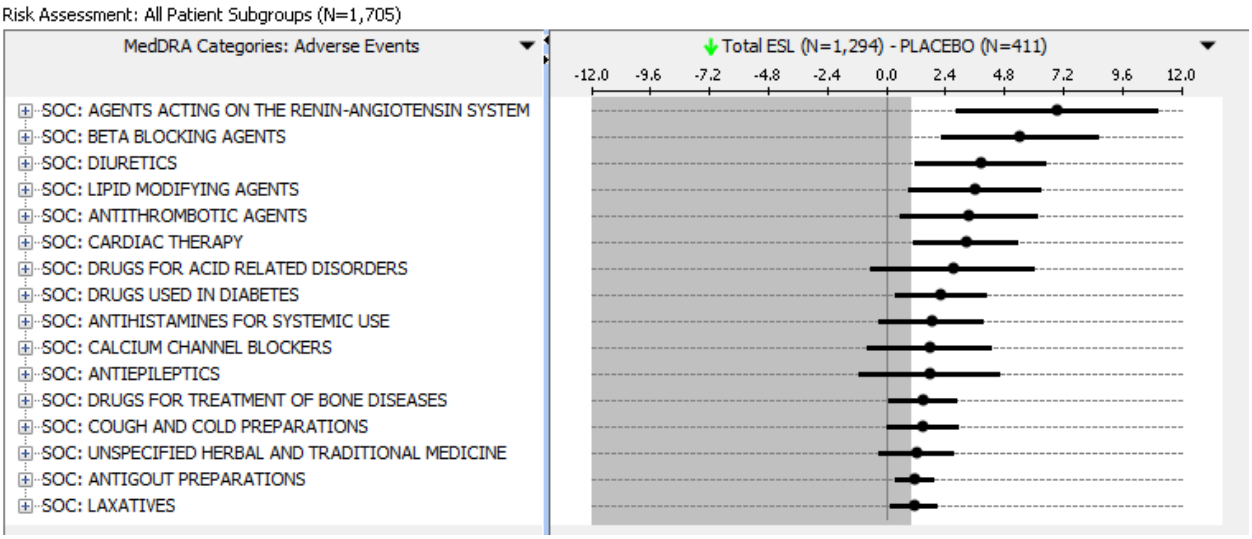
**Figure 3. Baseline Medical Conditions with ≥1% Difference (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool**




Source: Created by the reviewer using JReview (ADMH: MHDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

In the Nonepilepsy Controlled Pool, the most common (≥5%) concomitant medications in the total ESL group included paracetamol, omeprazole, acetylsalicylic acid, and levothyroxine sodium. The following forest plots summarize the concomitant medications (by class and specific drug name) with an incidence of ≥1% above placebo in the total ESL group.

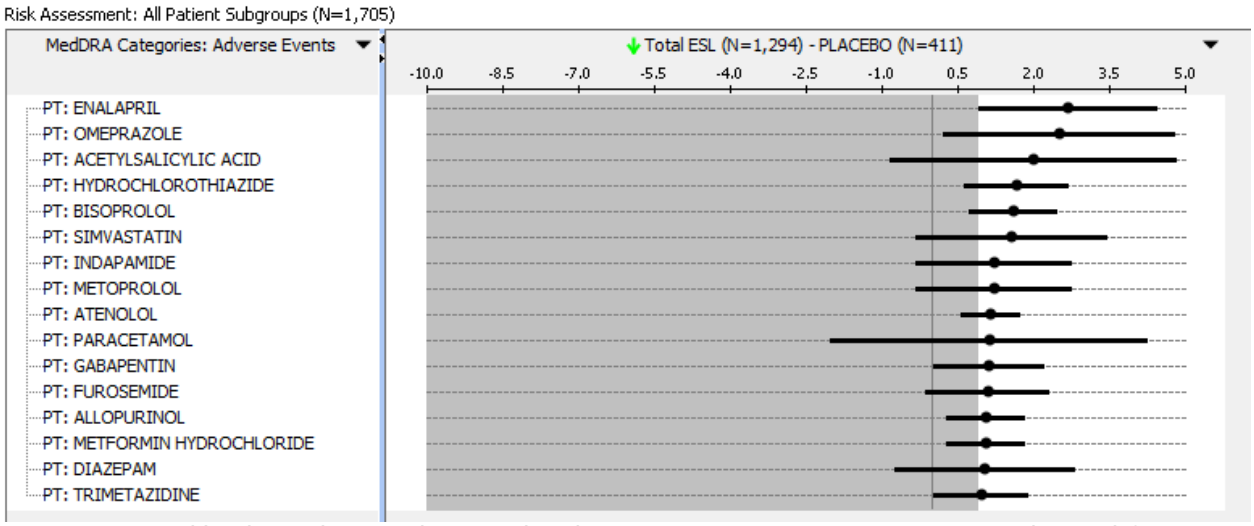
**Figure 4. Concomitant Medications by Medication Class with ≥1% Difference (Total ESL-Placebo), Nonepilepsy Controlled Pool (excludes Study 206)**




Source: Created by the reviewer using JReview (ADCM2: CMPOST=1, CMCLAS and ADSL) for studies 203, 204, 207, 209, 210 (PART ≠'Part 2', DOSCATC)

There were substantial differences in the concomitant medications used by the total ESL group compared to placebo subjects. A higher percentage of ESL subjects than placebo subjects reported concomitant use of classes of medications used for primary or secondary prevention of cardiovascular disease: antihypertensives (renin-angiotensin system agents, beta blockers, diuretics, calcium channel blockers), antihyperlipidemics (lipid modifying agents), antithrombotic agents, cardiac therapy, and antiglycemics (drugs used in diabetes).

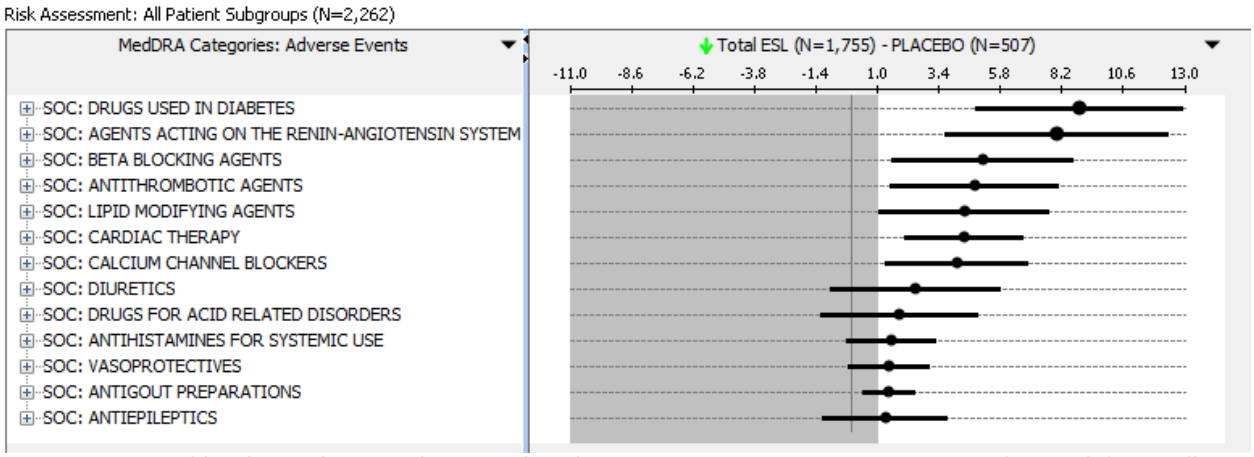
**Figure 5. Concomitant Medications by Drug Name with ≥1% Difference (Total ESL-Placebo), Nonepilepsy Controlled Pool (excludes Study 206)**




Source: Created by the reviewer using JReview (ADCM2: CMPOST=1, CMDECOD and ADSL) for studies 203, 204, 207, 209, 210 (PART ≠'Part 2', DOSCATC)

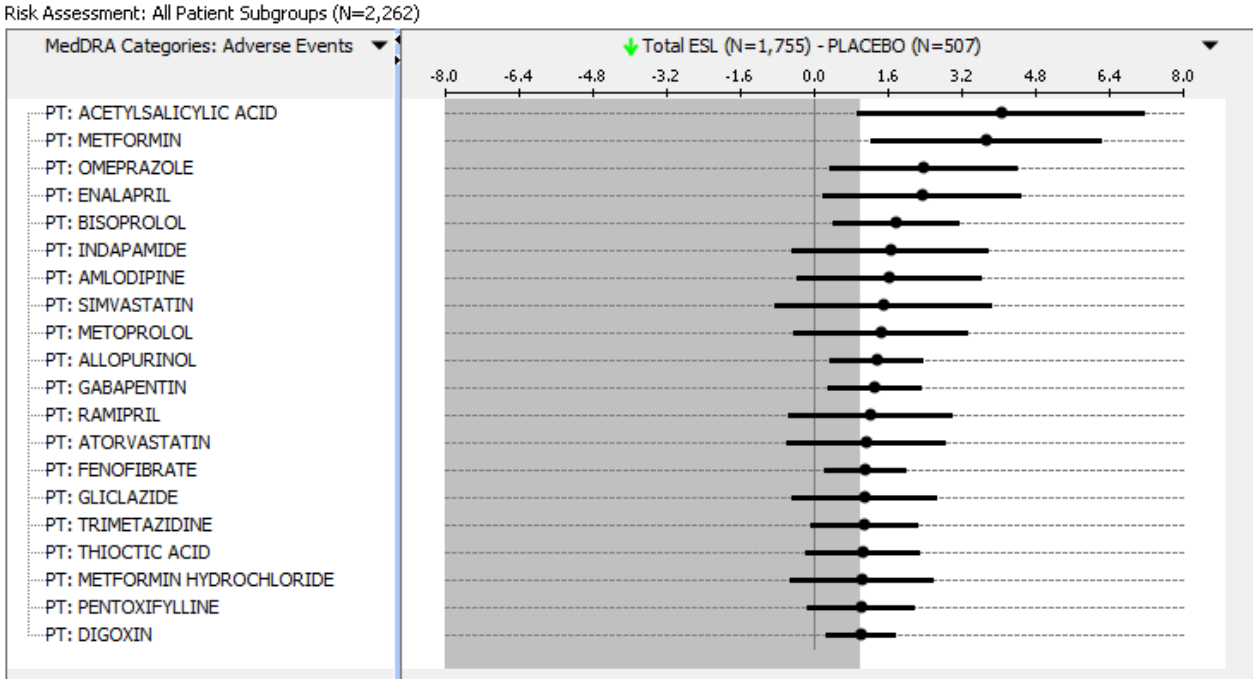
In Study 206 in painful diabetic neuropathy, the most common (>10% of subjects in any treatment group) concomitant non-analgesic medications were metformin, acetylsalicylic acid (used as antithrombotic agent), insulin human, amlodipine, enalapril, metoprolol, simvastatin, insulin glargine, and indapamide (Study 206 Part 1 CSR Table 17). The following forest plots summarize the concomitant medications (by class and specific drug name) with an incidence of ≥1% above placebo in the total ESL group in the nonepilepsy double-blind pool (that includes Study 206). After including Study 206, an even larger difference between ESL subjects and placebo subjects reporting concomitant use of diabetic medications and renin-angiotensin system agents is identified.

**Figure 6. Concomitant Medications by Medication Class with ≥1% Difference (Total ESL-Placebo), Nonepilepsy Double-blind Pool (includes Study 206)**




Source: Created by the reviewer using JReview (ADCM2: CMPOST=1, CMCLAS and ADSL) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

**Figure 7. Concomitant Medications by Drug Name with ≥1% Difference (Total ESL-Placebo), Nonepilepsy Double-blind Pool (includes Study 206)**

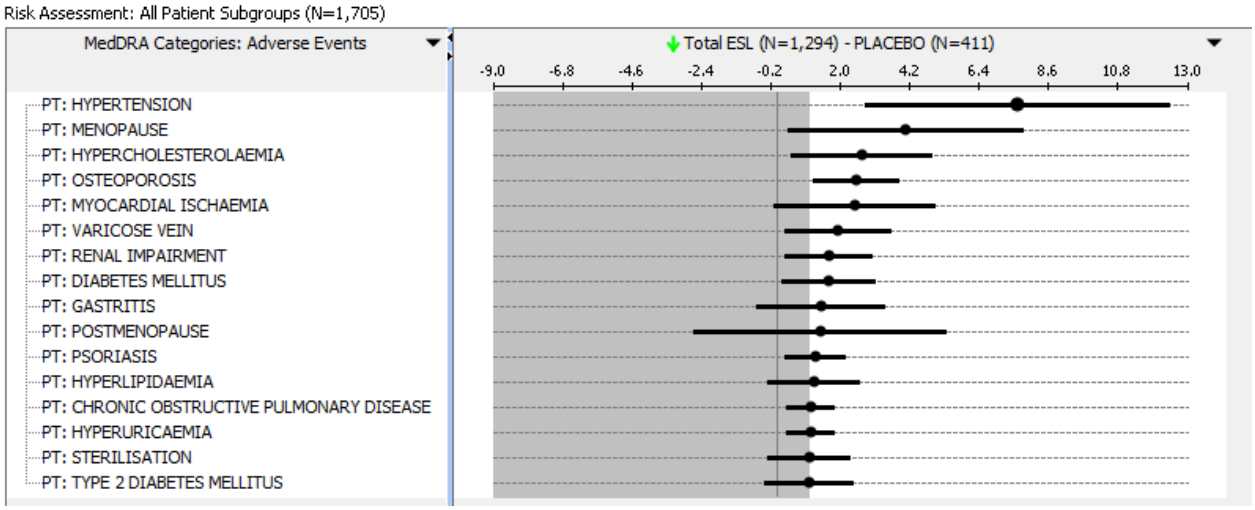



Source: Created by the reviewer using JReview (ADCM2: CMPOST=1, CMDECOD and ADSL) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

In the Nonepilepsy Controlled Pool, the most common (≥5%) concomitant medical conditions in the total ESL group included myocardial ischaemia, hypothyroidism, hypercholesterolaemia, obesity, osteoarthritis, menopause, postmenopause, appendectomy, cholecystectomy, hysterectomy, and hypertension. The following forest

plot summarizes the concomitant medical conditions with an incidence of ≥1% above placebo in the total ESL group. A higher percentage of ESL subjects than placebo subjects reported a prior cardiac history or cardiac risk factors such as hypertension, hypercholesterolaemia, hyperlipidemia, myocardial infarction, diabetes mellitus/type 2 diabetes mellitus, and menopause/postmenopause.

**Figure 8. Baseline Medical Conditions with ≥1% Difference (Total ESL-Placebo), Nonepilepsy Controlled Pool (excludes Study 206)**

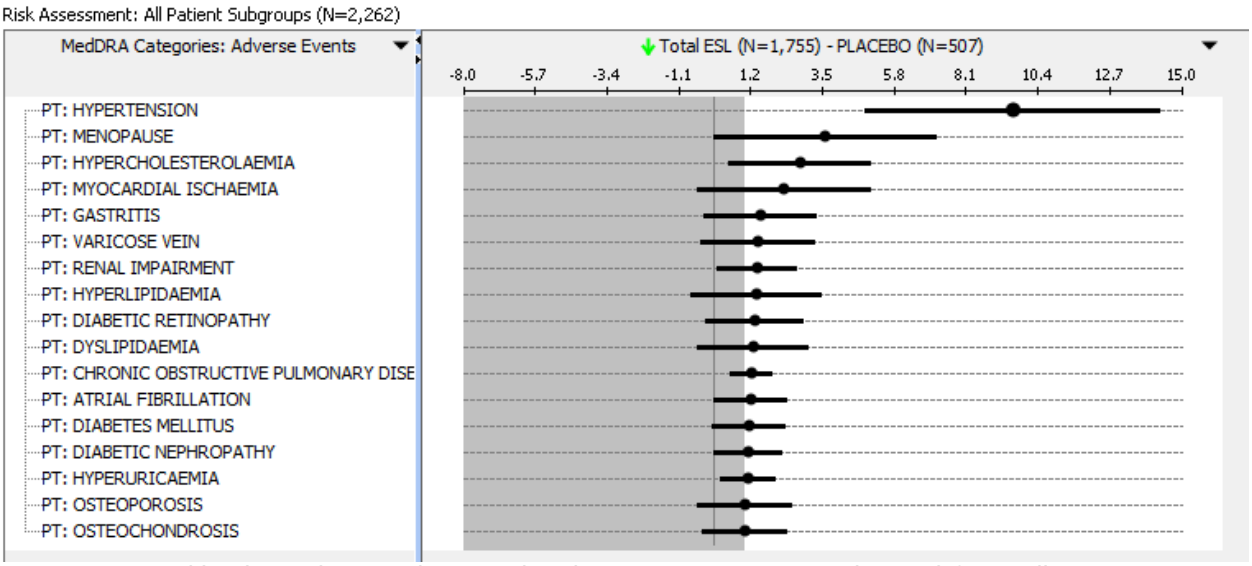



Source: Created by the reviewer using JReview (ADMH: MHDECOD and ADSL) for studies 203, 204, 207, 209, 210 (PART ≠'Part 2', DOSCATC)

The following forest plot summarizes the concomitant medical conditions with an incidence of ≥1% above placebo in the total ESL group in the nonepilepsy double-blind pool that includes Study 206. After including Study 206, an even larger difference between ESL subjects and placebo subjects reporting hypertension is identified.

Of note, these baseline differences in prior cardiac history and cardiac risk factors (and concomitant cardiac medications use) between the total ESL and placebo groups will be taken into account in the discussion of the incidence of cardiac-related adverse events in Section 7.3.5.

**Figure 9. Baseline Medical Conditions with ≥1% Difference (Total ESL-Placebo), Nonepilepsy Double-blind Pool (includes Study 206)**




Source: Created by the reviewer using JReview (ADMH: MHDECOD and ADSL) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

### 7.2.2 Explorations for Dose Response

The reader is referred to Dr. Podruchny's review of efficacy for explorations of dose-response with respect to efficacy. Safety analyses stratified by ESL dose were performed and are discussed in this review.

### 7.2.3 Special Animal and/or In Vitro Testing

The reader is referred to the Pharmacology/Toxicology Review by Dr. Christopher Toscano.

### 7.2.4 Routine Clinical Testing

In all of the populations (epilepsy, nonepilepsy, and Phase 1), safety was evaluated using the following parameters: AEs, clinical laboratory tests, physical examinations, vital signs, and ECGs. The number and timing of data measurements were dependent on trial design and duration (the reader is referred to the individual CSRs for further details for each study). The clinical testing in the Phase 3 trial protocols appeared adequate to allow assessment of the safety of ESL. Routine and special safety assessments are presented in the following table.

**Table 16. Schedule of Safety Assessments, Phase 3 Epilepsy Controlled Pool**

| **Phase** | Pre-randomization | Double-blind Phase | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Visit** | Visit 1 | 2 | 3 | TCI[a] | 4 | 5 | EDV[b] | PSV[c] |
| **Week** | Week -8 | 0 | 2 | 4 | 8 | 14 | | |
| **Visit windows (days)** | | ±3 | ±3 | ±3 | ±3 | ±3 | | |
| **Assessment** | | | | | | | | |
| Medications | X | X | X | | X | X | X | |
| Adverse events | X | X | X | | X | X | X | X |
| Vitals signs and weight | X | X | X | | X | X | X | X |
| Laboratory tests[d] | X | X | | | X | X | X | X |
| Thyroid function[e] | | X | | | | X | | |
| Serum β-hCG | X | | | | | | | |
| Urine pregnancy | | X | X | | X | X | X | X |
| 12-lead ECG[f] | X | X | X | | | X | X | |
| Physical examination | X | X | | | | X | X | X |

[a] Telephone contact
[b] Early discontinuation visit
[c] Post-study visit
[d] Following an 8-hour overnight fast
[e] In Study 304, thyroid tests included TSH, total T3, total T4, free T3, free T4. In Studies 301/302, only free T3, free T4 drawn at Visit 2, 4 and 5.
[f] In Studies 301/302, ECGs collected during Visit 1, 2, and 5
Source: CSR Study 301 Table 1, CSR Study 302 Table 9-1, CSR Study 304 Table 6

For the controlled pools in the ISS, the Sponsor defined baseline values as the last value of each individual laboratory parameter obtained with a date and time prior to the first dose of study medication. For the uncontrolled pools, baseline values were defined as the value of each individual laboratory parameter obtained at the start date of the open-label period (prior to the first dose of open label study treatment). The following table summarizes the laboratory data captured during the epilepsy trials that were integrated into the analysis datasets by the Sponsor.

**Table 17. Laboratory Assessments, Phase 3 Epilepsy Controlled Pool**

| | |
|---|---|
| Hematology | white blood cell count with differential, hematocrit, hemoglobin, red blood cell count, platelet count, INR, aPTT |
| Chemistry | |
| Electrolytes | sodium, potassium, chloride, calcium, bicarbonate*, phosphate |
| Liver function tests | alkaline phosphatase, ALT, AST, total bilirubin |
| Renal function tests | blood urea nitrogen and creatinine |
| Thyroid function tests | free T3, free T4 (additionally in Study 304: TSH, total T3, total T4) |
| Other | albumin, total protein, creatine phosphokinase, glucose, magnesium*, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol |
| Urinalysis | pH^, specific gravity^, RBC, WBC, bacteria, casts, crystals, epithelial cells, and yeast/fungi |

*In the Safety Information Amendment dated 5/20/13, the Sponsor reported that bicarbonate values were only collected in 5 Phase 1 studies (101, 102, 150, 153, and 155) and magnesium values were only collected in 3 Phase 1 studies (150, 153, and 155); they were not collected in the Phase 3 studies or in the Phase 2 studies.
^ In the Safety Information Amendment dated 5/20/13, the Sponsor reported that specific gravity and pH

values were only collected for Phase 1 studies, specifically Studies 101-123, 124 (pH only), 125, 126, 128, 129 (pH only), 130 (pH only), 150, 153, 155 (i.e., not in studies 106 and 127). The Sponsor also reports that in study 106, specific gravity and pH data were to be collected only in the case that values were outside the normal reference ranges, which did not occur.

*Comment: Of note, in a Safety Information Amendment dated 5/20/13, the Sponsor reported that additional laboratory parameters were obtained from Phase 3 epilepsy studies and included in the raw datasets, but were not integrated into the analysis laboratory datasets. These included the following laboratory parameters:*

- *Concomitant AED levels*
- *Red Cell Indices (MCH, MCHC, MCV)*
- *Uric acid (collected in only study 301 – no significant changes were reported in CSR)*
- *Hematology differentials in % form – the absolute values for hematology differentials were selected for integration, so the % unit results were not considered necessary by the Sponsor.*
- *HLA testing – (used only for screening subjects of Asian descent in study 304, with the exception of a single subject in study 304 who received HLA typing after developing a serious allergic reaction)*
- *Bone turnover markers (collected in only study 304 – no significant changes were reported in the CSR for Study 304)*
- *Urine Dip – (performed in only study 304)*

*The Sponsor also noted that "additional parameters from Phase 1 and 2 studies were collected but were not selected for integration and are not considered missing. These parameters include laboratory values that are unrelated to the safety of ESL (such as screening for drugs of abuse or virology), laboratory values that were collected at the discretion of the investigator and not specified in the protocol, or detailed characterization of parameters for which higher level parameters demonstrated no abnormality requiring further characterization (examples include red cell indices where hemoglobin and hematocrit were integrated; CK-MB where CPK was integrated; prothrombin time where APTT and INR were integrated)."*

A laboratory value was determined to be a potentially clinically significant (PCS) value if the post-baseline values crossed the threshold values listed below. The following table summarizes the PCS criteria for laboratory parameters used by the Sponsor.

**Table 18. PCS Criteria for Laboratory Parameters**

| | Parameter Name /Gender /Age Category | PCS Low | PCS High |
|---|---|---|---|
| **HEMATOLOGY** | WBC | ≤2.8 x$10^3$/$mm^3$ | ≥16 x$10^3$/$mm^3$ |
| | Neutrophils | <1.5 k/$mm^3$ | >13.5 k/$mm^3$ |
| | Lymphocytes | N/A | >12 k/$mm^3$ |
| | Monocytes | N/A | >2.5 k/$mm^3$ |
| | Eosinophils | N/A | >1.6 k/$mm^3$ |
| | Basophils | N/A | >1.6 k/$mm^3$ |
| | Hemoglobin | | |
| | Females: 6-13 years | ≤9.5 g/dL | ≥17.5 g/dL |
| | ≥14 years | ≤9.5 g/dL | ≥17.5 g/dL |
| | Males: 6-13 years | ≤9.5 g/dL | ≥17.5 g/dL |
| | ≥14 years | ≤11.5 g/dL | ≥19.0 g/dL |
| | Hematocrit | | |
| | Females 6-13 years | ≤30% | ≥50% |
| | ≥14 years | ≤32% | ≥54% |
| | Males 6-13 years | ≤30% | ≥50% |
| | ≥14 years | ≤37% | ≥60% |
| | RBC | ≤3.5 x$10^6$/$mm^3$ | ≥6.4 x$10^6$/$mm^3$ |
| | Platelet Count | ≤75 x$10^3$/$mm^3$ | ≥700 x$10^3$/$mm^3$ |
| **CHEMISTRY** | Sodium | ≤130 mEq/L | ≥150 mEq/L |
| | Potassium | ≤3 mEq/L | ≥5.5 mEq/L |
| | Chloride | ≤90 mEq/L | ≥118 mEq/L |
| | Calcium | <7 mg/dL | ≥12 mg/dL |
| | AST* | N/A | ≥3 xULN* |
| | ALT* | N/A | ≥3 xULN* |
| | Alkaline phosphatase | N/A | >400 U/L |
| | Creatinine | N/A | ≥2 mg/dL |
| | BUN | N/A | ≥30 mg/dL |
| | Total bilirubin | N/A | ≥2 mg/dL |
| | Total protein | ≤4.5 g/dL | ≥10 g/dL |
| | Albumin | ≤2.5 g/dL | N/A |
| | Glucose | ≤50 mg/dL | ≥250 mg/dL |
| | CPK | N/A | >2.5 xULN |
| | Phosphate | <2.0 mg/dL | >5.0 mg/dL |
| | HDL Cholesterol | <30 mg/dL | N/A |
| | LDL Cholesterol | N/A | >160 mg/dL |
| | Total Cholesterol | N/A | >300 mg/dL |
| | Triglycerides | N/A | >300 mg/dL |
| **BLOOD COAGULATION** | aPTT | N/A | >1.5 xULN |
| | INR | N/A | >1.5 xULN |
| **THYROID FUNCTION** | Free T3 | <200 pg/dL | >415 pg/dL |
| | Free T4 | <0.75 ng/dL | >1.75 ng/dL |

* ULN is age-dependent.
Source: ISS DARP Table 3

*Comment: I compared the PCS criteria used by the Sponsor with Grade 2 toxicity as defined in the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (published June 14, 2010 by the NCI).[1] The values were similar. However, the*

[1] Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Published June 14, 2010. U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute.

*following differences were noted between the Sponsor's PCS criteria and CTCAE Grade 2 toxicity:*

- *PCS criteria for WBC ≤ 2.8 x$10^3$/$mm^3$ identifies slightly more severe cases of leukopenia than the CTCAE Grade 2 toxicity of WBC <3.0 x$10^3$/$mm^3$.*
- *PCS criteria for glucose ≥250 mg/dL (fasting) identifies more severe cases of hyperglycemia as this value corresponds to CTCAE Grade 3 toxicity (not Grade 2).*
- *PCS criteria for calcium <7 mg/dL identifies more severe cases of hypocalcemia as this value corresponds to CTCAE Grade 3 toxicity (not Grade 2).*
- *PCS criteria for phosphate <2 mg/dL identifies more severe cases of hypophosphatemia as this value corresponds to CTCAE Grade 3 (not Grade 2).*
- *PCS criteria for 3 laboratory parameters (creatinine, total bilirubin, alkaline phosphatase) were absolute values instead of multiples of the upper limit of normal. For these 3 laboratory parameters, additional analyses were requested using 1.5 xULN or 2.5 xULN (corresponding to the respective CTCAE Grade 2 toxicity).*

Vital signs measurements included systolic blood pressure, diastolic blood pressure, heart rate, and weight. Criteria for identifying potentially clinically significant values are listed in the following table. The PCS criteria are extreme (e.g., systolic BP > 180 is in the category of hypertensive crisis). I have looked more granularly at blood pressure elevations in Section 7.4.3.

**Table 19. PCS Criteria for Vital Sign Parameters**

| Parameter Name / Age Category | Low | Decrease from Baseline | High | Increase from Baseline |
|---|---|---|---|---|
| Systolic BP | | | | |
| 6-12 years | <80 mm Hg | ≥20 mm Hg | >130 mm Hg | ≥20 mm Hg |
| 13-15 years | <90 mm Hg | ≥20 mm Hg | >160 mm Hg | ≥20 mm Hg |
| ≥16 years | <90 mm Hg | ≥20 mm Hg | >180 mm Hg | ≥20 mm Hg |
| Diastolic BP | | | | |
| 6-12 years | <40 mm Hg | ≥15 mm Hg | >80 mm Hg | ≥15 mm Hg |
| 13-15 years | <50 mm Hg | ≥20 mm Hg | >95 mm Hg | ≥20 mm Hg |
| ≥16 years | <50 mm Hg | ≥15 mm Hg | >105 mm Hg | ≥15 mm Hg |
| Heart Rate | | | | |
| 6-12 years | <60 bpm | ≥15 bpm | >150 bpm | ≥15 bpm |
| 13-15 years | <60 bpm | ≥15 bpm | >130 bpm | ≥15 bpm |
| ≥16 years | <50 bpm | ≥15 bpm | >120 bpm | ≥25 bpm |
| Weight | N/A | ≥7% | N/A | ≥7% |

bpm = beats per minute; mm Hg = millimeters of mercury
Source: ISS DARP Table 5

ECG parameters included ventricular heart rate, QT interval, P-R interval, QRS durations, R-R interval, and the QTc intervals corrected by Bazett (QTcB) and Fridericia (QTcF). The Sponsor reported that in the Phase 3 Epilepsy Controlled Pool, ECG results were over-read by a central cardiologist(s), whereas in the Nonepilepsy Controlled Pool, ECG data were taken from readings by the local investigator (and no

Accessed March 29, 2012. http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

central over-read was performed). The following table summarizes the PCS criteria for ECG parameters used by the Sponsor.

**Table 20. PCS Criteria for ECG Parameters**

| Parameter Name | Abnormal Criteria |
|---|---|
| Heart Rate | <50 bpm and >20% decrease from baseline OR >120 bpm and >20% increase from baseline |
| PR Interval | >200 ms and >20% increase from baseline |
| PR Interval | >200 ms not present at baseline |
| PR Interval | >220 ms not present at baseline |
| PR Interval | >250 ms not present at baseline |
| QRS Interval | >120 ms and >20% increase from baseline |
| QT Interval | ≥500 msec not present at baseline |
| QTcB Interval | ≥500 msec not present at baseline |
| QTcF Interval | ≥500 msec not present at baseline |
| QTcB Interval | ≥450 msec not present at baseline |
| QTcF Interval | ≥450 msec not present at baseline |
| QTcB Interval | Maximum change from baseline: <30 msec, ≥30 msec - <60 msec, ≥60 msec |
| QTcF Interval | Maximum change from baseline: <30 msec, ≥30 msec - <60 msec, ≥60 msec |
| QTcB Interval | Maximum ≥500 msec and maximum change from baseline ≥60 msec |
| QTcF Interval | Maximum ≥500 msec and maximum change from baseline ≥60 msec |
| QTcB Interval | ≥450 msec not present at baseline for males;<br>≥470 msec not present at baseline for females |
| QTcF Interval | ≥450 msec not present at baseline for males;<br>≥470 msec not present at baseline for females |
| QTcB Interval | <340 msec not present at baseline |
| QTcF Interval | <340 msec not present at baseline |

Source: ISS DARP Table 4

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to the Clinical Pharmacology Review.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Sponsor evaluated the database for potential adverse events for similar drugs in the drug class (oxcarbazepine and carbamazepine). The Sponsor evaluated the following adverse events as Special Interest Topics: hyponatremia, allergic reaction or hypersensitivity (including serious skin reactions and DRESS), drug-induced liver injury, depression/suicidality, cytopenias, cardiac rhythm/conduction disorders, SUDEP, and neurological adverse events (cognitive dysfunction, dizziness, visual disturbances, somnolence, ataxia, worsening seizures) along with falls/injuries in addition to hypothyroidism, nausea/vomiting, myocardial infarction/stroke, CPK elevations, and renal toxicity. This approach was acceptable to the reviewer.

## 7.3 Major Safety Results

### 7.3.1 Deaths

In the Epilepsy Phase 2/3 studies, there were a total of 12 deaths at the time of the data collection cut off of January 31, 2012 with the majority occurring during the OLE studies (n=8) rather than the DB studies (n=3). One death (subject 304-859-85901) occurred during the prerandomization phase of the double-blind Study 304 (did not receive study drug and will not be included in the subsequent analyses). After combining all of the Phase 2 and 3 epilepsy controlled studies (including Study 303), the mortality rate was lower in the ESL group (0.08%, 1/1313) than the placebo group (0.36%, 2/560). After including the OLE studies (including Study 303), the mortality rate for ESL-exposed subjects in the epilepsy studies is 0.63% (9/1427) or 6.84 per 1000 subject-years of exposure (9/1316 subject-years). Three of the deaths were considered by the investigators to be possibly related to ESL.

In terms of sudden, unexplained death in epilepsy (SUDEP) cases, there was only 1 ESL death classified as probable/possible SUDEP (subject 304-009-00901) by the Sponsor (although this case may have been secondary to status epilepticus). The incidence rate of SUDEP in this epilepsy population is 0.76 per 1000 subject-years of exposure (1/1316 subject-years). This incidence rate is low compared to rates reported in the literature of 3.5-9.3 per 1000 person-years in subjects with refractory epilepsy.[2] In the ongoing studies, there was 1 additional case coded to SUDEP (excluding the other case of SUDEP that occurred while off of ESL for 18 days).

In the postmarketing database, the Sponsor reported a total of 5 cases of possible SUDEP making the incidence rate 0.41 per 1000 patient-years (using the Sponsor's estimated exposure to marketed ESL as 12,279 patient-years).

In the nonepilepsy studies, there were a total of 7 deaths (2 in the bipolar studies, 4 in the neuropathic pain studies, and 1 in the fibromyalgia study) with the majority occurring during the DB studies (n=5) rather than the OLE studies (n=2). The deaths occurred sporadically with no more than 1 death occurring in each of these nonepilepsy studies except for the neuropathic pain study 207 in which 3 subjects died (2 in DB portion and 1 in OLE portion). After combining all of the nonepilepsy DB studies, the mortality rate was similar in the ESL group (0.23%, 4/1755) as compared to the placebo group (0.20%, 1/507). After including the OLE studies, the mortality rate of ESL-exposed subjects in the nonepilepsy population is 0.33% (6/1832) or 9.72 per 1000 subject-years of exposure (6/617.4 subject-years).

[2] Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol*. 2008; **7**: 1021–31.

**Table 21. Mortality Rate of ESL-Exposed Subjects by Indication**

| Indication | Total # Subjects | Total # Deaths | Crude Mortality | Subject-years Exposure | Mortality per 1000 Subject-years |
|---|---|---|---|---|---|
| Epilepsy | 1427 | 9 | 0.63% | 1316.0 | 6.84 |
| Nonepilepsy | 1832 | 6 | 0.33% | 617.4 | 9.72 |
| Total | 3259 | 15 | 0.46% | 1933.4 | 7.76 |

*Comment: Of note, the nonepilepsy ESL subjects were older (mean age of 51.9 years) than the epilepsy ESL subjects (mean age of 38.1 years). The neuropathy studies enrolled the oldest subjects (mean age of 63 years).*

In the Phase 1 trials, there was 1 death (in the ESL group). The following table summarizes the mortality between ESL and placebo subjects by indication in the DB pooled groups. In the epilepsy controlled studies, there is a lower mortality rate in the ESL-treated subjects when compared to placebo subjects. However, in some of the nonepilepsy populations (neuropathy pain), there is a higher mortality rate in the ESL-treated subjects when compared to placebo subjects. When all of the controlled studies were pooled together, there is a slightly lower mortality rate in the ESL-treated subjects (0.15%) when compared to placebo subjects (0.23%).

**Table 22. Mortality Rate by Treatment Group**

| Double-Blind Pool | Placebo | | ESL | |
|---|---|---|---|---|
| | n | Deaths (%) | n | Deaths (%) |
| Epilepsy Controlled Studies | 560 | 2 (0.36%) | 1313 | 1 (0.08%) |
| Phase 3 DB Pool (including 303) | 513 | 2 (0.39%) | 1186 | 1 (0.08%) |
| Phase 2 DB Pool (201, 202) | 47 | 0 | 127 | 0 |
| Nonepilepsy Controlled Studies | 507 | 1 (0.20%) | 1755 | 4 (0.23%) |
| Bipolar DB Pool | 51 | 1 (2.0%) | 148 | 0 |
| Neuropathic Pain DB Pool | 189 | 0 | 936 | 3 (0.32%) |
| Migraine/Fibromyalgia DB Pool | 267 | 0 | 671 | 1 (0.15%) |
| Phase I Pool | 223 | 0 | 847 | 1 (0.12%) |
| All studies | 1290 | 3 (0.23%) | 3915 | 6 (0.15%) |

The following table summarizes all of the deaths in the entire eslicarbazepine acetate drug development program. Additionally, in the following paragraphs, the available clinical details for the 16 deaths in patients treated with ESL (9 epilepsy, 6 nonepilepsy, 1 Phase I) are summarized.

**Table 23. Overview of Deaths, All Studies Pool (including 303)**

| Subject | Study | Age/sex /race | Last treatment dose | Days on Drug/ Days off Drug | Preferred Term(s) |
|---|---|---|---|---|---|
| **Epilepsy Studies** | | | | | |
| 123-90356 | 301 | 31/F/W | ESL 1400 mg | 2113 | Brain oedema, arteriosclerosis |
| 124-90486 | 301 | 52/M/W | ESL 800 mg | 947 | Brain oedema |
| 177-90425 | 301 | 55/F/W | ESL 800 mg | 314 | Drowning, asphyxia |
| 313-80267 | 302 | 29/M/W | ESL 800 mg | 357 | Arteriosclerosis coronary artery |
| 385-80426 | 302 | 31/M/W | ESL 400 mg | 658 / 21 | Drowning |
| 388-80468 | 302 | 30/F/B | ESL 800 mg | 367 | Drowning |
| 611-70327 | 303 | 54/M/W | ESL 400 mg | 92 | Astrocytoma |
| 703-70252 | 303 | 32/F/O | ESL 400 mg | 197 | Status epilepticus |
| 009-00901 | 304* | 27/M/W | ESL 400 mg | 8 | Status epilepticus |
| 194-90132 | 301* | 49/M/W | Placebo | 75 / 19 | Body temperature decreased |
| 303-30301 | 304* | 29/F/W | Placebo | 14 | Acute respiratory failure, pneumonia, septic shock |
| **Nonepilepsy Studies** | | | | | |
| 543-203154 | 205 | 30/F | ESL 900 mg | 95 / 10 | Suicide, completed |
| 763-763013 | 206* | 75/M | ESL 600 mg | 44 | Prostate cancer |
| 122-122011 | 207 | 63/F | ESL 800 mg | 284 | Bronchopneumonia |
| 206-206014 | 207* | 64/M | ESL 400 mg | 37 / 65 | Lung neoplasm malignant |
| 222-222011 | 207* | 76/M | ESL 400 mg | 33 / 44 | Gastric cancer, septic shock, tracheobronchitis |
| 589-589001 | 210* | 53/M | ESL 800 mg | 8 / 73 | Suicide, completed |
| 341-203181 | 203* | 42/F | Placebo | 22 | Ischaemic stroke |
| **Phase 1 Studies** | | | | | |
| 000-00005 | 105 | 65/M | ESL 600 mg | 2 | Coronary artery occlusion |

Source: ISS Tables 30, 7.6.1.1.s2 and respective narratives/CRFs
Race: W=white, B=black, O=other
*Death occurred during the double-blind portion of the study (Part 1)

**Epilepsy population**:
Excerpts of the Sponsor's narratives of the 9 deaths in ESL subjects are provided in the following paragraphs.

*Comment: After reviewing the available clinical details for the 9 deaths, it is difficult to draw any definitive conclusions about the causal role of ESL in these deaths which are summarized below:*

- *Death related to seizures (n=4)*
  - *Presumed to be related to seizure with brain edema on autopsy (n=2)*
  - *Status epilepticus (n=2)*
    - *1 subject (304-009-00901) considered by the Sponsor as possible/probably SUDEP (however likely due to status epilepticus according to the narrative)*
- *Death due to drowning (n=3)*
  - *1 drowning occurred after being off of ESL for 3 weeks*
- *Death related to cardiovascular disease in a subject with cardiac risk factors (n=1)*
- *Death related to recurrence of previous malignancy (n=1)*

*The reader is referred to Dr. Podruchny's review of efficacy for a detailed analysis of rebound epilepsy, worsening of seizures, and status epilepticus with ESL use. Of note, none of these deaths in ESL subjects were coded to SUDEP. There was 1 placebo subject (301-194-90132) whose death could have been due to SUDEP (found dead on the street and the death was attributed to hypothermia).*

Subject 301-123-90356 – 31 year-old WF completed DB Study 301 Part 1 (400 mg ESL) and was enrolled in OLE Parts 2-4. During the OLE trial, the subject experienced the following AEs: anxiety, increased seizure frequency, grand mal seizure, and dyspnea. On OLE Study Day 1987 while on 1400 mg ESL, the subject was found dead at home. Autopsy report listed the cause of death as **brain edema** (other findings included tongue hematomas, arteriosclerosis, and pulmonary edema). No potentially clinically significant values were reported with a temporal relationship to this event. Concomitant medications included gabapentin, lamotrigine, and piracetam (derivative of GABA). No other past medical history was reported.

Subject 301-124-90486 – 54 year-old WM completed DB Study 301 Part 1 (400-800 mg ESL) and was enrolled in OLE Parts 2-4. On OLE Study Day 820 while on 800 mg ESL, the subject was found dead at home. Based on the autopsy findings, the cause of death was reported as sudden death due to **brain edema**. No potentially clinically significant values were reported with a temporal relationship to this event. Past medical history included hypertension. Concomitant medications included carbamazepine, losartan, betaxolol (bblocker), and perindopril (ACE inhibitor).

Subject 301-177-90425 – 55 year-old WF completed DB Study 301 Part 1 (400-800 mg ESL) and was enrolled in OLE Part 2 (ESL 800 mg). During the OLE trial, the subject experienced the following nonserious AEs: dizziness, fever, nausea/vomiting. On OLE Study Day 187 while on 800 mg ESL, the subject was found dead in the bathroom. The morning of the death, the subject was reported as well. Based on the autopsy findings, the cause of death was reported as asphyxiation by **drowning** thought due to loss of consciousness as a result of a seizure. *(Of note, in the last seizure diary #09749, the seizure frequency was stable with 2 seizures recorded in the preceding 2 weeks along with 3-4 seizures per month in the preceding 4 months)*. No potentially clinically significant values were reported with a temporal relationship to this event. Past medical history included traumatic brain injury, tuberculosis, PUD, and hypercholesterolemia. Concomitant medications included gabapentin and valproic acid.

*Subject 302-313-80267 – 29 year-old WM completed DB Study 302 Part 1 (400 mg ESL) and was enrolled in OLE Part 2. During the OLE trial, the subject experienced the following nonserious AEs: hypertension, diarrhea, weight increased. On OLE Study Day 259 while on 800 mg ESL, the subject was found dead in his bedroom. The day preceding the death, the subject was reported as well. Based on the autopsy findings, the cause of death was reported as **severe coronary atherosclerosis**. Potentially clinically significant values included elevated LDL and weight increase of 11 kg (over 3 months). No other potentially clinically significant values (vitals, EKG) were reported prior to the sudden death. Past medical history included traumatic brain injury, hypertension, hyperlipidemia, obesity, asthma, and atrioventricular block (first degree). Concomitant medications included levetiracetam, carbamazepine, irbesartan, fluvoxamine (SSRI), and asthma inhalers.

Subject 302-385-80426 – 31 year-old WM completed DB Study 302 Part 1 (400 mg ESL for 100 days) and OLE Part 2 (400-1400 mg ESL for 558 days). During the OLE trial, the subject experienced the following nonserious AEs: headache, hyperthyroidism, somnolence, respiratory infection, nausea, constipation. After completing Study 302 (Parts 1 & 2) and off of ESL for 21 days, the subject died due to "severe fatal **drowning**." No other information regarding the death was provided (no CIOMS narrative was provided). Potentially clinically significant values included low free T4 levels along with elevated LDL

and sodium (155 mEq/L on Day 560). Past medical history included neurocysticercosis and headaches. Concomitant medications included topiramate, clobazam, and valacyclovir.

Subject 302-388-80468 – 30 year-old BF completed DB Study 302 Part 1 (placebo) and was enrolled in OLE Part 2 (ESL 400-1200 mg). On OLE Study Day 313 while on 800 mg ESL (for past 3 months), the subject was found dead due to **drowning** in the bathtub thought secondary to a seizure. In the 2 weeks preceding the death, the subject epilepsy was reportedly "poorly controlled" with ~2 seizures per day. *(Of note, in the seizure diary #15356 for the 6 week period preceding the death, there were no seizures recorded. In the seizure diary for the preceding 2 months, only 2 seizures were recorded)*. No autopsy was reported. Potentially clinically significant values included low free T4 levels (on Study Day 57). Past medical history included mild mental retardation. Concomitant medications included phenobarbital and phenytoin (stable doses).

Subject 303-611-70327 – 54 year-old WM completed DB Study 303 Part 1 (placebo) and was enrolled in OLE Part 2 (400-1200 mg ESL). While on 400 mg ESL, the subject developed aphasia and was found to have tumor recurrence (high grade **astrocytoma**) on OLE Study Day 61. Treatment included high dose IV dexamethasone. The subject died one month later. Past medical history included astrocytoma s/p resection (5 years prior to study entry). Concomitant medications included carbamazepine and lamotrigine.

*Subject 303-703-70252 – 32 year-old female completed DB Study 303 Part 1 (400-800 mg ESL) and was enrolled in OLE Part 2 (400-800 mg ESL). During the trial, the subject experienced the following nonserious AEs: dizziness, abnormal heart rate, somnolence, and leukopenia. On OLE Study Day 25 while on 400 mg ESL, the subject experienced **status epilepticus** and died (witnessed). No autopsy was performed. Death certificate listed the cause of death epilepsy grand mal and acute respiratory insufficiency. No potentially clinically significant values were reported with a temporal relationship to this event. No other past medical history was reported. Concomitant medications included carbamazepine and valproic acid.

*^Subject 304-009-00901 – 27 year-old WM was enrolled in DB Study 304. On Study Day 8 while on 400 mg ESL, the subject was found dead in bed. Mother reportedly noted that the subject's tongue was bitten. Based on the autopsy findings (lip laceration), the cause of death was reported as **status epilepticus**. No potentially clinically significant values were reported with a temporal relationship to this event. Past medical history included Weill-Marchesani syndrome. Concomitant medications included felbamate and carbamazepine.

*Considered possible related to ESL by study investigators
^Considered probable or possible SUDEP by the Sponsor

*Comment: I identified an additional death that was reported on 8/28/09 in the Appendix 13.1 of the 120-day safety update for the initial NDA submission. Even though the information regarding the subject's SAEs were reported in the narrative provided in this current NDA resubmission, the information regarding the death was missing from the narrative:*

*Subject 302-395-80794 – 61 year-old WF while enrolled in DB Study 302 Part 1 (800 mg ESL), the subject reported a mass on her neck on Day 47 of ESL. Pathology results revealed follicle center lymphoma. ESL was continued into OLE Part 2. Subject underwent "chemotherapy cycles" and developed pancytopenia. ESL was discontinued on Study Day 285. Subject underwent multiple hospitalizations due to severe leukopenia and thrombocytopenia with associated bleeding episodes (lower limb hematomas and oral hemorrhagic lesions). Bone marrow biopsy revealed severe "medullaraplasia." Subject also developed cutaneous nodules which were confirmed by biopsy to be Fusarium infections. Three months later (information only provided in the 120-day safety update from*

*8/28/09 and missing from the current narrative), the subject developed oliguria and a right pleural effusion and died of respiratory failure.*

*In the 2009 narrative, it is stated that "while this subject's death is not included in the death listings or summaries due to the timeframe of the death, the narrative is included here for completeness." This death occurred more than 6 months after ESL discontinuation and was unlikely attributable to ESL (as the onset of the neck mass occurred after only 1.5 months of ESL exposure). However, the information regarding the death should have been included in the narrative provided in this NDA resubmission.*

**Nonepilepsy population**:
The summaries of the Sponsor's narratives of the 6 deaths in ESL subjects are provided in the following paragraphs.

*Comment: After reviewing the available clinical details for these 6 deaths, it is difficult to draw any definitive conclusions about the causal role of ESL in these deaths. Most of these deaths occurred in subjects at high risk due to their older age (n=4, ≥63 years old). Most of the deaths were due to malignancies (n=3) or severe infections (n=1, pneumonia) that are more common in this older age cohort. Finally, there were 2 deaths due to completed suicides (1 subject had a history of bipolar disorder and the other event occurred 73 days after the last dose of ESL). Suicidality is further discussed in Section 7.3.4 of this review.*

Subject 205-543-203154 (same subject as 203-343-203154) – 30 year-old WF completed Bipolar DB Study 203 (ESL up to 2400 mg) and was enrolled in OLE Study 205 (ESL 900 mg). On OLE Study Day 96, the subject discontinued the study medication (reason listed = "withdrew consent"). Ten days later, the subject **committed suicide** by hanging. No potentially clinically significant values were reported with a temporal relationship to this event. Past medical history included bipolar disorder. No concomitant medications were reported.

Subject 206-763-763013 – 75 year-old WM was enrolled in diabetic neuropathy DB Study 206 (ESL 600 mg). On Study Day 41, the subject was diagnosed with prostate cancer and suspected renal cancer. On Study Day 59, the subject died in the hospital. The death certificate reported the cause of death as "**cancer of prostate**." No further information was provided. Past medical history included prostate adenoma, HTN, CAD, nephropathy, and diabetes mellitus.

Subject 207-122-122011 – 63 year-old WF completed Neuropathy DB Study 207 Part 1 (ESL 400 mg) and was enrolled in OLE Part 2 (ESL 400-800 mg). On OLE Study Day 202 while on 800 mg ESL, the subject experienced the serious adverse event of severe bilateral pneumonia. ESL was discontinued 19 days later. The subject died 5 days later. The clinical diagnosis in the autopsy report was "decompensated respiratory insufficiency, bilateral **bronchopneumonia**, severe temperature-intoxication syndrome, cardiocirculatory insufficiency, consumption coagulopathy and secondary anemia." The autopsy report also noted the presence of chronic bronchitis and pulmonary emphysema. Past medical history included HTN, chronic renal disease, sinus bradycardia. No concomitant medications were reported during the trial.

Subject 207-206-206014 – 64 year-old WM was enrolled in Neuropathy DB Study 207 (ESL 400 mg). On Study Day 1 (after 1 dose of ESL), the subject was diagnosed with malignant lung neoplasm. On Study Day 12, the subject was hospitalized for severe pneumonia (Klebsiella pneumoniae) and pulmonary

edema. ESL was discontinued and the subject died 65 days later. Based on the autopsy findings, the cause of death was reported as **pulmonary carcinoma**. Past medical history included hypertension and hypercholesterolemia.

Subject 207-222-222011 – 76 year-old WM was enrolled in Neuropathy DB Study 207 (ESL 400 mg). On Study Day 15, the subject experienced the serious adverse event of esophageal stenosis. Treatment included a dilatation procedure and ESL was discontinued. About 2 weeks later, the subject was hospitalized due to dysphagia, jaundice, and dyspnea. Imaging revealed a gastric mass and dilatation of the biliary tract. Biopsy revealed **gastric adenocarcinoma** involving the pancreatic head and compression of the common bile duct. During the hospitalization, the subject developed septic shock due to cholangitis and tracheobronchitis. The subject died (44 days after ESL was discontinued). Past medical history included myocardial ischemia, emphysema, hypertension, atrial fibrillation, and GERD.

Subject 210-589-589001 – 53 year-old WM was enrolled in Fibromyalgia DB Study 210 (ESL 400-800 mg). During the trial, the subject experienced the following serious AEs: depression and suicidal ideation. Treatment included escitalopram. ESL was discontinued on Study Day 8. According to the investigator, the subject withdrew from the study because that he felt "his overall status was worse." More than 2 months later (73 days later), the subject **committed suicide** by throwing himself off of a bridge. Past medical history included hypertension and polyps. No prior psychiatric history was reported but prior and concomitant medications included alprazolam, amitriptyline, and zopiclone (hypnotic).

### Phase 1 population:

Subject 105-000-00005 – 65 year-old WM enrolled in the elderly PK study received two doses of 600 mg of ESL (5 days apart). The subject reported "tiredness" 3 hours after the first dose of ESL. Approximately 24 hours after the second dose of ESL, the subject died at home. Autopsy revealed "complete occlusion of the left circumflex artery and other signs of sudden cardiac death secondary to myocardial infarction." Past medical history included "chronic supra-ventricular arrhythmia", palpitations, and tobacco use. No concomitant medications were reported. Baseline EKG revealed atrial fibrillation with normal rate (75 bpm). Post-dose EKGs and vitals during the trial were within normal limits (minimal increase in QTcB from 425 to 440 ms, 3 hours after the first dose of ESL). There were no post-dose laboratory values.

*Comment: Although this death was temporally related to doses of ESL, the causal role of ESL in this death is unlikely. This subject had underlying risk factors for coronary artery disease (age, sex, tobacco use) along with a history of cardiac arrhythmia. Furthermore, post-dose EKGs and vital signs were WNL.*

Ongoing Studies

In the 10 ongoing studies, there were a total of 13 deaths (5 blinded and 3 occurred after the January 31, 2012 data cut-off date). There were 2 additional deaths during screening and did not receive any study drug (046-6028-S005 and 308-1201-811 which were not included in the table below).

*Comment: Most of the 13 deaths were unlikely drug related as these events either occurred off of drug treatment for ≥ 18 days (n=4) or were due to accidental trauma (n=2, airway obstruction, stab wound), or in subjects with other significant risk factors (n=4 cardiac or vascular ischemia related). The 3 remained deaths were due to single events of seizures (1), esophageal carcinoma (1), and SUDEP (1).*

**Table 24. Overview of Deaths, Ongoing Studies**

| Subject # | Study | Age/sex /race | Treatment | Days on Drug/ off Drug | Preferred Term(s) |
|---|---|---|---|---|---|
| 010 01010 | 304 | 18/F/B | ESL | 229 | SUDEP (see details below) |
| 6038 S001 | 050 | 57/M/W | ESL 800 mg | 38 /18 | SUDEP (see details below) |
| 305 30505 | 304 | 35/M/B | ESL 800 mg | 204 | Stab wound (see details below) |
| 49202 | 401 | 76/M/W | ESL 400 mg | 19 / 8 | Ischaemic stroke (PMH: HTN, CAD, CVA) |
| 303 30308 | 304 | 28/F/W | ESL 800 mg | 524 / 42 | Partial seizures with secondary generalization (pregnancy) |
| 512 70196* | 303 | 35/F/W | ESL 800 mg | 715 | Oesophageal carcinoma (s/p total esophagectomy, partial gastrectomy) |
| 22502 | 305 | 5/F/W | Blinded ESL (10-30 mg/kg) | 135 | Asphyxia (airway obstruction while playing with plastic bag) |
| 46402^ | 401 | 76/M/W | ESL 400 mg | 132/111 | Glioblastoma multiforme, grand mal convulsion |
| 42202 | 401 | 79/F/W | Blinded (ESL or CBZ) | 111 | Cardiac failure (PMH: HTN, arteriosclerosis, obesity) |
| 1809 701 | 307 | 58/M/W | Blinded | 62 | Ventricular tachycardia Cardiac arrest (underlying cardiomyopathy due to alcohol use and diabetes mellitus) |
| 18502 | 305 | 6/F/W | Blinded | 55 | Convulsion “cluster seizures” Brain oedema and herniation (PMH: meningomyelocele and hydrocephalus) |
| 1404011 | 311 | 63/M/W | Blinded | 91 / 6 | Cardiac arrest (PMH: myocardial ischemia, HTN) |
| 1202017 | 311 | 61/M/W | Blinded | 12 / 63 | Glioblastoma multiforme |

Source: ISS Tables 30, 31 and respective narratives provided by the Sponsor
CBZ=carbamazepine
*Subject # corrected to 303-512-70196 from 303-702-70196 by the Sponsor in the Safety Information Amendment dated 3/11/13
^Narrative and CRF provided in Safety Amendment dated 3/28/13

## Ongoing studies:

Subject 304-010-01010 – 18 year-old BF completed DB Study 304 Part 1 (ESL 1200 mg) and was enrolled in OLE Part 2. Nonserious TEAEs reported during the study included amnesia and neck pain. On OLE Study Day 229 (ESL dose not provided in Sponsor’s narrative), the subject was found dead on the shower floor. Based on the autopsy results, the cause of death was **SUDEP**. Past medical history included asthma, obesity, memory loss, headache, and cardiomegaly. Concomitant medications included levetiracetam and valproic acid.

Subject 050-6038-S0001 – 57 year-old WM completed DB Study 045 (blinded) and was enrolled in OLE Study 050 (ESL 1600 mg for 2 weeks and 1200 mg for 3 weeks). On OLE Study Day 32, the subject experienced worsening seizures and feeling “increased stress” (ran out of desvenlafaxine ~1 week prior). Treatment included lorazepam and a decrease in ESL dose to 800 mg (along with an increase of levetiracetam). Two days later, the subject went to the emergency room for akathisia (restlessness, feeling “jumpy”) and “muscle jerks”. EEG revealed seizure activity. Treatment included lorazapam. ESL

was discontinued while levetiracetam was continued. The subject then reported feeling "depressed, extremely irritable, and homicidal." *(Of note, homicidal ideations was not coded as a TEAE in the safety database by the Sponsor).* These symptoms were thought secondary to levetiracetam and the subject was hospitalized for rapid withdrawal of levetiracetam. Subject was treated with lorazepam and continued on clonazepam. Events resolved and the subject was discharged from the hospital. Three days later (18 days after the last dose of ESL), the subject was found dead (face down) in bed by his wife (who also noted the bed was wet). Autopsy was not performed. Death certificate listed the cause of death as status epilepticus. Investigators changed the cause of death to **SUDEP** (as the wife was with the subject in bed and did not witness the subject as having a seizure). Past medical history included obstructive sleep apnea, hypertension, atrial fibrillation, depression (suicidal ideation). Concomitant medications included levetiracetam, desvenlafaxine, nebivolol, lorazepam, and clonazepam.

Subject 304-305-30505 – 35 year-old BM completed DB Study 304 Part 1 (blinded) and was enrolled in OLE Part 2 (ESL 800 mg). On OLE Study Day 204, the subject was involved in a fight and was **stabbed**. The subject died as a result of his injuries. The Investigator confirmed that the subject did not have any past history of aggressive, violence, police records, or psychiatric diagnosis. No changes in personality, behavior, or social relations during the study were noted by the Investigator. Concomitant medications included carbamazepine and clobazam.

Postmarketing Database

As of the data cutoff date, there were a total of 8 deaths in the postmarketing database: 5 cases of possible SUDEP, 1 drowning, 1 suicide, and 1 "convulsion grand mal." The Sponsor provides an estimated exposure to marketed ESL as 12,279 patient-years. Therefore, mortality per 1000 patient-years in the postmarketing database was 0.65 (which is at least 10 times lower than the mortality rate in the clinical trials). The rate of deaths due to SUDEP was 0.41 per 1000 patient-years (also much lower than rates in the literature).

### 7.3.2 Nonfatal Serious Adverse Events

The Sponsor defined serious adverse events (SAEs) as any adverse event that resulted in death, was life-threatening, required inpatient hospitalization (≥24 hrs in the hospital or an overnight stay) or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect. Additionally, other important medical events that could jeopardize the subject or required intervention to prevent one of the serious outcomes were also considered to be SAEs by the Sponsor. All SAEs were followed by the investigators until resolution or stabilization. This approach was acceptable to the reviewer.

Phase 3 Epilepsy Controlled Pool

In the Phase 3 Epilepsy Controlled Pool, the number of subjects with at least 1 serious TEAE was higher in the total ESL group than placebo. After stratifying by study, Study 302 had the largest risk difference (4.8%) between the total ESL group and the placebo group compared to Study 301 (2.8%) and Study 304 (0.9%). After stratifying by randomized dose group, there was suggestion of an inverse dose-response relationship with the lower dose groups (400 mg and 800 mg) having a higher frequency of SAEs then the highest dose group (1200 mg). However, the low number of subjects with

SAEs precludes any definitive conclusions. The following table summarizes the incidence of SAEs by randomized dose group and study.

*Comment: After analyzing the SAEs using different ISS adverse event datasets, there was a larger risk difference (2.5%) between the total ESL group and the placebo group using the ADEVENTX dataset (that included audit findings of potential events, review events, and signs and symptoms, but excluded crossed out events) than the ADAE dataset (1.7%). This finding suggests that the multiple audits of the integrated adverse event datasets (performed by the Sponsor in response to the Division's requests) resulted in a differential identification of serious adverse events between ESL and placebo subjects (with a larger quantity of serious adverse events uncovered during these audits in ESL subjects than placebo subjects). Additionally, more SAEs were identified during these audits in ESL subjects in Studies 301 and 302 (but not in the newest Study 304).*

*It is also important to note that there were no SAEs reported in the placebo group for Study 302 in the original ADAE dataset (and only 1 SAE reported in the ADEVENTX dataset). Subjects in the placebo group in this trial were taking at least 1 AED (up to 3 AEDs). Thus, it is unusual for there to be no SAEs reported for epilepsy subjects on AED therapy. Furthermore, the SAE rate for the placebo group for other AED development programs are much higher (2.7-10.5%) (Sponsor's table 2-1, referenced by Dr. Podruchny in her Clinical Review of Eslicarbazepine acetate, 2010, page 55). Therefore, the lower incidence of SAEs in the placebo group in Study 302 may represent an overall underreporting of adverse events.*

**Table 25. Treatment-emergent SAEs, Phase 3 Epilepsy Controlled Pool**

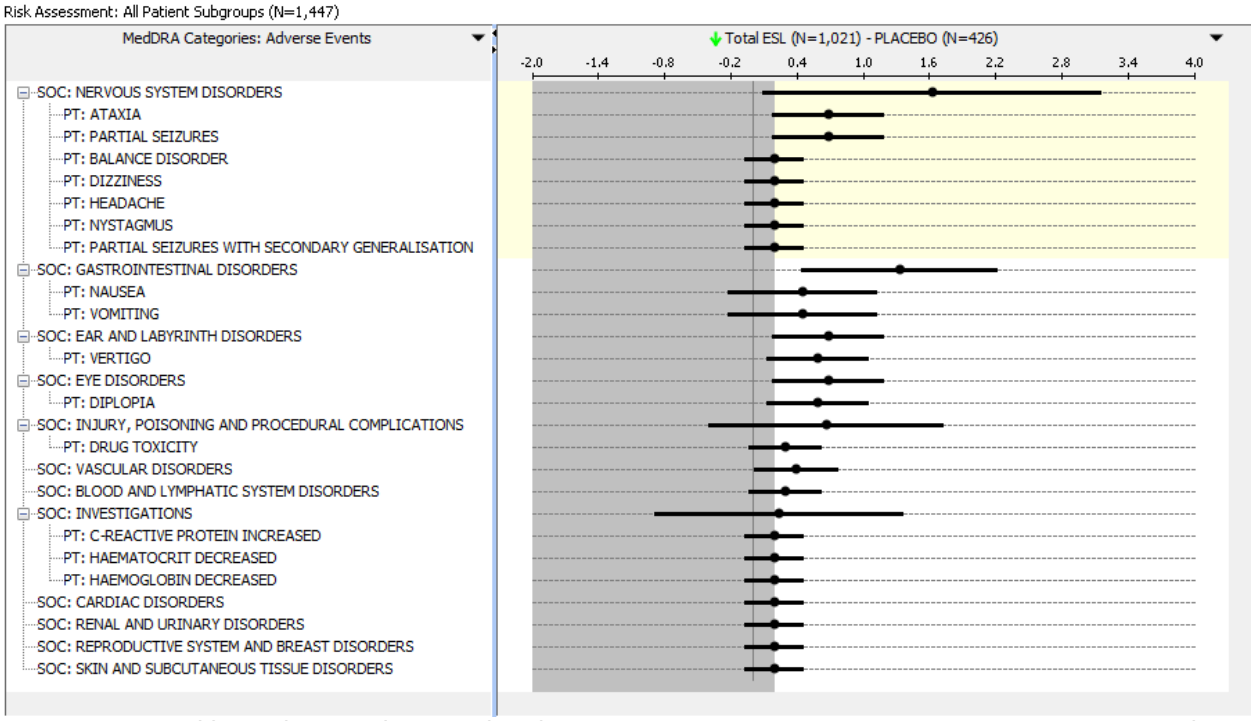
| Subjects with any SAE | **Placebo n (%)** | **ESL n (%)** | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=426 | n=196 | n=415 | n=410 | n=1021 |
| Using ADAE dataset | 11 (2.6) | 9 (4.6) | 24 (5.8) | 11 (2.7) | 44 (4.3) |
| Study 301 Part 1 | 4 (3.9) | 5 (5.0) | 4 (4.1) | 6 (5.9) | 15 (5.0) |
| Study 302 Part 1 | 0 | 4 (4.2) | 6 (6.0) | 2 (2.0) | 12 (4.1) |
| Study 304 Part 1 | 7 (3.1) | 0 | 14 (6.5) | 3 (1.4) | 17 (4.0) |
| Using ADEVENTX | 12 (2.8) | 14 (7.1) | 29 (7.0) | 11 (2.7) | 54 (5.3) |
| Study 301 Part 1 | 4 (3.9) | 7 (7.0) | 7 (7.1) | 6 (5.9) | 20 (6.7) |
| Study 302 Part 1 | 1 (1.0) | 7 (7.3) | 8 (7.9) | 2 (2.0) | 17 (5.8) |
| Study 304 Part 1 | 7 (3.1) | 0 | 14 (6.5) | 3 (1.4) | 17 (4.0) |

Source: ISS Table 33 and created by the reviewer using JReview (ADAE/ADEVENTX: AESER='Y' and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

The following forest plot summarizes the treatment-emergent SAEs sorted by SOC (and then by PT) with a risk difference of ≥ 0.2% (or ≥ 2 subjects) between the total ESL group and placebo. The largest risk difference for SAEs between ESL and placebo subjects was identified for the SOC Nervous system disorders (seizure-related PTs and ataxia/dizziness/balance disorder/nystagmus). Additionally, ESL subjects reported SAEs more frequently than placebo subjects in the SOC Gastrointestinal disorders

(nausea/vomiting) and coded to the following PTs: vertigo, diplopia, drug toxicity, and to some laboratory abnormalities (C-reactive protein increased and haematocrit and haemoglobin decreased). There were other SOCs with smaller risk differences but did not have any PTs with a risk difference of ≥ 2 subjects between the total ESL group and placebo.

**Figure 10. SAEs with ≥ 0.2% Risk Difference (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool**




Source: Created by reviewer using JReview (ADEVENTX: AESER='Y', AEDECOD, AEBODSYS and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

In the Phase 3 Epilepsy Controlled Pool, there were no ESL subjects who developed treatment-emergent SAEs of acute pancreatitis, acute hepatic failure (or hepatic failure), acute respiratory failure, agranulocytosis, anaphylaxis, aplastic anemia, pancytopenia, rhabdomyolysis, septic shock, Stevens Johnson syndrome, toxic epidermal necrolysis, torsade de pointes, ventricular fibrillation, ventricular tachyarrhythmia, or ventricular tachycardia (ISS Table 7.1.11.1.s2 that included audit findings of potential events, review events, and signs and symptoms and included crossed out events). However, there was 1 ESL case each of acute renal failure, blindness, loss of consciousness, and hyperthermia (reviewed in detail in Sections7.3.4 and 7.3.5).

In Study 303 Part 1, only 1 SAE was reported by the Sponsor (ESL subject 303-703-70374 with PT cerebellar syndrome) (Study 303 CSR Section 12.3.3.2). Of note, SAEs were reported in only 0.6% of ESL subjects (1/165) in Study 303 which is much less

than the 4.3% (or 5.3% using ADEVENTX) reported for ESL subjects for Phase 3 Epilepsy Controlled Pool.

In Studies 201 and 202, 4 ESL subjects developed SAEs (versus 1 placebo subject). The only SAE reported in ≥ 1 ESL subject was the PT epilepsy.

Phase 3 Epilepsy Uncontrolled and Controlled Pool
The following tables summarize the treatment-emergent SAEs reported by SOC and by HLT in the Phase 3 Epilepsy Controlled and Uncontrolled Pool. The MedDRA SOC for which ESL subjects most frequently reported a SAE was Nervous System Disorders (5.1%), followed by Injury, poisoning and procedural complications (2.3%), General disorders and administration site conditions (2.2%), Gastrointestinal disorders (2.1%), Investigations (1.6%), and Psychiatric disorders (1.5%). No dose response relationship was identified using modal dose groups (Table 7.3.5.1.r2 in Safety Information Amendment dated 3/8/13).

**Table 26. SAEs by SOC, Phase 3 Epilepsy Uncontrolled and Controlled Pool**

| Body System or Organ Class | Total ESL |
|---|---|
| NERVOUS SYSTEM DISORDERS | 61 (5.1%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 28 (2.3%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 26 (2.2%) |
| GASTROINTESTINAL DISORDERS | 25 (2.1%) |
| INVESTIGATIONS | 19 (1.6%) |
| PSYCHIATRIC DISORDERS | 18 (1.5%) |
| EAR AND LABYRINTH DISORDERS | 11 (0.9%) |
| EYE DISORDERS | 9 (0.8%) |
| CARDIAC DISORDERS | 7 (0.6%) |
| INFECTIONS AND INFESTATIONS | 7 (0.6%) |
| SURGICAL AND MEDICAL PROCEDURES | 7 (0.6%) |
| VASCULAR DISORDERS | 7 (0.6%) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 6 (0.5%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 6 (0.5%) |
| METABOLISM AND NUTRITION DISORDERS | 5 (0.4%) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED | 5 (0.4%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 5 (0.4%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 4 (0.3%) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 4 (0.3%) |
| RENAL AND URINARY DISORDERS | 3 (0.3%) |
| HEPATOBILIARY DISORDERS | 2 (0.2%) |
| PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS | 1 (0.1%) |
| SOCIAL CIRCUMSTANCES | 1 (0.1%) |
| Subjects with SAEs | 105 (8.8%) |
| Total number of subjects | 1194 (100.0%) |

Source: Safety Information Amendment 3/8/13 Table 7.3.5.1.r2 and created by reviewer using JReview (ADEVENTX: AESER='Y', AEBODSYS and ADSL: DOSCATH) for studies 301, 302, 304

**Table 27. SAEs by HLT (in ≥0.5% of Total ESL Group), Phase 3 Epilepsy Uncontrolled and Controlled Pool**

| High Level Term | Total ESL |
|---|---|
| SEIZURES AND SEIZURE DISORDERS NEC | 35 (2.9%) |
| NAUSEA AND VOMITING SYMPTOMS | 13 (1.1%) |
| CEREBELLAR COORDINATION/BALANCE DISTURBANCES | 13 (1.1%) |
| INNER EAR SIGNS AND SYMPTOMS | 11 (0.9%) |
| DISTURBANCES IN CONSCIOUSNESS NEC | 10 (0.8%) |
| NON-SITE SPECIFIC INJURIES NEC | 10 (0.8%) |
| SITE SPECIFIC INJURIES NEC | 8 (0.7%) |
| POISONING AND TOXICITY | 7 (0.6%) |
| RED BLOOD CELL ANALYSES | 7 (0.6%) |
| ASTHENIC CONDITIONS | 7 (0.6%) |
| VISUAL DISORDERS NEC | 7 (0.6%) |
| PSYCHOTIC DISORDER NEC | 6 (0.5%) |
| GAIT DISTURBANCES | 6 (0.5%) |

Source: Safety Information Amendment 3/8/13 Table 7.3.5.1.r2 and created by reviewer using JReview (ADEVENTX: AESER='Y', AEHLT and ADSL: DOSCATH) for studies 301, 302, 304

The following table summarizes the treatment-emergent SAEs reported by PT in the Phase 3 Epilepsy Controlled and Uncontrolled Pool. The MedDRA PT for which the ESL subjects reported as a SAE most frequently was partial seizures (1.6%), followed by vertigo (0.8%) and fall (0.8%). The SAEs reported by ESL subjects after pooling together the open-label extension trials were similar to those reported in the DB studies.

**Table 28. SAEs by PT (in ≥3 ESL subjects), Phase 3 Epilepsy Uncontrolled and Controlled Pool**

| Dictionary-Derived Term | Total ESL |
|---|---|
| PARTIAL SEIZURES | 19 (1.6%) |
| VERTIGO | 10 (0.8%) |
| FALL | 10 (0.8%) |
| VOMITING | 9 (0.8%) |
| CONVULSION | 9 (0.8%) |
| ATAXIA | 9 (0.8%) |
| NAUSEA | 8 (0.7%) |
| DIPLOPIA | 7 (0.6%) |
| STATUS EPILEPTICUS | 6 (0.5%) |
| GAIT DISTURBANCE | 6 (0.5%) |
| DRUG TOXICITY | 5 (0.4%) |
| PSYCHOTIC DISORDER | 5 (0.4%) |
| HEAD INJURY | 5 (0.4%) |
| LOSS OF CONSCIOUSNESS | 4 (0.3%) |
| ASTHENIA | 4 (0.3%) |
| HAEMOGLOBIN DECREASED | 3 (0.3%) |
| WHITE BLOOD CELL COUNT DECREASED | 3 (0.3%) |
| POSTICTAL STATE | 3 (0.3%) |
| EPILEPSY | 3 (0.3%) |
| PYREXIA | 3 (0.3%) |
| DROWNING | 3 (0.3%) |
| DIZZINESS | 3 (0.3%) |
| SOMNOLENCE | 3 (0.3%) |
| SPEECH DISORDER | 3 (0.3%) |
| CONFUSIONAL STATE | 3 (0.3%) |
| COMPLEX PARTIAL SEIZURES | 3 (0.3%) |
| C-REACTIVE PROTEIN INCREASED | 3 (0.3%) |
| HEADACHE | 3 (0.3%) |
| HYPONATRAEMIA | 3 (0.3%) |

| | |
|---|---|
| BALANCE DISORDER | 3 (0.3%) |

Source: Safety Information Amendment 3/8/13 Table 7.3.5.1.r2 and created by reviewer using JReview (ADEVENTX: AESER='Y', AEDECOD and ADSL: DOSCATH) for studies 301, 302, 304

Nonepilepsy Double-blind Pool

In the Nonepilepsy Double-blind Pool, the number of subjects with at least 1 serious TEAE was more than 2 times higher in the total ESL group than placebo. After stratifying by indication, the neuropathy studies had the largest risk difference (3.0%) between the total ESL group and placebo group compared to the studies for the other indications (-0.5% to 1.0%). After stratifying by randomized dose group, there was suggestion of again an inverse dose-response relationship. The following table summarizes the incidence of SAEs by study indication.

*Comment: After analyzing the SAEs using different ISS adverse event datasets, there were similar risk differences (1.8%) between the total ESL group and the placebo group using the ADEVENTX dataset (that included audit findings of potential events, review events, and signs and symptoms, but excluded crossed out events) and the ADAE dataset (1.6%).*

**Table 29. Treatment-emergent SAEs, Nonepilepsy Pooled Groups**

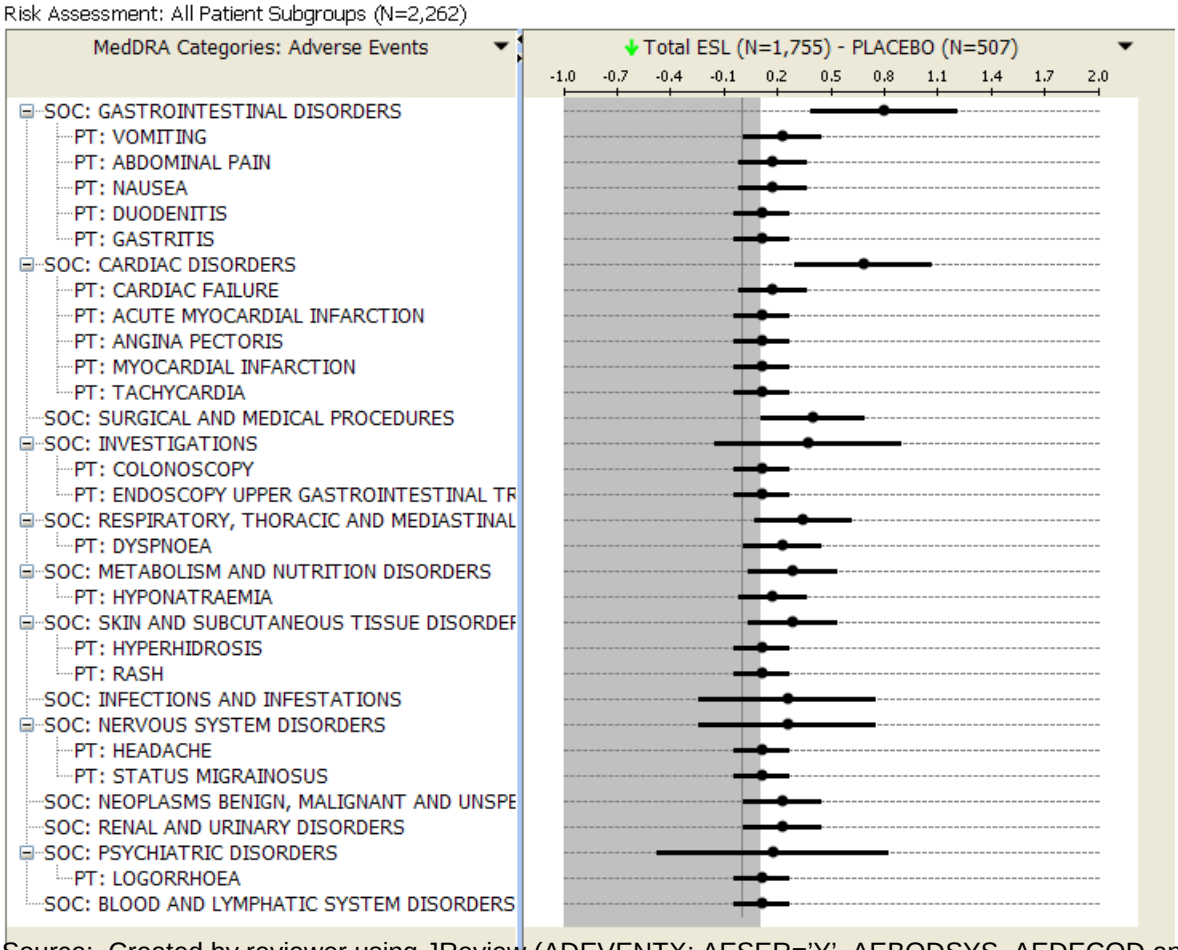
| Pooled DB Group | Placebo n (%) | ESL n (%), Randomized Dose Groups | | | | |
|---|---|---|---|---|---|---|
| | | <600 mg | 600-<1000 | 1000-<1400 | ≥1400 mg | Total |
| Total # of subjects | | | | | | |
| Bipolar (203+204) | 51 | 0 | 129 | 9 | 10 | 148 |
| Neuropathy (206+207) | 189 | 0 | 369 | 376 | 190 | 936 |
| Migraine/Fibromyalgia | 267 | 130 | 270 | 271 | 0 | 671 |
| Nonepilepsy DB Pool* | 507 | 130 | 768 | 657 | 200 | 1755 |
| Nonepi Controlled Pool^ | 411 | 303 | 571 | 321 | 99 | 1294 |
| | | | | | | |
| Subjects with SAEs | | | | | | |
| Bipolar (203+204) | 2 (3.9) | 0 | 4 (3.1) | 0 | 1 (10.0) | 5 (3.4) |
| Neuropathy (206+207) | 0 | 0 | 10 (2.7) | 13 (3.5) | 5 (2.6) | 28 (3.0) |
| Migraine/Fibromyalgia | 4 (1.5) | 5 (3.8) | 7 (2.6) | 5 (1.8) | 0 | 17 (2.5) |
| Nonepilepsy DB Pool* | 6 (1.2) | 5 (3.8) | 21 (2.7) | 18 (2.7) | 6 (3.0) | 50 (2.8) |
| using ADEVENTX | 7 (1.4) | 5 (3.8) | 25 (3.3) | 19 (2.9) | 7 (3.5) | 56 (3.2) |
| Nonepi Controlled Pool^ | 6 (1.5) | 13 (4.3) | 11 (1.9) | 7 (2.2) | 3 (3.0) | 34 (2.6) |
| using ADEVENTX | 7 (1.7) | 14 (4.6) | 14 (2.5) | 7 (2.2) | 3 (3.0) | 38 (2.9) |

Source: ISS Table 7.4.6.1.s1 and created by reviewer using JReview (ADAE/ADEVENTX: AESER='Y' and ADSL) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)
*Nonepilepsy DB Pool includes Study 206 Part 1
^Nonepilepsy Controlled Pool excludes Study 206 Part 1 and uses mean dose group

The following forest plot summarizes the treatment-emergent SAEs sorted by SOC (and then by PT) with a risk difference of ≥ 0.1% (or ≥ 2 subjects) between the total ESL group and placebo. The largest risk difference for SAEs between ESL and placebo subjects was identified for the SOC Gastrointestinal disorders (nausea/vomiting, abdominal pain). ESL subjects also reported SAEs more frequently than placebo subjects in the SOC Cardiac Disorders (cardiac failure, myocardial infarction,

tachycardia), predominantly in the neuropathy studies (cardiac adverse events are reviewed in detail in Section 7.3.5). Additionally, the following PTs were reported as SAEs in ≥2 ESL subjects and greater than placebo: colonoscopy/endoscopy, dyspnoea, hyponatremia, rash/hyperhidrosis, headache/status migrainosus, and logorrhoea. There were other SOCs with smaller risk differences but did not have any PTs with a risk difference of ≥ 2 subjects between the total ESL group and placebo. Interestingly, there were fewer subjects with SAEs in the SOC Nervous System Disorders than in the epilepsy studies.

**Figure 11. SAEs with ≥ 0.1% Risk Difference (Total ESL-Placebo), Nonepilepsy Double-blind Pool (includes study 206)**




Source: Created by reviewer using JReview (ADEVENTX: AESER='Y', AEBODSYS, AEDECOD and ADSL) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

Nonepilepsy Uncontrolled and Controlled Pool

The following tables summarize the treatment-emergent SAEs reported by SOC and by HLT in the Nonepilepsy Uncontrolled and Controlled Pool. The MedDRA SOC for which ESL subjects most frequently reported a SAE was Gastrointestinal disorders (1.1%), followed by General disorders and administration site conditions (1.1%), Nervous

System disorders (1.0%), Psychiatric disorders (1.0%), Investigations (0.9%), and Cardiac disorders (0.7%).

*Comment: The order of the SOCs is different in the nonepilepsy studies (#1 SOC Gastrointestinal disorders) compared to the epilepsy studies (#1 SOC Nervous system disorders). Furthermore, cardiac conditions and psychiatric disorders were reported as SAEs more frequently in the nonepilepsy studies than in the epilepsy studies. These differences in the SOC distribution between the epilepsy and nonepilepsy pools were likely due to the underlying diseases and comorbidities.*

*The overall percentage of SAEs reported in the nonepilepsy studies (4.8%) was lower than in the epilepsy studies (8.8%). However, after adjusting for duration of exposure, the incidence rate for SAEs was higher in the nonepilepsy uncontrolled/controlled pool (0.15 patient-years) than the epilepsy uncontrolled/controlled pool (0.10 patient-years). This is likely due to the older subjects with different comorbidities and risk factors in the nonepilepsy population (e.g., patients with diabetes mellitus in the diabetic neuropathy study 206).*

**Table 30. SAEs by SOC, Nonepilepsy Uncontrolled and Controlled Pool**

| Body System or Organ Class | Total ESL |
|---|---|
| GASTROINTESTINAL DISORDERS | 22 (1.1%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 21 (1.1%) |
| NERVOUS SYSTEM DISORDERS | 20 (1.0%) |
| PSYCHIATRIC DISORDERS | 19 (1.0%) |
| INVESTIGATIONS | 18 (0.9%) |
| CARDIAC DISORDERS | 14 (0.7%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 13 (0.7%) |
| INFECTIONS AND INFESTATIONS | 13 (0.7%) |
| SURGICAL AND MEDICAL PROCEDURES | 12 (0.6%) |
| METABOLISM AND NUTRITION DISORDERS | 11 (0.6%) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 9 (0.5%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 7 (0.4%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 7 (0.4%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 6 (0.3%) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED | 6 (0.3%) |
| VASCULAR DISORDERS | 5 (0.3%) |
| EAR AND LABYRINTH DISORDERS | 5 (0.3%) |
| RENAL AND URINARY DISORDERS | 5 (0.3%) |
| SOCIAL CIRCUMSTANCES | 3 (0.2%) |
| HEPATOBILIARY DISORDERS | 2 (0.1%) |
| PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS | 1 (0.1%) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 1 (0.1%) |
| Subjects with SAEs | 93 (4.8%) |
| Total number of subjects | 1936 (100.0%)* |

Source: Created by reviewer using JReview (ADEVENTX: AESER='Y', AEBODSYS and ADSL: DOSCATH) for studies 203, 204, 206, 207, 209, 210
*Double counts 104 subjects that are in both Study 203/204 and 205

**Table 31. SAEs by HLT (in ≥0.2% of Total ESL Group), Nonepilepsy Uncontrolled and Controlled Pool**

| High Level Term | Total ESL |
|---|---|
| NAUSEA AND VOMITING SYMPTOMS | 9 (0.5%) |
| GENERAL SIGNS AND SYMPTOMS NEC | 8 (0.4%) |
| MOOD ALTERATIONS WITH MANIC SYMPTOMS | 8 (0.4%) |
| MUSCULOSKELETAL/CONNECTIVE TISSUE PAIN AND DISCOMFORT | 7 (0.4%) |
| ISCHAEMIC CORONARY ARTERY DISORDERS | 6 (0.3%) |
| NON-SITE SPECIFIC INJURIES NEC | 6 (0.3%) |
| DISTURBANCES IN CONSCIOUSNESS NEC | 6 (0.3%) |
| HEART FAILURES NEC | 6 (0.3%) |
| BEHAVIOUR AND SOCIALISATION DISTURBANCES | 6 (0.3%) |
| LOWER RESPIRATORY TRACT AND LUNG INFECTIONS | 5 (0.3%) |
| INNER EAR SIGNS AND SYMPTOMS | 5 (0.3%) |
| ASTHENIC CONDITIONS | 5 (0.3%) |
| FEBRILE DISORDERS | 5 (0.3%) |
| GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL/THROAT) | 5 (0.3%) |
| PHYSICAL EXAMINATION PROCEDURES | 5 (0.3%) |
| BREATHING ABNORMALITIES | 5 (0.3%) |
| DISTURBANCES IN INITIATING AND MAINTAINING SLEEP | 4 (0.2%) |
| BIPOLAR DISORDERS | 4 (0.2%) |
| ANXIETY SYMPTOMS | 4 (0.2%) |
| SODIUM IMBALANCE | 4 (0.2%) |
| THERAPEUTIC PROCEDURES NEC | 4 (0.2%) |
| EMOTIONAL AND MOOD DISTURBANCES NEC | 4 (0.2%) |
| CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS NEC | 4 (0.2%) |
| NEUROLOGICAL SIGNS AND SYMPTOMS NEC | 4 (0.2%) |
| RATE AND RHYTHM DISORDERS NEC | 4 (0.2%) |

Source: Created by reviewer using JReview (ADEVENTX: AESER='Y', AEHLT and ADSL: DOSCATH) for studies 203, 204, 206, 207, 209, 210

The following table summarizes the treatment-emergent SAEs reported by PT in the Nonepilepsy Controlled and Uncontrolled Pool. The MedDRA PT for which the ESL subjects reported as a SAE most frequently was mania (0.4%), followed by vomiting (0.4%) and nausea (0.3%). The SAEs reported by ESL subjects after pooling together the open-label extension trials are similar to those reported in the double-blind trials.

**Table 32. SAEs by PT (in ≥0.2% of ESL subjects), Nonepilepsy Uncontrolled and Controlled Pool**

| Dictionary-Derived Term | Total ESL |
|---|---|
| MANIA | 8 (0.4%) |
| VOMITING | 8 (0.4%) |
| NAUSEA | 6 (0.3%) |
| PYREXIA | 5 (0.3%) |
| UNEVALUABLE EVENT | 5 (0.3%) |
| VERTIGO | 5 (0.3%) |
| DYSPNOEA | 5 (0.3%) |
| CARDIAC FAILURE | 5 (0.3%) |
| BACK PAIN | 4 (0.2%) |
| HYPONATRAEMIA | 4 (0.2%) |
| ABDOMINAL PAIN | 4 (0.2%) |
| FALL | 4 (0.2%) |
| DIZZINESS | 3 (0.2%) |
| DEHYDRATION | 3 (0.2%) |
| BIPOLAR DISORDER | 3 (0.2%) |
| HEADACHE | 3 (0.2%) |
| PSYCHOMOTOR HYPERACTIVITY | 3 (0.2%) |

| | |
|---|---|
| VERTEBROBASILAR INSUFFICIENCY | 3 (0.2%) |
| GASTRITIS | 3 (0.2%) |
| DYSPEPSIA | 3 (0.2%) |
| INFECTION | 3 (0.2%) |
| ASTHENIA | 3 (0.2%) |
| INSOMNIA | 3 (0.2%) |
| IRRITABILITY | 3 (0.2%) |
| LOGORRHOEA | 3 (0.2%) |
| CHEST PAIN | 3 (0.2%) |

Source: Created by reviewer using (ADEVENTX: AESER='Y', AEDECOD and ADSL: DOSCATH) for studies 203, 204, 206, 207, 209, 210

*Comment: The preferred term of "unevaluable event" is unusual in adverse event databases. I will discuss these events further in Section 7.4.1.*

Phase 1 Study Pool
In the Phase 1 Study Pool, there were 6 ESL subjects (0.7%) who reported SAEs compared to 0 placebo subjects. The following serious TEAEs were each reported in 1 ESL subject: cardiac failure, tonsillitis, hepatic encephalopathy (from the hepatic impairment study 111), pregnancy, Stevens-Johnson syndrome, and hypertension.

In the entire eslicarbazepine acetate drug development program (including 303 and including audit findings, review events, signs and symptoms), there was 1 ESL case each of SAEs coded to the following PTs: acute renal failure, acute respiratory failure, hyperthermia, ventricular arrhythmia, pancytopenia, septic shock, hepatic encephalopathy, blindness, Stevens Johnson syndrome, and toxic skin eruption (reviewed in detail in Sections 7.3.4 and 7.3.5). Furthermore there were 6 ESL cases of loss of consciousness, and 2 cases of syncope. However, there were no ESL subjects (in the ISS datasets submitted by the Sponsor) who developed serious TEAEs coded to the following PTs: acute pancreatitis, acute hepatic failure (or hepatic failure), agranulocytosis, anaphylaxis, aplastic anemia, rhabdomyolysis, toxic epidermal necrolysis, torsade de pointes, ventricular fibrillation, or ventricular tachycardia.

Ongoing Studies
The following table summarizes the additional SAEs by treatment group that were reported by the Sponsor for the ongoing studies. Overall, the SAEs in the ongoing trials are consistent with those reported in the clinical trials. The majority of the SAEs in the SOC Nervous System Disorders were seizures related (61% of the SAEs in this SOC in the ESL group), in the SOC Injury were head or bone/joint injuries (67% of the SAEs in this SOC in the ESL group), and in the SOC Metabolism Disorders were due to hyponatremia (82% of the SAEs in this SOC in the ESL group). Additionally, notable SAEs included angioedema, DRESS, acute respiratory failure, acute renal failure/renal failure, suicidal ideation/attempt, pregnancy/abortion spontaneous, cardiac arrest, cardiogenic shock, ventricular tachycardia, and pancreatitis. Further details regarding these SAEs are described in appropriate sections of this review (7.3.1, 7.3.4, and 7.3.5). For a detailed analysis of rebound epilepsy, worsening of seizures, and status epilepticus with ESL use, the reader is referred to Dr. Podruchny's review of efficacy.

**Table 33. SAEs by SOC, Ongoing Studies**

| | Treatment Group | | |
|---|---|---|---|
| MedDRA SOC | Placebo | ESL group | Blinded |
| Nervous System Disorders | 0 | 44 | 45 |
| Infections and Infestations | 3 | 18 | 23 |
| Injury, Poisoning and Procedural Complications | 0 | 18 | 6 |
| Gastrointestinal Disorders | 1 | 13 | 3 |
| Metabolism and Nutrition Disorders | 0 | 11 | 2 |
| Cardiac Disorders | 0 | 9 | 6 |
| Psychiatric Disorders | 0 | 8 | 4 |
| General Disorders and Administration Site Conditions | 0 | 6 | 4 |
| Skin and Subcutaneous Tissue Disorders | 0 | 4 | 6 |
| Investigations | 0 | 4 | 3 |
| Neoplams Benign, Malignant and Unspecified | 0 | 3 | 4 |
| Respiratory, Thoracic and Mediastinal Disorders | 1 | 3 | 3 |
| Pregnancy, Puerperium, and Perinatal Conditions | 0 | 3 | 0 |
| Renal and Urinary Disorders | 0 | 3 | 0 |
| Musculoskeletal and Connective Tissue Disorders | 1 | 2 | 1 |
| Ear and Labyrinth Disorders | 0 | 2 | 1 |
| Vascular Disorders | 0 | 2 | 1 |
| Eye Disorders | 0 | 1 | 0 |
| Hepatobiliary Disorders | 1 | 1 | 0 |
| Immune System Disorders | 0 | 1 | 0 |
| Reproductive System and Breast Disorders | 0 | 1 | 0 |
| Blood and Lymphatic System Disorders | 0 | 1 | 0 |
| Surgical and Medical Procedures | 0 | 0 | 1 |
| Not yet coded | 0 | 4 | 1 |

Source: Safety Information Amendment 4/19/13 Table 2

Postmarketing Database

The Sponsor identified a total of 266 serious events reported in the postmarketing database. The most common SAEs reported were hyponatremia, seizures (of various types), neurologic effects (dizziness, ataxia, vertigo, aphasia, diplopia, altered state of consciousness, somnolence), and rash (of various types). In the Sponsor's table of SAEs reported in ≥ 2 patients, there were a total of 2 deaths and 2 sudden deaths (described further in Section 7.3.1 above). The 2 cases of spontaneous abortion are described in Section 7.6.2. Overall, the postmarketing SAE reports are consistent with those reported in the clinical trials.

*Comment: In response to the Division's information request for a tabular list of all postmarketing SAEs reported in 1 patient, the Sponsor reported the following additional SAEs (in the Safety Information Amendment dated 4/19/13): three additional deaths (completed suicide, drowning, sudden unexplained death in epilepsy), 1 hepatorenal syndrome (in addition to hepatic enzyme increased, ALT increased), 1 cardiac arrest, 1 circulatory collapse, 1 pancytopenia, 1 Stevens-Johnson syndrome (in addition to dermatitis bullous, mouth ulceration, rash pruritic, rash vesicular), 1 angioedema (in addition to hypersensitivity, laryngospasm). The case reports were submitted by the*

*Sponsor in the Safety Information Amendment dated 6/10/13. Further details regarding these cases are located in the appropriate areas of this review in Sections 7.3.1, 7.3.4, and 7.3.5. Additionally, the reader is referred to Dr. Podruchny's review of efficacy for a detailed analysis of rebound epilepsy, worsening of seizures, and status epilepticus with ESL use.*

**Table 34. Postmarketing SAEs reported in ≥2 Patients**

| MedDRA Preferred Term | Total (N=266) | Person-Time Incidence Rate per patient-year (using 12279 patient-year exposure to ESL) |
|---|---|---|
| Hyponatraemia | 86 | 0.70% |
| Blood sodium decreased | 12 | 0.10% |
| Partial Seizures | 26 | 0.21% |
| Epilepsy | 3 | 0.02% |
| Grand mal convulsion | 7 | 0.06% |
| Status epilepticus | 4 | 0.03% |
| Complex partial seizures | 2 | 0.02% |
| Petit mal epilepsy | 2 | 0.02% |
| Dizziness | 5 | 0.04% |
| Ataxia | 4 | 0.03% |
| Vertigo | 4 | 0.03% |
| Aphasia | 3 | 0.02% |
| Diplopia | 3 | 0.02% |
| Somnolence | 2 | 0.02% |
| Altered state of consciousness | 2 | 0.02% |
| Rash | 3 | 0.02% |
| Rash generalized | 2 | 0.02% |
| Rash erythematous | 3 | 0.02% |
| Drug eruption | 2 | 0.02% |
| Death | 2 | 0.02% |
| Sudden death | 2 | 0.02% |
| Thrombocytopenia | 3 | 0.02% |
| Bicytopenia | 2 | 0.02% |
| Abortion spontaneous | 2 | 0.02% |
| Gamma-glutamyltransferase | 3 | 0.02% |
| Hypertensive crisis | 2 | 0.02% |
| Vomiting | 2 | 0.02% |

Source: ISS Table 37

## 7.3.3 Dropouts and/or Discontinuations

Epilepsy Studies

In the Phase 3 Epilepsy Controlled Pool, a much higher percentage of ESL subjects (22.2%, 227/1021) discontinued compared to placebo subjects (3.8%, 59/426). This result is mainly driven by discontinuations due to adverse events occurring at a much higher frequency in ESL subjects (13.6%) than in placebo subjects (2.8%). However, discontinuations due to withdrew consent, protocol related, and "other" occurred in ESL subjects at approximately the same or lower frequency than in placebo subjects. The following table summarizes the discontinuations for Phase 3 Epilepsy Controlled Pool.

**Table 35. Disposition, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo n (%) | ESL n (%), Randomized Dose Groups | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| **n** | 426 | 196 | 415 | 410 | 1021 |
| **Completed** | 367 (86.2%) | 174 (88.8%) | 339 (81.7%) | 281 (68.5%) | 794 (77.8%) |
| **Discontinued** | 59 (13.8%) | 22 (11.2%) | 76 (18.3%) | 129 (31.5%) | 227 (22.2%) |
| Study 301 Part 1 | 18 (17.6%) | 10 (10%) | 13 (13.3%) | 31 (30.3%) | 54 (18%) |
| Study 302 Part 1 | 6 (6.0%) | 12 (12.5%) | 20 (19.8%) | 30 (30.6%) | 62 (21%) |
| Study 304 Part 1 | 35 (15.6%) | 0 | 43 (19.9%) | 68 (32.3%) | 111 (26%) |
| | | | | | |
| **Primary reason for discontinuation from therapy:** | | | | | |
| Adverse event | 12 (2.8%) | 12 (6.1%) | 42 (10.1%) | 85 (20.7%) | 139 (13.6%) |
| Study 301 Part 1 | 1 (1.0%) | 4 (4.0%) | 6 (6.1%) | 15 (14.7%) | 25 (8.3%) |
| Study 302 Part 1 | 2 (2.0%) | 8 (8.3%) | 15 (15.0%) | 25 (25.5%) | 38 (12.9%) |
| Study 304 Part 1 | 9 (4.0%) | NA | 21 (9.7%) | 45 (21.4%) | 66 (15.5%) |
| Withdrew Consent | 17 (4.0%) | 5 (2.6%) | 13 (3.1%) | 23 (5.6%) | 41 (4.0%) |
| Protocol related | 16 (3.8%) | 0 | 7 (1.7%) | 10 (2.4%) | 17 (1.7%) |
| Disallowed Concomitant Med | 1 (0.2%) | 0 | 0 | 0 | 0 |
| Lack of Compliance | 9 (2.1%) | 0 | 1 (0.2%) | 6 (1.5%) | 7 (0.7%) |
| Pregnancy | 2 (0.5%) | 0 | 2 (0.5%) | 0 | 2 (0.2%) |
| Protocol violation | 4 (0.9%) | 0 | 4 (1.0%) | 3 (0.7%) | 7 (0.7%) |
| Subject Inelig ble | 0 | 0 | 0 | 1 (0.2%) | 1 (0.1%) |
| Other | 11 (2.6%) | 3 (1.5%) | 10 (2.4%) | 4 (1.0%) | 17 (1.7%) |
| Administrative reasons | 2 (0.5%) | 0 | 4 (1.0%) | 5 (1.2%) | 9 (0.9%) |
| Inadequate therapy | 1 (0.2%) | 2 (1.0%) | 0 | 2 (0.4%) | 4 (0.4%) |
| Exacerbation of Seizures | 1 (0.2%) | 2 (1.0%) | 0 | 1 (0.2%) | 3 (0.3%) |
| Lack of Efficacy | 0 | 0 | 0 | 1 (0.2%) | 1 (0.1%) |
| Lost to follow-up | 0 | 0 | 0 | 0 | 0 |

Source: ISS Table 4

*Comment: The strongest dose-response relationship was observed for discontinuations due to adverse events. Discontinuations due to adverse events in the highest dose group (1200 mg) occurred at 7 times higher frequency (20.7%) than that of the placebo group (2.8%). Even in the lowest dose group (400 mg), discontinuations due to adverse events occurred at twice the frequency than that of the placebo group. After stratifying by study, subjects randomized to the 1200 mg dose group in Studies 301 and 302 withdrew due to adverse events at an even greater frequency (>12x) than that of the placebo group. The Sponsor reports that approximately one-third of all withdrawals occurred during the titration period (first 2 weeks), with the remainder occurring primarily during the maintenance period.*

In the Phase 3 Epilepsy Uncontrolled and Controlled Pool, over one-third of the ESL subjects (36.8%) withdrew from the studies. The most common reasons for discontinuation was adverse events (15.3%), withdrew consent (10.0%), and “other” (5.6%). An inverse dose response relationship was identified for some of the reasons for discontinuation from therapy (e.g., withdrew consent). The following table summarizes the discontinuations by ESL dose for the Phase 3 Epilepsy Uncontrolled and Controlled Pool.

**Table 36. Disposition, Phase 3 Epilepsy Uncontrolled and Controlled Pool**

| Category | ESL n (%), Modal dose groups | | | | |
|---|---|---|---|---|---|
| | <600 mg | 600-<1000 | 1000-<1400 | ≥1400 mg | Total |
| **n** | 158 | 646 | 388 | 3 | 1195 |
| **Completed** | 46 (29.1%) | 436 (67.5%) | 273 (70.4%) | 0 | 755 (63.2%) |
| **Discontinued** | 112 (70.9%) | 210 (32.5%) | 115 (29.6%) | 3 (100%) | 440 (36.8%) |
| | | | | | |
| **Primary reason for discontinuation from therapy:** | | | | | |
| Adverse event | 51 (32.3%) | 92 (14.2%) | 39 (10.1%) | 1 (33.3%) | 183 (15.3%) |
| Withdrew Consent | 27 (17.1%) | 60 (9.3%) | 32 (8.2%) | 0 | 119 (10.0%) |
| Administrative reasons | 6 (3.8%) | 14 (2.2%) | 13 (3.4%) | 1 (33.3%) | 34 (2.8%) |
| Protocol related | 8 (5.1%) | 12 (1.9%) | 6 (1.5%) | 1 (33.3%) | 27 (2.3%) |
| Disallowed Concomitant Med | 0 | 0 | 0 | 0 | 0 |
| Lack of Compliance | 3 (1.9%) | 8 (1.2%) | 2 (0.5%) | 1 (33.3%) | 14 (1.2%) |
| Pregnancy | 1 (0.6%) | 2 (0.3%) | 1 (0.3%) | 0 | 4 (0.3%) |
| Protocol violation | 4 (2.5%) | 2 (0.3%) | 2 (0.5%) | 0 | 8 (0.7%) |
| Subject Inelig ble | 0 | 0 | 1 (0.3%) | 0 | 1 (0.1%) |
| Inadequate therapy | 4 (2.5%) | 2 (0.3%) | 4 (1.0%) | 0 | 10 (0.8%) |
| Exacerbation of Seizures | 4 (2.5%) | 2 (0.3%) | 3 (0.8%) | 0 | 9 (0.8%) |
| Lack of Efficacy | 0 | 0 | 1 (0.3%) | 0 | 1 (0.1%) |
| Other | 16 (10.1%) | 30 (4.6%) | 21 (5.4%) | 0 | 67 (5.6%) |
| Lost to follow-up | 0 | 0 | 0 | 0 | 0 |

Source: Safety Amendment 3/28/13 Table 2

*Comment: The listings of subjects with "other" and withdrawal consent reason for discontinuation were reviewed for the 186 ESL subjects (Safety Amendment 3/8/13 Table 2.6.1.r1). Approximately one-third of the subjects (31%) reported adverse events that started within a few days before drug discontinuation. These adverse events included the following preferred terms occurring in ≥ 2 subjects: SOC Nervous system disorders (seizures [of any type], dizziness, vertigo, gait disturbance, coordination abnormal, balance disorder, ataxia, headache, somnolence, asthenia, fatigue, lethargy, disturbance in attention, memory impairment, vision blurred, diplopia), SOC Gastrointestinal disorders (nausea, vomiting, dyspepsia, gastritis, constipation, abdominal discomfort/pain), SOC Skin and subcutaneous tissue disorders (rash, pruritus), SOC Psychiatric disorders (abnormal behavior, mood altered, anxiety, irritability), along with back pain and hyponatremia/blood sodium decreased.*

*It was noted in the discontinuation comments that many of the subjects in the "other" category discontinued due to lack of efficacy. Of note, one subject with the primary reason for discontinuation as "other" was actually due to death (subject 301-177-90425 discussed in Section 7.3.1 of this review).*

In Study 201, a lower percentage of ESL subjects (19.8%, 19/96) discontinued compared to placebo subjects (23.4%, 11/47). Although the frequency of discontinuations due to adverse events was similar between the ESL subjects (7.3%) and placebo subjects (8.5%), discontinuations due to withdrawal of consent was higher in the ESL subjects (6.3%) than placebo subjects (4.3%) (CSR 201 Figure 2).

In pediatric Study 202, there were discontinuations due to withdrawal of consent by the patient/caregiver (9.7%, 3/31) and by the investigator due to a SAE (6.5%, 2/31) (CSR 202 Figure 2).

*Comment: The listings of subjects with "other" and withdrawal consent reason for discontinuation were reviewed for the 10 ESL subjects (Safety Amendment 3/8/13 Table 2.6.1.r1). A few of these subjects (n=3) reported adverse events that started within a few days before drug discontinuation. These adverse events included the following preferred terms: blood cholesterol increased, dyspepsia, nausea, dizziness, headache, and blood creatine phosphokinase increased.*

Nonepilepsy Studies
In the nonepilepsy double-blind pool, a higher percentage of ESL subjects (24%, 429/1755) discontinued compared to placebo subjects (17.0%, 88/507) (see table below). This result is mainly driven by discontinuations due to adverse events occurring at a much higher frequency in ESL subjects (14.4%) than in placebo subjects (5.7%). The incidence of discontinuations due to consent withdrawal was also higher in ESL subjects (5.2%) than placebo subjects (3.9%).

**Table 37. Disposition, Nonepilepsy Pooled Groups**

| Category | Placebo n (%) | ESL n (%), Randomized Dose Groups | | | | |
|---|---|---|---|---|---|---|
| | | <600 mg | 600-<1000 | 1000-<1400 | ≥1400 mg | Total |
| **Treated** | | | | | | |
| Bipolar (203+204) | 51 | 0 | 129 | 9 | 10 | 148 |
| Neuropathy (206+207) | 189 | 0 | 369 | 376 | 190 | 936 |
| Migraine/Fibromyalgia | 267 | 130 | 270 | 271 | 0 | 671 |
| Nonepilepsy DB Pool | 507 | 130 | 768 | 657 | 200 | 1755 |
| **Discontinued** | | | | | | |
| Bipolar DB | 12 (24%) | 0 | 30 (23%) | 3 (33.3%) | 5 (50%) | 38 (26%) |
| Neuropathic Pain DB | 36 (19%) | 0 | 79 (21%) | 91 (24.2%) | 66 (35%) | 236 (25%) |
| Migraine/Fibromyalgia | 40 (15%) | 32 (25%) | 46 (17%) | 77 (28.4%) | 0 | 155 (23%) |
| Nonepilepsy DB Pool | 88 (17%) | 32 (25%) | 155 (20%) | 171 (26.0%) | 71 (36%) | 429 (24%) |
| | | | | | | |
| **Primary reason for discontinuation from therapy:** | | | | | | |
| **Adverse event** | | | | | | |
| Bipolar DB | 2 (3.9%) | NA | 7 (5.4%) | 2 (22%) | 2 (20%) | 11 (7.4%) |
| Neuropathic Pain DB | 13 (6.9%) | NA | 44 (11.9%) | 55 (15%) | 43 (23%) | 142 (15.2%) |
| Migraine/Fibromyalgia | 14 (5.2%) | 15 (11.5%) | 33 (12.2%) | 51 (19%) | NA | 99 (14.8%) |
| Nonepilepsy DB Pool | 29 (5.7%) | 15 (11.5%) | 84 (10.9%) | 108(16%) | 45 (23%) | 252(14.4%) |
| **Withdrew consent** | | | | | | |
| Nonepilepsy DB Pool | 20 (3.9%) | 6 (4.6%) | 32 (4.2%) | 35 (5.3%) | 18 (9.0%) | 91 (5.2%) |
| **Protocol related^** | | | | | | |
| Nonepilepsy DB Pool | 11 (2.2%) | 2 (1.5%) | 7 (0.9%) | 14 (2.1%) | 5 (2.5%) | 28 (1.6%) |
| **Lack of efficacy** | | | | | | |
| Nonepilepsy DB Pool | 22 (4.3%) | 7 (5.4%) | 25 (3.3%) | 9 (1.4%) | 3 (1.5%) | 44 (2.5%) |
| **Other** | | | | | | |
| Nonepilepsy DB Pool | 6 (1.2%) | 2 (1.5%) | 7 (0.9%) | 5 (0.8%) | 0 | 14 (0.8%) |

Source: Created by reviewer using JReview (ADSL: COMPLETE='N', P1COMP is null or P1COMP='N') for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)
^Protocol related includes pregnancy, lack of compliance, subject ineligible, protocol violation, administrative reasons

*Comment: A dose-response relationship was observed for discontinuations due to adverse events. The incidence of discontinuations due to adverse events in the highest dose group (≥1400 mg) was 4 times greater (23%) than that of the placebo group (5.7%). Even in the lowest dose group (<600 mg), discontinuations due to adverse events occurred at twice the frequency than that of the placebo group. After stratifying by study indication, subjects in the bipolar studies (at the higher dose groups) withdrew due to adverse events at an even greater frequency (>5x) than that of the placebo group. Of note in the ISS, an inverse dose-response relationship for discontinuations due to adverse events was presented when mean daily dose groups were used (20.5%, 14.9%, 7.5%, 7.1%, respectively) (ISS Table 6).*

*The listings of subjects with "other" and withdrawal consent reason for discontinuation were reviewed for the 168 ESL subjects (Safety Amendment 3/8/13 Table 2.6.1.r1). Approximately half of these subjects (45%) reported adverse events that started within a few days before drug discontinuation. These adverse events included the following preferred terms occurring in ≥ 2 subjects: SOC Nervous system disorders (dizziness, headache, vertigo, gait disturbance, balance disorder, paraesthesia oral, somnolence, asthenia, fatigue, disturbance in attention), SOC Gastrointestinal disorders (nausea, vomiting, dyspepsia, constipation), SOC Skin and subcutaneous tissue disorders (rash macular, pruritus), SOC Cardiac disorders (blood pressure systolic decreased, hypotension, hypertension, oedema peripheral/oedema) along with influenza/viral infection, blood creatine phosphokinase increased. Notably, there was one subject (205-543-203154) who discontinued due to withdrawal of consent who completed suicide 10 days after ESL discontinuation.*

Phase 1 Studies
During the Phase 1 trials, a lower percentage of ESL subjects (9.1%, 77/847) discontinued compared to placebo subjects (25.1%, 56/223). The most common reason for discontinuation for ESL treated subjects was due to AEs (5.4%, n=46). Other reasons for discontinuation included withdrawal of consent (1.9%), administrative reasons (0.8%), lost to follow-up (0.4%), other (0.4%), and lack of compliance (0.2%) (ISS Table 2.5.1). Conversely, for placebo treated subjects, the most common reason for discontinuation was due to subject ineligible (11.2%, n=25). Other reasons for discontinuation included adverse event (5.8%), withdrawal of consent (2.7%), administrative reasons (2.2%), other (1.8%), lack of compliance (0.9%), and protocol violation (0.4%) (ISS Table 2.5.1).

*Comment: The listings of subjects with "other" and withdrawal consent reason for discontinuation were reviewed for the 19 ESL subjects (Safety Amendment 3/8/13 Table 2.6.1.r1). Most of the subjects (84%) reported adverse events that started within a few*

*days before drug discontinuation. These adverse events included the following preferred terms occurring in ≥ 2 subjects: SOC Nervous system disorders (dizziness, headache, somnolence, fatigue, disturbance in attention, paraesthesia), SOC Gastrointestinal disorders (nausea, vomiting, constipation, dry mouth, abdominal pain), SOC Skin and subcutaneous tissue disorders (rash). There were reports of 3 adverse events that were severe: rash/somnolence (both in subject 119-000-0005) and dizziness.*

Discontinuations Due to TEAEs
The following section further analyzes the TEAEs leading to treatment discontinuation.

Phase 3 Epilepsy Controlled Pool
In the Phase 3 Epilepsy Controlled Pool, the incidence of developing TEAEs that resulted in drug discontinuation was higher in the ESL subjects than in the placebo subjects. The following table summarizes the incidence of TEAEs leading to discontinuation by randomized dose group and study.

*Comment: After analyzing the SAEs using both of the ISS adverse event datasets, there were similar risk differences (10.9%) between the total ESL group and the placebo group using the ADEVENTX dataset (that included audit findings of potential events, review events, and signs and symptoms, but excluded crossed out events) and the ADAE dataset (10.8%).*

**Table 38. TEAEs leading to discontinuation, Phase 3 Epilepsy Controlled Pool**

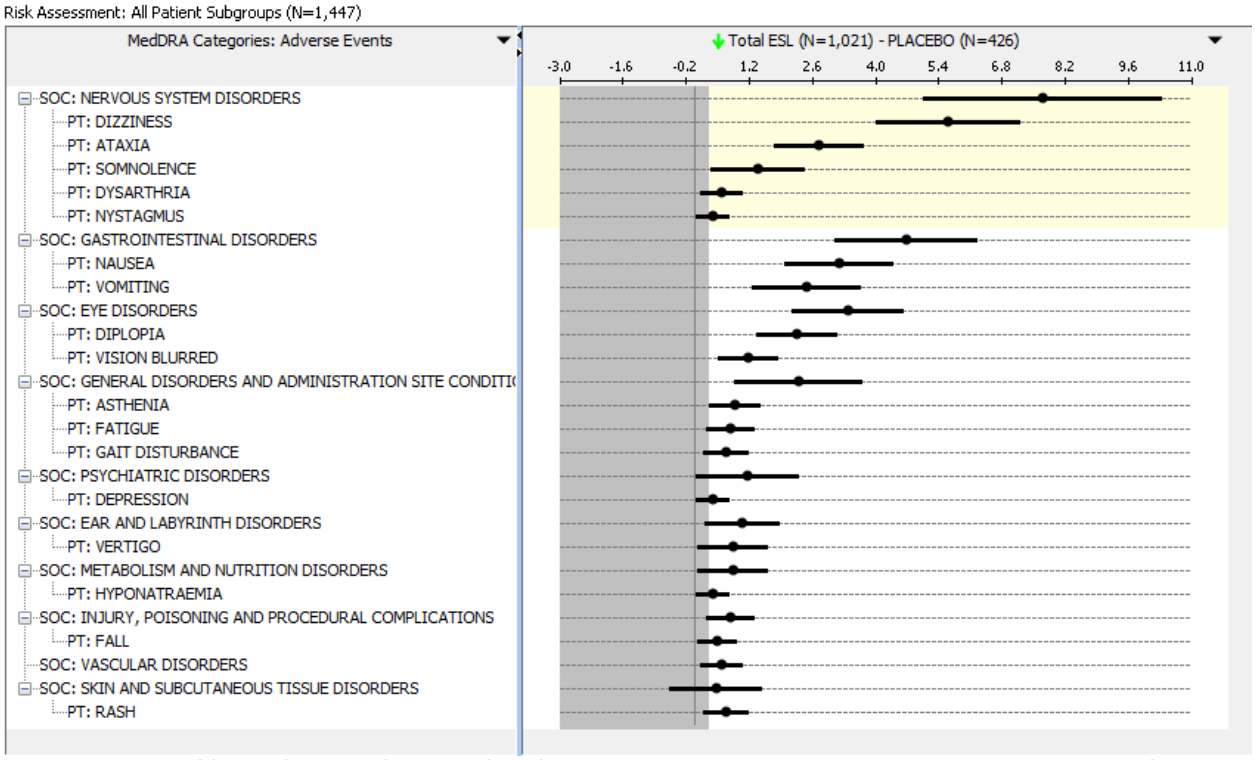
| | **Placebo** | **ESL n (%), Randomized Dose Groups** | | | |
|---|---|---|---|---|---|
| | **n (%)** | 400 mg | 800 mg | 1200 mg | Total |
| | n=426 | n=196 | n=415 | n=410 | n=1021 |
| Using ADAE dataset | 26 (6.1) | 17 (8.7) | 56 (13.5) | 100 (24.4) | 173 (16.9) |
| Using ADEVENTX | 28 (6.6) | 19 (9.7) | 56 (13.5) | 104 (25.4) | 179 (17.5) |

Source: ISS Section 2.1.4 Table 38 and created by the reviewer using JReview (ADEVENTX: DISC=1, and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

*Comment: The Division sent an information request to the Sponsor to reconcile the discrepancies between the number of subjects who discontinued due to adverse events listed in ISS Section 1.2.2 Subject Disposition and the corresponding numbers of subjects listed in ISS Section 2.1.4 Adverse events leading to discontinuation (approximately 3% higher in every treatment groups). In the Safety Information Amendment dated April 8, 2013, the Sponsor stated that the "discrepancies in the number of subjects who discontinued due to an adverse event occurred due to the different sources of data used to develop these two sections of the ISS. The CRF Termination page was the source of data for the disposition summary tables (ISS Section 1.2.2). The CRF Adverse Event pages were used as the source for the summary tables of adverse events leading to study drug discontinuation (ISS Section 2.1.4). In conclusion, all subjects who discontinued due to an adverse event have been accounted for, regardless of the CRF source page."*

The following forest plot summarizes the TEAEs leading to discontinuation sorted by SOC (and then by PT) with a risk difference of ≥ 0.4% between the total ESL group and placebo. The largest risk difference for these TEAEs between ESL and placebo subjects was identified for the SOC Nervous system disorders (PTs dizziness, ataxia, somnolence, dysarthria, nystagmus). Additionally, ESL subjects reported TEAEs leading to discontinuation more frequently than placebo subjects in the SOC Gastrointestinal disorders (nausea/vomiting), Eye Disorders (diplopia/vision blurred), General Disorders (asthenia, fatigue, gait disturbance) and for the following PTs: depression, vertigo, hyponatremia, fall, and rash.

**Figure 12. TEAEs leading to discontinuation with ≥ 0.4% Risk Difference (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool**




Source: Created by reviewer using JReview (ADEVENTX: DISC=1, AEBODSYS, AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

The Sponsor reported that the median time to AEs leading to discontinuation was 2.7 weeks, 1.1 weeks, and 1.9 weeks for the ESL 400 mg, 800 mg, and 1200 mg groups, respectively, compared with 4.1 weeks for placebo (ISS Table 7.1.12.2).

In Study 303 Part 1, TEAEs leading to premature discontinuation occurred more frequently in the total ESL group (10.3%) than in the placebo group (6.9%) with a dose-response relationship. In the following SOCs, TEAEs leading to discontinuation occurred more frequently in the total ESL group than placebo group: SOC

Gastrointestinal disorders (nausea, vomiting), SOC Ear and labyrinth disorders (vertigo), SOC Eye disorders (diplopia, vision blurred), SOC Nervous system disorders (ataxia, sedation, cerebellar syndrome, memory impairment, paraesthesia), SOC General disorders (malaise, asthenia, face oedema, gait disturbance), SOC Metabolism and nutrition disorders (hyponatremia), and SOC Psychiatric disorders (depression).

In Study 201, there were 23 AEs that led to premature study discontinuation in 14 subjects (Study 201 CSR Table 62). In the following SOCs, TEAEs leading to discontinuation occurred more frequently in the total ESL group than placebo group: SOC Nervous system disorders (complex partial seizures, dizziness, headache, coordination abnormal, ischaemic stroke), SOC Gastrointestinal disorders (vomiting, dry mouth, and dyspepsia), SOC Eye disorders (diplopia, vision blurred), and SOC Skin (rash).

Phase 3 Epilepsy Uncontrolled and Controlled Pool
The following tables summarize the TEAEs leading to discontinuation by SOC and by HLT in the Phase 3 Epilepsy Controlled and Uncontrolled Pool. The MedDRA SOC for which ESL subjects most frequently reported a SAE was Nervous System Disorders (12.2%), followed by Gastrointestinal disorders (5.4%), Eye Disorders (3.5%), General disorders and administration site conditions (3.4%), Psychiatric disorders (2.3%) and Skin and Subcutaneous Tissue Disorders (1.6%).

**Table 39. TEAEs leading to discontinuation by SOC, Phase 3 Epilepsy Uncontrolled and Controlled Pool**

| Body System or Organ Class | Total ESL |
|---|---|
| NERVOUS SYSTEM DISORDERS | 146 (12.2%) |
| GASTROINTESTINAL DISORDERS | 65 (5.4%) |
| EYE DISORDERS | 42 (3.5%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 41 (3.4%) |
| PSYCHIATRIC DISORDERS | 28 (2.3%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 19 (1.6%) |
| INVESTIGATIONS | 17 (1.4%) |
| EAR AND LABYRINTH DISORDERS | 15 (1.3%) |
| METABOLISM AND NUTRITION DISORDERS | 13 (1.1%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 10 (0.8%) |
| VASCULAR DISORDERS | 8 (0.7%) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 5 (0.4%) |
| INFECTIONS AND INFESTATIONS | 4 (0.3%) |
| SURGICAL AND MEDICAL PROCEDURES | 3 (0.3%) |
| CARDIAC DISORDERS | 3 (0.3%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 3 (0.3%) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED | 2 (0.2%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 2 (0.2%) |
| PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS | 1 (0.1%) |
| SOCIAL CIRCUMSTANCES | 1 (0.1%) |
| Subjects with TEAEs leading to discontinuation | 233 (19.5%) |
| Total number of subjects | 1194 (100.0%) |

Source: Created by reviewer using JReview (ADEVENTX: DISC=1, AEBODSYS and ADSL: DOSCATH) for studies 301, 302, 304

**Table 40. TEAEs leading to discontinuation by HLT (in ≥0.3% of Total ESL Group), Phase 3 Epilepsy Uncontrolled and Controlled Pool**

| High Level Term | Total ESL |
|---|---|
| NEUROLOGICAL SIGNS AND SYMPTOMS NEC | 73 (6.1%) |
| NAUSEA AND VOMITING SYMPTOMS | 54 (4.5%) |
| VISUAL DISORDERS NEC | 40 (3.4%) |
| CEREBELLAR COORDINATION AND BALANCE DISTURBANCES | 38 (3.2%) |
| DISTURBANCES IN CONSCIOUSNESS NEC | 28 (2.3%) |
| ASTHENIC CONDITIONS | 18 (1.5%) |
| SEIZURES AND SEIZURE DISORDERS NEC | 18 (1.5%) |
| INNER EAR SIGNS AND SYMPTOMS | 14 (1.2%) |
| HEADACHES NEC | 10 (0.8%) |
| RASHES, ERUPTIONS AND EXANTHEMS NEC | 9 (0.8%) |
| SPEECH AND LANGUAGE ABNORMALITIES | 8 (0.7%) |
| GAIT DISTURBANCES | 8 (0.7%) |
| ANXIETY SYMPTOMS | 6 (0.5%) |
| PSYCHOTIC DISORDER NEC | 6 (0.5%) |
| GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL/THROAT) | 5 (0.4%) |
| TREMOR (EXCL CONGENITAL) | 5 (0.4%) |
| DEPRESSIVE DISORDERS | 5 (0.4%) |
| GENERAL SIGNS AND SYMPTOMS NEC | 5 (0.4%) |
| NON-SITE SPECIFIC INJURIES NEC | 5 (0.4%) |
| DISTURBANCES IN INITIATING AND MAINTAINING SLEEP | 4 (0.3%) |
| SODIUM IMBALANCE | 4 (0.3%) |
| WHITE BLOOD CELL ANALYSES | 4 (0.3%) |
| THINKING DISTURBANCES | 4 (0.3%) |
| DYSKINESIAS AND MOVEMENT DISORDERS NEC | 4 (0.3%) |

Source: Created by reviewer using JReview (ADEVENTX: DISC=1, AEHLT and ADSL: DOSCATH) for studies 301, 302, 304

The following table summarizes the TEAEs leading to discontinuation reported by PT in the Phase 3 Epilepsy Controlled and Uncontrolled Pool. The most frequently reported TEAEs leading to discontinuation by the ESL subjects was dizziness (5.9%), followed by nausea (3.0%), vomiting (2.8%), ataxia (2.6%), diplopia (2.3%), and somnolence (1.8%). These TEAEs reported by ESL subjects after pooling together the open-label extension trials are similar to those reported in the double-blind trials.

**Table 41. TEAEs leading to discontinuation by PT (in ≥0.3% of ESL subjects), Phase 3 Epilepsy Uncontrolled and Controlled Pool**

| Dictionary-Derived Term | Total ESL |
|---|---|
| DIZZINESS | 71 (5.9%) |
| NAUSEA | 36 (3.0%) |
| VOMITING | 34 (2.8%) |
| ATAXIA | 31 (2.6%) |
| DIPLOPIA | 27 (2.3%) |
| SOMNOLENCE | 21 (1.8%) |
| VISION BLURRED | 13 (1.1%) |
| PARTIAL SEIZURES | 13 (1.1%) |
| VERTIGO | 13 (1.1%) |
| HEADACHE | 10 (0.8%) |
| ASTHENIA | 10 (0.8%) |
| FATIGUE | 9 (0.8%) |
| RASH | 9 (0.8%) |
| GAIT DISTURBANCE | 8 (0.7%) |
| DYSARTHRIA | 7 (0.6%) |
| FALL | 5 (0.4%) |
| IRRITABILITY | 5 (0.4%) |

| | |
|---|---|
| DEPRESSION | 5 (0.4%) |
| TREMOR | 5 (0.4%) |
| INSOMNIA | 4 (0.3%) |
| BALANCE DISORDER | 4 (0.3%) |
| NYSTAGMUS | 4 (0.3%) |
| HYPONATRAEMIA | 4 (0.3%) |

Source: Created by reviewer using JReview (ADEVENTX: DISC=1, AEDECOD and ADSL: DOSCATH) for studies 301, 302, 304

Nonepilepsy Double-blind Pool

In the Nonepilepsy Double-blind Pool, the incidence of developing TEAEs that resulted in drug discontinuation was higher in the ESL subjects than in the placebo subjects. The following table summarizes the incidence of TEAEs leading to discontinuation by randomized dose group.

*Comment: After analyzing the TEAEs leading to discontinuation using different ISS adverse event datasets, there were similar risk differences between the total ESL group and the placebo group using the ADEVENTX dataset (that included audit findings of potential events, review events, and signs and symptoms, but excluded crossed out events) and the ADAE dataset.*

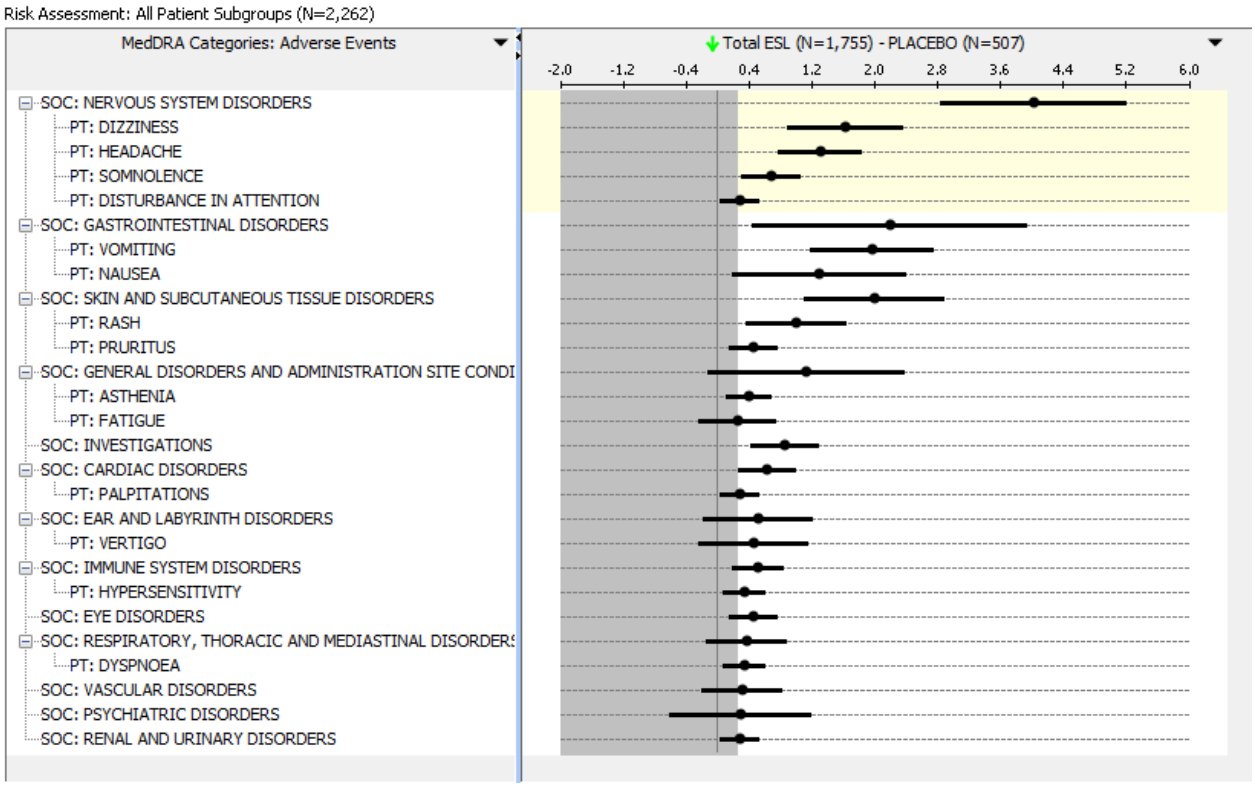
**Table 42. TEAEs leading to discontinuation, Nonepilepsy Pooled Groups**

| Pooled Group | Placebo n (%) | ESL n (%), Randomized Dose Groups | | | | |
|---|---|---|---|---|---|---|
| | | <600 mg | 600-<1000 | 1000-<1400 | ≥1400 mg | Total |
| Total # of subjects | | | | | | |
| Nonepilepsy DB Pool* | 507 | 130 | 768 | 657 | 200 | 1755 |
| Nonepi Controlled Pool^ | 411 | 303 | 571 | 321 | 99 | 1294 |
| | | | | | | |
| Subjects with TEAEs DC | | | | | | |
| Nonepilepsy DB Pool* | 28 (5.5) | 15 (11.5) | 82 (10.7) | 108 (16.4) | 45 (42.6) | 250 (14.2) |
| using ADEVENTX | 31 (6.1) | 16 (12.3) | 85 (11.1) | 111 (16.9) | 45 (42.6) | 257 (14.6) |
| Nonepi Controlled Pool^ | 22 (5.4) | 61 (20.1) | 83 (14.5) | 26 (8.1) | 7 (7.1) | 177 (13.7) |
| using ADEVENTX | 25 (6.1) | 64 (21.1) | 86 (15.1) | 26 (8.1) | 7 (7.1) | 183 (14.1) |

Source: ISS Table 7.4.7.1 and created by reviewer using JReview (ADEVENTX: DISC=1, and ADSL: TRTP1) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')
*Nonepilepsy DB Pool includes Study 206 Part 1
^Nonepilepsy Controlled Pool excludes Study 206 Part 1 and uses mean dose group

The following forest plot summarizes the TEAEs leading to discontinuation by SOC (and by PT) with a risk difference of ≥ 0.4% between the total ESL group and placebo. The largest risk difference for these TEAEs between ESL and placebo subjects was identified for the SOC Nervous system disorders (PTs dizziness, headache, somnolence, disturbance in attention). Additionally, ESL subjects reported TEAEs leading to discontinuation more frequently than placebo subjects in the SOC Gastrointestinal disorders (nausea/vomiting), Skin and Subcutaneous Tissue Disorders (rash/pruritus), General Disorders (asthenia, fatigue), and for the following PTs: palpitations, vertigo, hypersensitivity, and dyspnoea.

**Figure 13. TEAEs leading to discontinuation with ≥0.3% Risk Difference (Total ESL-Placebo), Nonepilepsy Double-blind Pool (includes Study 206)**




Source: Created by reviewer using JReview (ADEVENTX: DISC=1, AEBODSYS, AEDECOD and ADSL: TRTP1) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')

Nonepilepsy Uncontrolled and Controlled Pool

The following tables summarize the treatment-emergent SAEs reported by SOC and by HLT in the Nonepilepsy Uncontrolled and Controlled Pool. The MedDRA SOC for which ESL subjects most frequently reported TEAEs leading to discontinuation was Gastrointestinal disorders (4.9%), followed by Nervous System disorders (4.7%), General disorders and administration site conditions (2.6%), Skin and Subcutaneous Tissue Disorders (2.3%), and Psychiatric disorders (1.7%).

*Comment: The order (and frequency) of the SOCs is different in the nonepilepsy studies (#1 SOC Gastrointestinal disorders 4.9%) compared to the epilepsy studies (#1 SOC Nervous system disorders 12.2%). These differences in the SOC distribution between the epilepsy and nonepilepsy pools were likely due to the underlying diseases. Interestingly, compared to SAEs, ESL subjects developed TEAEs leading to discontinuation more frequently in the SOC Skin and Subcutaneous Tissue Disorders.*

*The overall percentage of TEAEs leading to discontinuation reported in the nonepilepsy studies (15.7%) was lower than in the epilepsy studies (19.5%). However, after adjusting for duration of exposure, the incidence rate for TEAEs leading to*

*discontinuation was higher in the nonepilepsy uncontrolled/controlled pool (0.49 patient-years) than the epilepsy uncontrolled/controlled pool (0.21 patient-years).*

**Table 43. TEAEs leading to discontinuation by SOC, Nonepilepsy Uncontrolled and Controlled Pool**

| Body System or Organ Class | Total ESL |
|---|---|
| GASTROINTESTINAL DISORDERS | 95 (4.9%) |
| NERVOUS SYSTEM DISORDERS | 91 (4.7%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 51 (2.6%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 45 (2.3%) |
| PSYCHIATRIC DISORDERS | 32 (1.7%) |
| EAR AND LABYRINTH DISORDERS | 18 (0.9%) |
| INVESTIGATIONS | 16 (0.8%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 15 (0.8%) |
| VASCULAR DISORDERS | 13 (0.7%) |
| INFECTIONS AND INFESTATIONS | 12 (0.6%) |
| CARDIAC DISORDERS | 12 (0.6%) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 12 (0.6%) |
| IMMUNE SYSTEM DISORDERS | 10 (0.5%) |
| EYE DISORDERS | 8 (0.4%) |
| METABOLISM AND NUTRITION DISORDERS | 7 (0.4%) |
| RENAL AND URINARY DISORDERS | 5 (0.3%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 5 (0.3%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 5 (0.3%) |
| HEPATOBILIARY DISORDERS | 2 (0.1%) |
| SOCIAL CIRCUMSTANCES | 2 (0.1%) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 2 (0.1%) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED | 2 (0.1%) |
| SURGICAL AND MEDICAL PROCEDURES | 1 (0.1%) |
| Subjects with TEAEs leading to discontinuation | 303 (15.7%) |
| Total number of subjects | 1936 (100.0%)* |

Source: Created by reviewer using JReview (ADEVENTX: DISC=1, AEBODSYS and ADSL: DOSCATH) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')
*Double counts 104 subjects that are in both Study 203/204 and 205

**Table 44. TEAEs leading to discontinuation by HLT (in ≥0.3% of Total ESL Group), Nonepilepsy Uncontrolled and Controlled Pool**

| High Level Term | Total ESL |
|---|---|
| NAUSEA AND VOMITING SYMPTOMS | 71 (3.7%) |
| NEUROLOGICAL SIGNS AND SYMPTOMS NEC | 34 (1.8%) |
| HEADACHES NEC | 27 (1.4%) |
| RASHES, ERUPTIONS AND EXANTHEMS NEC | 21 (1.1%) |
| DISTURBANCES IN CONSCIOUSNESS NEC | 20 (1.0%) |
| ASTHENIC CONDITIONS | 18 (0.9%) |
| INNER EAR SIGNS AND SYMPTOMS | 17 (0.9%) |
| GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL/THROAT) | 16 (0.8%) |
| OEDEMA NEC | 12 (0.6%) |
| PRURITUS NEC | 11 (0.6%) |
| DEPRESSIVE DISORDERS | 8 (0.4%) |
| DYSPEPTIC SIGNS AND SYMPTOMS | 8 (0.4%) |
| MUSCULOSKELETAL/CONNECTIVE TISSUE PAIN AND DISCOMFORT | 8 (0.4%) |
| ALLERGIC CONDITIONS NEC | 7 (0.4%) |
| ANXIETY SYMPTOMS | 7 (0.4%) |
| BREATHING ABNORMALITIES | 6 (0.3%) |
| DISTURBANCES IN INITIATING AND MAINTAINING SLEEP | 6 (0.3%) |
| SENSORY ABNORMALITIES NEC | 6 (0.3%) |
| CEREBELLAR COORDINATION AND BALANCE DISTURBANCES | 6 (0.3%) |
| CARDIAC SIGNS AND SYMPTOMS NEC | 6 (0.3%) |
| MENTAL IMPAIRMENT (EXCL DEMENTIA AND MEMORY LOSS) | 6 (0.3%) |

Source: Created by reviewer using JReview (ADEVENTX: DISC=1, AEHLT and ADSL: DOSCATH) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')

The following table summarizes the TEAEs leading to discontinuation reported by PT in the Nonepilepsy Controlled and Uncontrolled Pool. The most frequently reported TEAEs leading to discontinuation in ESL subjects were nausea (2.2%), followed by vomiting (2.1%), dizziness (1.7%), headache (1.3%), and rash (1.1%). The TEAEs leading to discontinuation reported by ESL subjects after pooling together the open-label extension trials are similar to those reported in the double-blind trials.

**Table 45. TEAEs leading to discontinuation by PT (in ≥0.2% of ESL subjects), Nonepilepsy Uncontrolled and Controlled Pool**

| Dictionary-Derived Term | Total ESL |
|---|---|
| NAUSEA | 42 (2.2%) |
| VOMITING | 41 (2.1%) |
| DIZZINESS | 33 (1.7%) |
| HEADACHE | 25 (1.3%) |
| RASH | 21 (1.1%) |
| VERTIGO | 17 (0.9%) |
| SOMNOLENCE | 14 (0.7%) |
| ABDOMINAL PAIN UPPER | 9 (0.5%) |
| FATIGUE | 9 (0.5%) |
| PRURITUS | 8 (0.4%) |
| DEPRESSION | 8 (0.4%) |
| ABDOMINAL PAIN | 7 (0.4%) |
| ASTHENIA | 7 (0.4%) |
| DYSPEPSIA | 7 (0.4%) |
| HYPERSENSITIVITY | 7 (0.4%) |
| DYSPNOEA | 6 (0.3%) |
| DISTURBANCE IN ATTENTION | 6 (0.3%) |
| PALPITATIONS | 5 (0.3%) |
| INSOMNIA | 5 (0.3%) |
| HYPERTENSION | 5 (0.3%) |
| OEDEMA PERIPHERAL | 5 (0.3%) |
| BACK PAIN | 5 (0.3%) |
| CONSTIPATION | 5 (0.3%) |
| MANIA | 4 (0.2%) |
| DRUG INEFFECTIVE | 4 (0.2%) |
| PYREXIA | 4 (0.2%) |
| BIPOLAR DISORDER | 4 (0.2%) |
| FACE OEDEMA | 4 (0.2%) |
| BLOOD PRESSURE INCREASED | 4 (0.2%) |
| HYPERHIDROSIS | 4 (0.2%) |
| DIARRHOEA | 4 (0.2%) |

Source: Created by reviewer using JReview (ADEVENTX: DISC=1, AEDECOD and ADSL: DOSCATH) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')

Phase 1 Study Pool

In the Phase I Study Pool, the incidence of TEAEs leading to discontinuation for the total ESL group (3.4%) was higher than the placebo group (1.8%) (ISS Table 7.5.4.1). ESL subjects discontinued due to adverse events more frequently than placebo subjects in the following SOCs: Skin and subcutaneous tissue disorders (1.5% vs 0), Gastrointestinal disorders (1.1% vs 0.9%), and Nervous system disorders (0.6% vs 0). The preferred terms were consistent with the Phase 2 and 3 trials. However, there was

1 ESL subject who discontinued due to hepatic encephalopathy (in the hepatic impairment study 111).

In the entire eslicarbazepine acetate drug development program (including 303 and including audit findings, review events, signs and symptoms), there was 1 ESL case each of TEAEs leading to discontinuation coded to the following PTs: acute renal failure, acute respiratory failure, hyperthermia, hepatic encephalopathy, pancreatitis, and toxic skin eruption (reviewed in detail in Sections 7.3.4 and 7.3.5). Furthermore there were 2 ESL cases of syncope and loss of consciousness. However, there were no ESL subjects (in the ISS datasets submitted by the Sponsor) who discontinued due to TEAEs coded to the following PTs: acute hepatic failure, agranulocytosis, anaphylaxis, aplastic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson syndrome, toxic epidermal necrolysis, torsade de pointes, ventricular fibrillation, or ventricular tachyarrhythmia (or tachycardia).

Ongoing Studies
The following table summarizes the TEAEs leading to discontinuation that were reported by the Sponsor for the ongoing studies by treatment group. Overall, the TEAEs leading to discontinuation in the ongoing trials are consistent with those reported in the clinical trials.

**Table 46. TEAEs leading to discontinuation by SOC, Ongoing Studies**

| | Treatment Group | | |
|---|---|---|---|
| MedDRA SOC | Placebo | ESL group | Blinded |
| Nervous System Disorders *(79% of PTs in ESL group are dizziness/ataxia, somnolence, headache, or seizure related)* | 0 | 95 | 33 |
| Gastrointestinal Disorders *(79% PTs Nausea, Vomiting)* | 1 | 53 | 18 |
| Metabolism and Nutrition Disorders *(92% PT hyponatremia)* | 0 | 26 | 3 |
| Skin and Subcutaneous Tissue Disorders | 0 | 23 | 27 |
| General Disorders and Administration Site Conditions | 0 | 19 | 12 |
| Psychiatric Disorders | 2 | 18 | 11 |
| Ear & Labyrinth Disorders *(PTs Vertigo, vestibular syndrome)* | 1 | 17 | 2 |
| Investigations *(42% PT blood sodium decreased)* | 2 | 12 | 12 |
| Injury, Poisoning and Procedural Complications | 1 | 9 | 0 |
| Eye Disorders *(all PTs Diplopia, Vision blurred)* | 0 | 7 | 1 |
| Cardiac Disorders | 0 | 6 | 3 |
| Vascular Disorders | 0 | 5 | 0 |
| Immune System Disorders | 0 | 4 | 2 |
| Infections and Infestations | 0 | 3 | 2 |
| Respiratory, Thoracic and Mediastinal Disorders | 0 | 1 | 2 |
| Musculoskeletal and Connective Tissue Disorders | 6 | 1 | 1 |
| Pregnancy, Puerperium, and Perinatal Conditions | 0 | 1 | 0 |
| Blood and Lymphatic System Disorders | 0 | 0 | 5 |
| Reproductive System and Breast Disorders | 0 | 0 | 2 |
| Neoplams Benign, Malignant and Unspecified | 0 | 0 | 1 |
| Renal and Urinary Disorders | 0 | 0 | 1 |
| Hepatobiliary Disorders | 1 | 0 | 0 |
| Not yet coded | 0 | 6 | 2 |

Source: Safety Information Amendment 4/19/13 Table 4

## 7.3.4 Significant Adverse Events

In this section, I will discuss my analyses along with the Sponsor's analyses of the following major safety issues: drug-induced liver injury, serious skin and hypersensitivity reactions, neurologic reactions, psychiatric reactions, and endocrine events. These safety issues should be incorporated into labeling and/or further evaluated in the postmarketing period.

### 7.3.4.1 Drug Induced Liver Injury

The Sponsor assessed the potential for drug induced liver injury with ESL by reviewing lab data results and liver-related AE risks from ESL clinical trials. The following table summarizes the liver related lab test outlier results for the epilepsy and nonepilepsy DB pools. In both the epilepsy and nonepilepsy DB pools, the incidence of transaminase elevations was slightly higher for subjects receiving ESL than those receiving placebo. In the Nonepilepsy Double-blind Pool, only ESL subjects (0.2%) and no placebo subjects developed concurrent elevations of transaminases (>3xULN) and bilirubin (>2x ULN). There was 1 ESL subject (203-337-203058, described in more detail below) who had laboratory values that met the criteria for Hy's Law: transaminase elevations >3xULN associated with total bilirubin >2xULN and alkaline phosphatase <2xULN.

**Table 47. Liver Test Outliers**

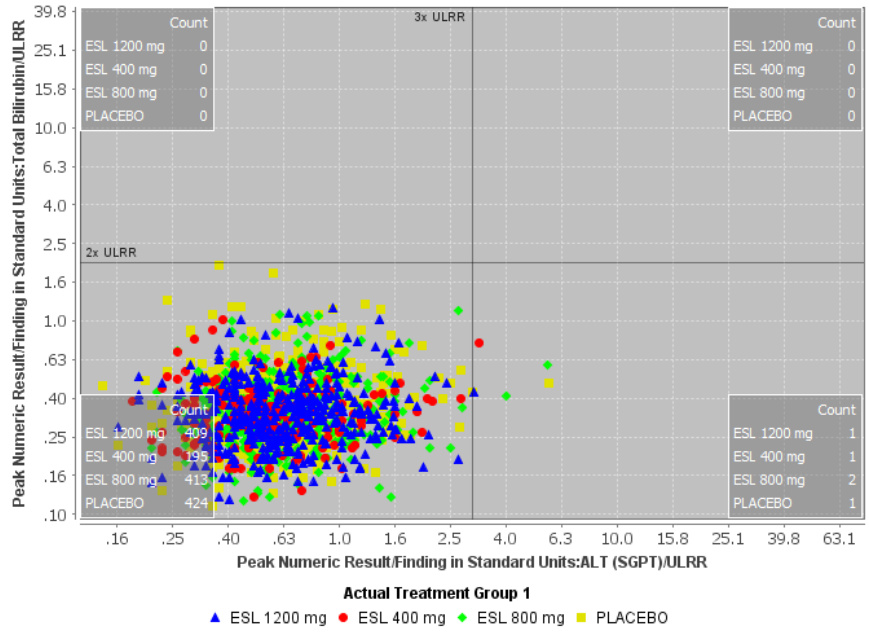
| | **Phase 3 Epilepsy DB** | | **Nonepilepsy DB Pool^** | |
|---|---|---|---|---|
| **Test/Cutoff threshold** | **Placebo** n=426 | **ESL** n=1021 | **Placebo** n=506 | **ESL** n=1752 |
| ALT | | | | |
| ALT >3xULN | 1 (0.2) | 3 (0.3) | 3 (0.6) | 16 (0.9) |
| ALT >5xULN | 1 (0.2) | 0 | 0 | 7 (0.4) |
| ALT >10xULN | 0 | 0 | 0 | 2 (0.1) |
| ALT >20xULN | 0 | 0 | 0 | 1 (<0.1)* |
| AST | | | | |
| AST >3xULN | 1 (0.2) | 1 (<0.1) | 1 (0.2) | 10 (0.6) |
| AST >5xULN | 0 | 1 (<0.1) | 0 | 4 (0.2) |
| AST >10xULN | 0 | 0 | 0 | 3 (0.2) |
| AST >20xULN | 0 | 0 | 0 | 2 (0.1) |
| Total bilirubin | | | | |
| Total bilirubin >ULN | 2 (0.5) | 0 | 17 (3.4) | 40 (2.2) |
| Total bilirubin >1.5xULN | 1 (0.2) | 0 | 4 (0.8) | 10 (0.6) |
| Total bilirubin >2xULN | 0 | 0 | 1 (0.2) | 4 (0.2) |
| ALP | | | | |
| ALP >1.5xULN | 5 (1.2) | 8 (0.8) | 1 (0.2) | 13 (0.7) |
| ALT or AST >3xULN and total bilirubin >ULN | 0 | 0 | 0 | 3 (0.2) |
| ALT or AST >3xULN and total bilirubin >2xULN | 0 | 0 | 0 | 3 (0.2) |

| | | | | |
|---|---|---|---|---|
| ALT or AST >3xULN and total bilirubin >2xULN and ALP <2xULN | 0 | 0 | 0 | 1 (<0.1)* |

Source: ISS Tables 7.7.1.3.1
^includes Study 206
*Subject 203-337-203058 described in Table of Narratives below

The following figures represent the graphical analyses that I performed of ALT outliers (>3xULN) versus total bilirubin outliers (>2xULN) after filtering out alkaline phosphatase values < 2xULN. The subjects fitting Hy's lab criteria would be located in the upper-right quadrant. In the Phase 3 Epilepsy Controlled Pool, there were no subjects who developed liver enzyme elevations in this "Hy's Law" quadrant. There were 3 ESL subjects (two 800 mg and one 1200 mg) and 1 placebo subject who had elevated ALT values >3xULN (bottom-right quadrant). There were no subjects who had elevated total bilirubin values >2xULN (upper-left quadrant). The vast majority of the subjects in the Phase 3 Epilepsy Controlled Pool were in the bottom-left quadrant.

**Figure 14. Hy's Law Plot: ALT>3xULN vs TBili>2xULN with ALP <2xULN, Phase 3 Epilepsy Controlled Pool**

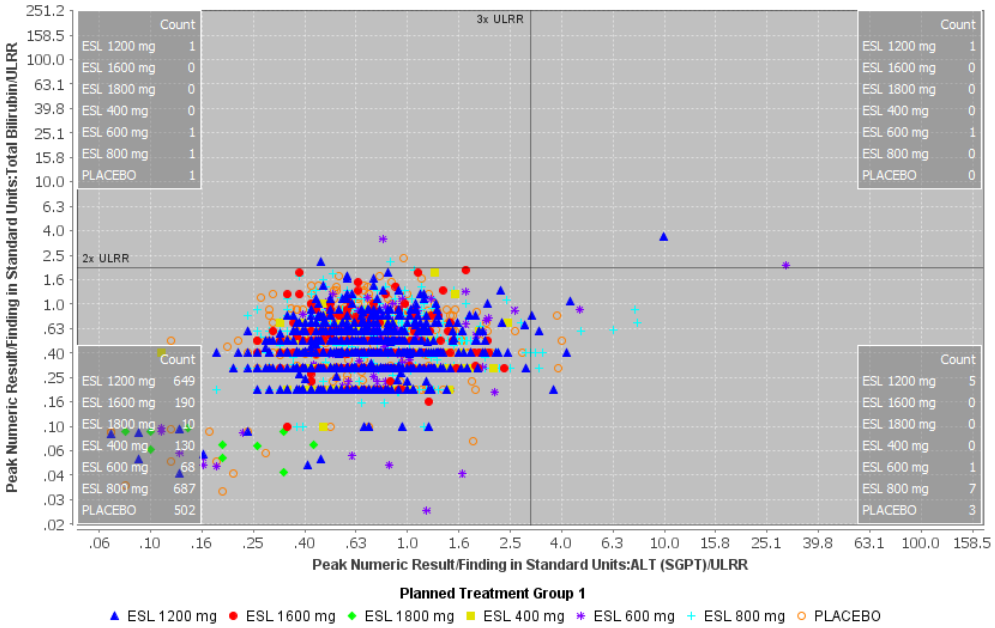



Source: Created by the reviewer using JReview (ADLAB: LBTESTCD='AP' and LBSTRESN<LBSTNRHI*2, LBTESTCD='SGPT' and LBSTRESN>LBSTNRHI*3, LBTESTCD='TBILI' and LBSTRESN>LBSTNRHI*2 and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

In the Nonepilepsy Double-blind Pool, I identified 2 subjects (206-563-563010 and 203-337-203058 described below) who developed liver tests in the "Hy's Law" quadrant (of note, only 1 of these subjects was identified by the Sponsor in the ISS as "partially" meeting Hy's Law). Additionally, there were subjects (both ESL and placebo) who had elevated ALT values >3xULN (bottom-right quadrant). There were fewer number of

subjects (both ESL and placebo) who had elevated total bilirubin values >2xULN (upper-left quadrant). The vast majority of the subjects in the Nonepilepsy Double-blind Pool were in the bottom-left quadrant.

**Figure 15. Hy's Law Plot: ALT>3xULN vs TBili>2xULN with ALP <2xULN, Nonepilepsy Double-blind Pool (includes Study 206)**




Source: Created by the reviewer using JReview (ADLAB: LBTESTCD='AP' and LBSTRESN<LBSTNRHI*2, LBTESTCD='SGPT' and LBSTRESN>LBSTNRHI*3, LBTESTCD='TBILI' and LBSTRESN>LBSTNRHI*2 and ADSL: TRTP1) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')

*Comment: Of note, I also performed these graphical analyses using AST values instead of ALT values and similar results were obtained. Furthermore, I performed similar analyses for the All Studies Pool (including 303) and no additional subjects in the "Hy's Law" quadrant were identified.*

In response to the Division's information request, the Sponsor performed similar analyses using the individual subjects' baseline liver enzyme measurements rather than upper limit of normal values (see table below). Reassuringly, using this conservative approach, there was a similar or lower incidence in ESL subjects of concurrent increases in transaminases and bilirubin than placebo subjects.

**Table 48. Liver Test Outliers (using baseline values)**

| | Phase 3 Epilepsy | | Nonepilepsy^ | |
|---|---|---|---|---|
| **Test/Cutoff threshold** | **Placebo** n=426 | **ESL** n=1021 | **Placebo** n=507 | **ESL** n=1755 |
| ALT or AST >3x baseline and total bilirubin > baseline | 6 (1.4%) | 9 (0.9%) | 6 (1.2%) | 18 (1.0%) |
| ALT or AST >3x baseline and total bilirubin >2x baseline | 1 (0.2%) | 3 (0.3%) | 3 (0.6%) | 7 (0.4%) |
| ALT or AST >3x baseline and total bilirubin >2x baseline and ALP <2x baseline | 1 (0.2%) | 2 (0.2%) | 3 (0.6%) | 4 (0.2%)* |

Source: Safety Information Amendment 6/10/13 Table 9.7.1.r1
^including Study 206
*Subjects 203-337-203058 and 206-563-563010 were not included in the Sponsor's listing of subjects in the Table 9.7.2.3.r1

The following table summarizes the Sponsor's liver test outlier results for the All Studies Pool (including 303). The incidence of concurrent elevations in transaminases and bilirubin (or INR) was extremely low in ESL subjects (even after using baseline values rather than ULN). No additional subjects with Hy's lab criteria were identified by the Sponsor.

**Table 49. Liver Test Outliers, All Studies Pool (including 303)**

| Test/Cutoff threshold | Total ESL |
|---|---|
| **Using x ULN:** | n=4307 |
| ALT or AST >3xULN and total bilirubin >ULN | 8 (0.2) |
| ALT or AST >3xULN and total bilirubin >1.5xULN | 6 (0.1) |
| ALT or AST >3xULN and total bilirubin >2xULN | 6 (0.1) |
| ALT or AST >3xULN and total bilirubin >2xULN and ALP <2xULN | 1 (<0.1)* |
| ALT or AST >3xULN and INR >ULN | 1 (<0.1) |
| **Using x Baseline:** | |
| ALT or AST >3x baseline and total bilirubin >2x baseline and ALP <2x baseline | 16 (0.4)^ |

Source: ISS Table 7.7.6.3.1 and Safety Information Amendment 6/10/13 Table 9.7.2.3.r1
^Total of 20 subjects (16 ESL, 4 placebo])
*Subject 203-337-203058 described in Table of Narratives below

Hepatic TEAEs
I performed additional analyses of hepatic TEAEs, SAEs, and TEAEs leading to discontinuation. The following table summarizes the percentages of ESL and placebo subjects with TEAEs in the hepatic-related SOCs and SMQs. Overall, only a small percentage of ESL subjects developed TEAEs in these SOCS and SMQs. A slightly higher percentage of ESL subjects compared to placebo developed TEAEs in the HLT Liver function analyses (0.8% vs 0.2%) and in the SMQ Hepatic disorders ((1.3% vs 0.5%, driven by the liver-related investigations SMQ). There was only 1 ESL subject (vs 0 placebo) who developed PTs in the SOC Hepatobiliary disorders and the SMQ Drug

related hepatic disorders – severe events (specifically the SMQ hepatic failure, fibrosis and cirrhosis):

Subject 301-124-90358 with nonserious PT "liver disorder" treated with ESL 400 mg and developed an isolated elevation of ALT on DB Study Day 56 (increasing to 2-3xULN). This subject completed the DB portion of the study but did not continue in the OLE portion.

**Table 50. Hepatobiliary disorders SOC and SMQs, Phase 3 Epilepsy Controlled Pool**

| MedDRA SOC, SMQ | Placebo n = 426 | ESL n = 1021 |
|---|---|---|
| **SOC** Hepatobiliary disorders | 0 | 1 (0.1)* |
| **SOC** Investigations | | |
| HLT Liver function analyses | 1 (0.2) | 8 (0.8) |
| | | |
| **SMQs (broad):** | | |
| (1) Hepatic disorders | 2 (0.5) | 13 (1.3) |
| (2) Liver infections | 0 | 1 (0.1) |
| (2) Drug related hepatic disorders -Comprehensive search | 2 (0.5) | 12 (1.2) |
| (3) Liver related investigations, signs and symptoms | 2 (0.5) | 11 (1.1) |
| (3) Drug related hepatic disorders -Severe events only | 0 | 1 (0.1)* |
| (4) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions | 0 | 1 (0.1)* |

Source: Created by the reviewer using MAED (MedDRA-based Adverse Event Diagnostic) tool (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')
*Subject 301-124-90358 described above

In the Phase 3 Epilepsy Controlled Pool, there were no SAEs in the SOC hepatobiliary disorders or SOC investigations (HLT liver function analyses). There was 1 ESL subject who discontinued due to "ALT increased":

Subject 304-955-95501 with ALT slightly elevated at baseline who was treated with ESL and developed a mild AST elevation (<2xULN).

In the Nonepilepsy Double-blind Pool, again, while a similar percentage of ESL subjects (0.7%) and placebo subjects (0.6%) developed TEAEs in the SOC Hepatobiliary disorders, more ESL subjects (4.2%) developed TEAEs in the HLT liver function analyses than placebo subjects (1.4%). There was 1 ESL subject who experienced an SAE (subject 207-222-222011 described below with PTs biliary dilatation, cholangitis, cholestasis, and jaundice). Three ESL subjects discontinued due to liver-related AEs:

Subject 207-222-222011 with liver disorder (described below)
Subject 210-642-642008 with ALT/AST increased and rash (described in the section on DRESS).
Subject 206-661-661005 with hepatic enzyme increased who at baseline had a slightly elevated ALT and then on ESL developed a mild increase in AST (<2xULN) and ALT (<2xULN).

In the Phase 2 studies, there was 1 ESL subject with hepatic pain. There were fewer ESL subjects (3.1%) who developed liver function TEAEs than placebo (4.3%). There were no SAEs or TEAEs leading to discontinuation.

In the Phase 1 Pool, there was 1 ESL subject with an SAE coded to hepatic encephalopathy (subject 111-000-0009 described below). Discontinuations due to liver-related AEs occurred in 2 ESL subjects: AST increased (153-001-09058 described below) and hepatic encephalopathy (same subject with SAE 111-000-0009).

For the All Studies Pool (including 303), I performed an additional search for SAEs using the TEAEs in the SMQ Hepatic Disorders. There were a total of 32 ESL subjects (0.7%) with SAEs in this SMQ. I reviewed all of these narratives and further describe the relevant and notable cases below.

In the ongoing studies, the Sponsor reported 1 ESL subject who developed an SAE in Hepatobiliary Disorders (PT cholelithiasis obstructive).

In the postmarketing database, the Sponsor identified adverse events that could suggest hepatic disorders or hepatotoxicity by considering all events recorded to the Hepatobiliary Disorders SOC and events retrieved by using the MedDRA SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions along with the SMQ Liver related investigations, signs and symptoms. Overall, the Sponsor reported these spontaneous reports were uncommon (9 reports and 9 events), representing a reporting rate of 0.00073 per patient-year (ISS Table 110). The following SAEs were reported: 1 abdominal pain, 2 vomiting, 1 ALT increased, 2 GGT increased, 1 hepatic enzyme increased, and 1 hepatorenal syndrome (described below).

*Comment: I reviewed the case reports for all of these SAEs that were provided by the Sponsor in the Safety Information Amendment dated 6/10/13 in response to the Division's information request. The case of hepatorenal syndrome is further described below. Although the details provided in the other case reports were limited, none of these cases reported labs with ALT/AST >3xULN and/or Tbili >2xULN. Of note, there was 1 patient (BIAL 01654) with adverse events coded to abdominal pain and increased urine amylase who was reported to have an episode of acute pancreatitis in the case report (but lacked details on date of ESL initiation, concomitant medications, medical history, or outcome of the event).*

Importantly, the Sponsor did not report any cases of severe DILI (fatal or requiring transplantation) in the entire ESL development program including all of the completed clinical studies, ongoing studies, and postmarketing database. However, as noted above and discussed in detail below, I have identified 2 subjects fitting Hy's lab criteria (subjects 203-337-203058 and 206-563-563010).

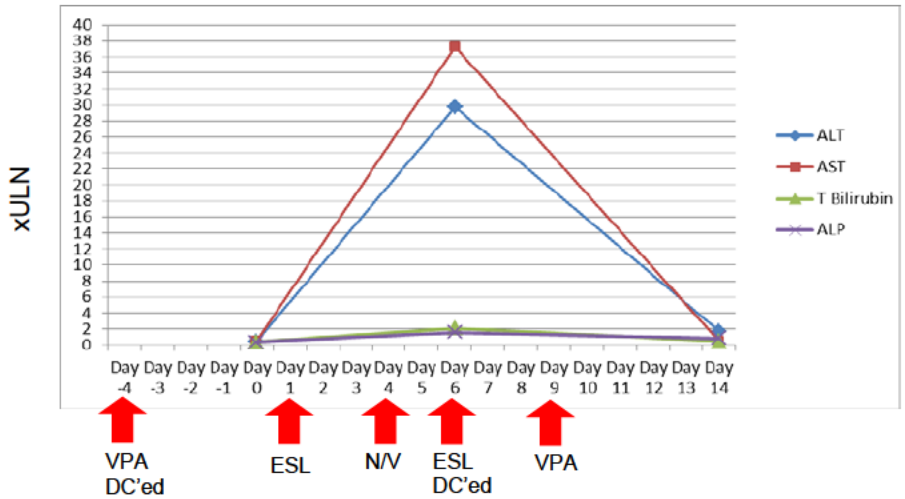
The following table summarizes the narratives of the ESL subjects with significant liver enzyme abnormalities and/or liver-related TEAEs in the All Studies Pool (including 303). In addition to these cases described below, there were ESL subjects who developed transaminase elevations (>3xULN) without bilirubin elevations which led to the discontinuation of ESL and subsequent resolution of the elevations within 15 days.

Other elevations occurred in the OLE studies with a long latency (>1 year). Some subjects developed hepatic enzyme increases which improved while remaining on ESL continued (at the same or lower doses). A few subjects had liver enzymes that were already trending upwards prior to the initiation of ESL. Liver enzyme elevations were also confounded by other etiologies such as Stevens-Johnson syndrome or chronic cholecystitis.

**Table 51. Narratives of Subjects with Significant Liver Abnormalities, All Studies Pool (including 303)**

| Subject # | Age,Sex, Race | Dose | Related adverse events | Study day | Prior hepatic history |
|---|---|---|---|---|---|
| **Hy's Lab Criteria (ALT/AST >3xULN and total bilirubin >2xULN with ALP <2xULN or <2xbaseline):** | | | | | |
| 203-337-203058 | 57, F, W | 1200mg | Vomiting, diarrhea | Day 4 | Yes |

Subject with h/o chronic pancreatitis, bipolar disorder, and HTN who developed vomiting (severe) and diarrhea on Study Day 4 (b) (6) Two days later (Study Day 6), ESL was discontinued and labs revealed elevated ALT (37xULN), AST (>30xULN), total bilirubin (>2xULN). ALP values were 1.5xULN. INR was within normal range. *(Of note, the serum ESL concentration on this day was 13,400 ng/mL).* Treatment included silybum marianum (milk thistle thought to be hepatoprotective). There were no other PCS values for lab, vital, or ECG parameters. Eight days after ESL discontinuation, AST, total bilirubin, and ALP returned to normal while ALT decreased to 1.7xULN. One month later, all labs (AST, ALT, bilirubin, ALP, INR) were within normal limits (WNL).
Baseline results for liver enzymes were all WNL.
Prior medications included valproic acid (for ~3 years and stopped 5 days prior to first dose of ESL).




*Comment: This is the most concerning case as the liver test values meet Hy's Law criteria along with the striking level of transaminase increases (>>20xULN). Furthermore, the concurrent elevations of transaminases and bilirubin (without a substantial elevation in ALP) have a close temporal relationship with ESL initiation. The presence of a positive dechallenge also supports a possible causal role of ESL. However, a thorough investigation for alternative etiologies (e.g., viral hepatidities, concomitant medications, alcohol, autoimmune hepatitis) for these liver test abnormalities was not performed by the investigator at the time of the event (confirmed by the Sponsor in the Safety Information Amendment dated 6/5/13). Therefore, without this information, ESL-induced liver injury in this subject cannot definitively be ruled out.*

*Of note, in response to the Division's information request, the Sponsor provided additional information regarding this case in the Safety Information Amendment dated 6/5/13. The Sponsor provided documentation after reaching out to the clinical investigator (for site 337 in Slovakia) that the subject had a history of "chronic hepatopathy, probably of metabolic and drug-related origin" thought due to psychiatric medications ("previously unreported"). The Sponsor also provided information regarding the subject's remote history of an infection with the helminth, Ascaris lumbricoides (in 1992, 14 years prior to the ESL study) that was temporally associated with an increase in ALT 21xULN and AST 9xULN with normal ALP and total bilirubin. The subject had a cholecystectomy performed for recurrent biliary colic 3 months prior. Treatment with the antihelmintic, mebendazole, was administered. The transaminitis improved quickly. It is unclear whether the transaminitis (from 1992) was due to ascariasis (as the medical notes did not include information regarding alternative causes). Ascariasis can cause hepatobiliary events such as acute pancreatitis, biliary colic, cholangitis, cholecystitis, hepatic abscess, and even hepatitis. However, these 2 events (14 years apart) are likely unrelated.*

| | | | | | |
|---|---|---|---|---|---|
| 206-563-563010 | 57, M, W | 1200mg | (None reported) | Day 36 | Yes |

Subject with a history of hepatic steatosis, diabetes, HTN developed elevated liver tests of AST 25xULN, ALT 10xULN, TBili 3.6xULN, ALP 2.8xULN (365 U/L or 1.6x baseline) on Study Day 36 of ESL (b) (6) *(Of note, the serum ESL concentration was 35,416 ng/mL while the mean of the patients for the study was 14888 ng/mL).* No symptoms were reported. ESL was continued. Five days later, liver test abnormalities decreased: AST 2.3xULN, ALT 2xULN, TBili 1.5XULN, ALP 1.9xULN *(along with a decrease in all other laboratory values except for sodium and chloride values that may be a result of a sample diluted with normal saline [sodium chloride])*. ESL was continued and the subject completed the study 2 months later. One day after ESL discontinuation, liver tests remained elevated with AST 5xULN, ALT 1.5xULN, total bilirubin 3.8xULN, ALP 5xULN. There were also associated decreases in albumin and glucose levels along with increases in triglycerides and cholesterol.
Baseline ALP was elevated at 229 U/L or 1.8xULN (while ALT/AST, TBili were all normal).
Concomitant medications included perindopril (started 1 month prior to ESL) and the following medications started 1 year prior to ESL: metoprolol, atorvastatin, spironolactone, insulin, silybum marianum (for hepatic steatosis), and acetylsalicylic acid.
*(Of note, INR values were not included in the dataset or narrative. The Sponsor confirmed that INR was not measured in this study).*

(b) (4)

*Comment: In response to the Division's information request, the Sponsor provided additional information regarding this case in the Safety Information Amendment dated 6/5/13. After reaching out to the investigator, the Sponsor obtained an infectious disease outpatient report and gastroenterology discharge report (from a hospitalization that occurred after the subject completed the study which "had not been previously reported by the investigator"). The subject was reported to be an "occasional drinker 1xweekly" in the hospital notes, with "more beer in the past." The subject had been hospitalized 5 months prior to study participation due to "jaundice associated with decompensation of chronic alcoholic liver lesion." The discharge report documents another hospitalization for jaundice that occurred 21 days after the subject completed the study. The final diagnosis was again "chronic alcohol-related liver damage, probably decompensated cirrhosis of the liver with jaundice." The subject was also reportedly taking concomitant paracetamol during the study (previously unreported). Hepatic parameters reported during the hospitalization ranged from normal/minimally elevated to values 3xULN (dates and reference ranges not included but I used the normal range provided by the Sponsor for subject 203-337-203058 above). The Sponsor stated that "[g]iven this new information, we do not consider this subject to meet Hy's law as the elevation in ALT and AST experienced during Study 2093-206 may be attributable to pre-existing chronic hepatic impairment."*

*However, a history of drinking alcohol does not always lead to alcoholic hepatitis or cirrhosis. Furthermore, pre-existing liver disease does not rule out the possibility of additional liver injury that is drug-induced (especially in this case where the concurrent elevations of transaminases and bilirubin were temporally related to ESL initiation). While the presence of pre-existing liver disease may not necessarily increase the risk of drug-induced liver injury, it may make recovery more difficult or lead to worse liver injury. The liver test values in this case meet Hy's Law criteria (although technically, the alkaline phosphatase was <2x baseline instead of <2xULN on Day 36).*

*However, a definite positive dechallenge was not seen in this case (as the transaminases were already lower while the TBili and ALP remained elevated during the hospitalization 21 days after ESL was discontinued). Additionally, there were other potential confounders such as paracetamol use (previously unreported) and perindopril started 1 month prior to the study (which includes information in Warnings and Precautions regarding hepatic failure with cholestatic jaundice). A thorough investigation for additional alternative etiologies (e.g., viral hepatidities, autoimmune hepatitis) was not performed by the investigator at the time of this event. Although the causal role of ESL in this subject's liver injury cannot be entirely ruled out, it is less likely.*

**ESL Subjects with ALT or AST >3xULN and total bilirubin >2xULN:**

| | | | | | |
|---|---|---|---|---|---|
| 111-000-00003 | 32, M, B | 800mg | Abdominal pain upper | | Yes |

Subject with a history of hepatic impairment who received ESL and experienced persistent liver test elevations. Labs prior to ESL dose: AST 299, ALT 205, TBili 39.3, ALP 1753. Liver tests continued to be elevated after starting ESL. All post-dose liver test elevations were lower than the pre-ESL dose values. Baseline values (~2 weeks prior to ESL): AST 144 (ULN 40), ALT 104 (ULN 44), TBili 23.6 (ULN 1.8), ALP 799 (ULN 122).
*Comment: Due to baseline elevations in liver tests, it is difficult to attribute the persistent liver test elevations (which were lower post-dose) to ESL.*

| | | | | | |
|---|---|---|---|---|---|
| 111-000-00011 | 60, M, B | 800mg | Diarrhea, dyspepsia | | Yes |

Subject with a history of sclerosing cholangitis, cirrhosis, and ulcerative colitis who received ESL and 7 days later experienced an increase above baseline of AST and ALT (AST 85, ALT 113) with TBili and ALP close to baseline (TBili 2.2, ALP 416). Trial was completed and 8 days later, further increases in AST/ALT were noted (AST 129, ALT 193) with TBili and ALP close to baseline (Tbili 4.3 and ALP 506). Labs prior to ESL dose: AST 82, ALT 94, TBili 2.3, ALP 511.
Baseline values (~2 weeks prior to ESL): AST 39, ALT 47, TBili 4.1, ALP 591.
Concomitant medications included propranolol and sulfasalazine. Also amoxicillin and Bactrim were discontinued 2 weeks prior to ESL and ciprofloxacin was discontinued 1 week prior to ESL.
*Comment: Due to baseline elevations in liver tests, it is difficult to attribute these events to ESL alone.*

| | | | | | |
|---|---|---|---|---|---|
| 111-000-00017 | 20, M,B | 800mg | Abdominal pain lower | | Yes |
| Subject with a history of cirrhosis/portal HTN who received ESL and experienced persistent liver test elevations. Labs prior to ESL dose: AST 143, ALT 121, TBili 8.5, ALP 847. Liver tests continued to be elevated after starting ESL. All post-dose liver test elevations were lower than the pre-ESL dose values. Baseline values (~2 weeks prior to ESL): AST 178, ALT 143, TBili 9.7, ALP 965.<br>*Comment: Due to baseline elevations in liver tests, it is difficult to attribute these events to ESL alone.* | | | | | |
| 207-222-222011 | 76, M, W | 400mg | Liver disorder, cholestatis, jaundice | Day 34 | No |
| Subject with a history of neuropathy developed elevated liver tests in the setting of newly diagnosed gastric cancer with extension to the pancreatic head/biliary tree with severe dilatation of the biliary tract.<br>*Comment: These events are unlikely due to ESL in the setting of ongoing biliary tract obstruction.* | | | | | |
| **Hy's Lab Criteria using baseline values (some values not substantially increased above ULN):** | | | | | |
| 153-001-09058 | 45, M, W | 1600-2400mg | Paraesthesia, oral hypoesthesia | Day 6 of ESL | No |
| Subject in Study 153 that investigated the abuse potential of ESL in recreational CNS depressant users compared to placebo and alprazolam. He developed elevated liver tests after 3 doses of ESL 1600-2400 mg (34 days after subject received one dose of active control medication) with AST 3x baseline, total bilirubin 2.6x baseline (but <ULN), and alkaline phosphatase 1x baseline (but <ULN). Events resolved 2 weeks later. | | | | | |
| 206-567-567012 | 61, F, W | 1600mg | Vision blurred, headache | Day 60 | No |
| Subject developed elevated liver tests with ALT 3.5x baseline (1.4xULN), total bilirubin 6.5x baseline (1.3xULN), and alkaline phosphatase 1x baseline on Study Day 91 (1 day after the last dose of ESL). All parameters were normal at baseline and on Study Day 39 | | | | | |
| 206-682-682009 | 43, M, W | 1200mg | Influenza (Day 20) | Day 97 | No |
| Subject developed elevated liver tests with ALT 3.8x baseline, AST 8xULN baseline, total bilirubin 4.3x baseline, and alkaline phosphatase 1x baseline on day 97 of ESL 1200 mg. ESL dosing was interrupted but later restarted at lower dose (400 mg) and no further LFT increases were noted after receiving a total of 456 days of ESL. | | | | | |
| **Serious hepatic-related TEAEs (in the SMQ Hepatic Disorders):** | | | | | |
| 111-000-0009 | 58, F, W | 800mg | Hepatic encephalopathy | Day 5 | Yes |
| Subject with a history of liver disease/portal HTN and hepatic encephalopathy experienced hepatic encephalopathy on Study Day 5. Baseline liver tests included an elevated AST 1.4xULN, total bilirubin 1.5xULN, and INR 1.38 (ULN=1.24). On Day 5, the subject was "feeling dizzy," disoriented, vomiting, and had difficulty responding to commands. Subject was admitted to the hospital. Vitals were WNL. Exam revealed ascites and edema. Ammonia was elevated at 140 mcgmol/l (other liver labs were close to baseline). ESL was discontinued and the subject recovered after treatment with lactulose, metronidazole, ciprofloxacin, and thiamine. Subject admitted to recent excessive dietary intake of protein but no alcohol intake.<br>Concomitant medications included furosemide, propranolol, and spironolactone.<br>Twelve days later, liver labs were close to baseline levels.<br><br>*Comment: Due to the confounding factor of recent excessive dietary intake of protein, it is difficult to attribute these events to ESL alone.* | | | | | |
| 301-141-90181 | 39, F, W | 800mg | Hepatectomy, Liver operation | Day 182 | No |
| Subject was diagnosed with colorectal cancer with metastasis to the liver on OLE Study Day 182. Surgical treatment included exploratory laparotomy with excision of the left lobe of the liver (hemihepatectomy). | | | | | |
| 302-401-80732 | 23, F, W | 800mg | Hepatic rupture | Day 300 | No |
| Subject experienced "(laceration) liver rupture" of severe intensity. No physical examination, CT, liver function tests or other medical assessment results were provided according to the narrative report. ESL was continued and the subject recovered. | | | | | |
| 303-503-70008 | 43, M, W | 1200mg | Hepatitis | Day 441 | No |

| | | | | | |
|---|---|---|---|---|---|
| Subject was hospitalized for hepatitis on OLE Day 441. Subject experienced fever, upper abdominal discomfort, dizziness, and asthenia. Labs revealed elevated WBC, C-reactive protein, ALT 6xULN, AST 5xULN, ALP 1.3xULN, and low platelets. (Total bilirubin not reported). Immunoglobulins (IgG, IgM, IgA), ferritin, thyroid function tests were normal. The following serological tests were negative: HBV, HCV, HIV, toxoplasma, EBV, VDRL, CMV, Leishmania, Rickettsia, and Wright test. Abdominal CT was normal. ESL was continued. Subject gradually recovered. Labs one month later revealed normal values for AST/ALT, total bilirubin, and ALP. Final diagnosis was "suspicion of viral hepatitis." Concomitant medications included carbamazepine, primidone. | | | | | |
| 303-703-70349 | 40, F, O | 800mg | ALT/AST increased | Day 375 | No |
| Subject developed elevated ALT 3XULN, AST 2xULN, ALP 2.5xULN (normal total bilirubin) on OLE Study Day 375 (2 days after last study medication dose and study completion). | | | | | |
| **Postmarketing:** | | | | | |
| BIAL 00494 | 60, M | 1200mg | Hepatorenal syndrome | Unknown | No |
| Subject with a history of diabetes, multi-infarct dementia and cardiac failure developed a rash and fever after an "unknown" number of days on ESL therapy. Ten days later, the subject experienced "quincke's oedema, hepatorenal syndrome, oliguria, icterus, and somnolence." Labs revealed elevated WBC (no differential provided), CRP, ALT 2xULN, AST 2xULN, ALP 5.5xULN, and TBili 5.9xULN (with normal creatinine). Abdominal ultrasound revealed no cholestasis or dilated bile ducts. All medications (including ESL) were discontinued. Treatment was initiated with intravenous steroids and diuretics. Events improved. Subject recovered with unspecified sequelae after 10 days. An allergic reaction to ESL was suspected by the hospital physicians.<br>Concomitant medications included levetiracetam, risperidone, torsemide, aspirin, and bisoprolol. Baseline AST, ALT, and ALP were normal.<br><br>*Comment: Of note, this summary incorporates the additional information submitted by the Sponsor upon the Division's request as a Safety Information Amendment dated 6/27/13. This case unlikely represents hepatorenal syndrome with normal renal function. This case could possibly be DRESS. However, with the unknown timing of the onset of the symptoms after ESL initiation (relative to the other concomitant medications), it is difficult to attribute these events to ESL.* | | | | | |

Source: Created by the reviewer using narratives provided by the Sponsor and JReview Graphical Patient Profile using ADLAB, ADSL, ADEVENTX, ADVS datasets

In summary, there was a slightly higher incidence of ALT/AST >3xULN in ESL treated subjects than in placebo subjects. This evidence of hepatocellular injury may be the initial signal of DILI. However, there were very few ESL subject (0.4%, 0.2%, and 0.1%) with the more marked peak ALT/AST elevations (5x-, 10x-, and 20 xULN, respectively), the more specific signal. There were 2 ESL subjects who developed liver test abnormalities meeting Hy's law criteria. This criteria is considered to be the most specific predictor of a drug's potential for severe hepatotoxicity when there is no other explanation. However, in these 2 cases, alternative etiologies were not thoroughly investigated by the Sponsor. The Sponsor concludes that "[w]hile both meet the chemical abnormality portion of criteria for Hy's law, both are seen to have pre-existing conditions that exclude them from the full criteria." However, pre-existing liver disease does not preclude a subject from developing DILI. Therefore, ESL-induced liver injury cannot be completely ruled out in these cases. A hepatology consult request was sent to Dr. John Senior but had not been completed at the time of this review.

These 2 subjects did not progress to liver failure but these cases indicate that ESL may have the potential to cause severe liver injury. The number of possible Hy's Law cases

equals 2 out of 4225 total subjects (in the All Studies Pool including Study 303) or 4.7 per 10,000 subjects (or 2 out of 1983.7 total subject-years or 1.0 per 1,000 subject-years). The theoretical risk of severe DILI (fatal or requiring transplantation) will be 10% of this rate of Hy's Law cases or 0.47 per 10,000 patients (1.0 per 10,000 patient-years). Of note, this rate for ESL is lower than the frequencies of severe DILI for most of the drugs withdrawn from the market for hepatotoxicity (in the range of at least 1 per 10,000 patients). Furthermore, the estimated exposure to eslicarbazepine acetate based on worldwide sales data (provided by the Sponsor) equals 12,279 patient-years of exposure from 4/21/09 through 10/21/12. There have not been any postmarketing cases of severe DILI reported by the Sponsor.

In conclusion, ESL has been associated with elevations of serum ALT and AST. In rare cases, there were concurrent elevations in total bilirubin values (without substantial elevations in alkaline phosphatase) that were possibly related to ESL use. In most cases, reversibility of ALT/AST elevations was present. Therefore, I recommend that information regarding drug-induced liver injury be included in the Warnings of Precautions section of ESL labeling. In order to mitigate the risk of liver injury, monitoring of liver tests (ALT, AST, total bilirubin, and alkaline phosphatase) should be performed prior to initiation of ESL and at regular intervals after initiation (especially when signs and symptoms of hepatitis develop). If liver tests are abnormal, other laboratory measurements to assess liver function (e.g., INR, albumin, glucose) in addition to a full work up of other non-drug etiologies should be performed. Discontinuation and/or interruption of ESL treatment along with additional testing of liver enzymes should be performed according to the FDA's DILI Guidance for Industry (2009). Along with reporting any case of severe DILI in an expedited manner, the Sponsor should also be required to perform annual analyses of drug-induced liver injury. Of note, carbamazepine is also labeled for liver injury in the Warnings section (Tegretol®) or the Warnings and Precautions section (Equetro®).

7.3.4.2 Skin and Immune System Disorders

The following table summarizes the percentages of subjects reporting TEAEs in the SMQs Severe cutaneous adverse reactions, Anaphylactic reaction, Angioedema, Neuroleptic malignant syndrome, and Anticholinergic syndrome in the Phase 3 Epilepsy Controlled Pool. (Of note, the DRESS SMQ is not yet available). ESL subjects reported TEAEs in these SMQs at similar frequencies as placebo subjects. The preferred terms in the algorithmic or narrow searches (with the highest specificity to their respective clinical syndromes) were only reported by a small percentage of subjects (<1.0%) in both the placebo and ESL groups.

**Table 52. Skin and Immune System SOCs and SMQs, Phase 3 Epilepsy Controlled Pool**

| SMQ | Placebo n = 426 | ESL n = 1021 |
|---|---|---|
| SOC Immune system disorders | 1 (0.2) | 7 (0.7) |
| SOC Skin/subcu tissue disorders | 28 (6.6) | 65 (6.4) |
| SMQ Severe cutaneous adverse reactions | | |
| Narrow | 0 | 1 (0.1)[a] |
| Broad | 5 (1.2) | 7 (0.7) |
| SMQ Anaphylactic reaction | | |
| Algorithmic | 1 (0.2) | 4 (0.4)[b] |
| Narrow | 0 | 0 |
| Broad | 29 (6.8) | 82 (8.0) |
| SMQ Angioedema | | |
| Narrow | 3 (0.7) | 3 (0.3)[c] |
| Broad | 11 (2.6) | 26 (2.5) |
| SMQ Neuroleptic malignant syndrome | | |
| Algorithmic | 0 | 1 (0.1)[d] |
| Narrow | 0 | 0 |
| Broad | 38 (8.9) | 120 (11.8) |
| SMQ Anticholinergic syndrome | | |
| Algorithmic | 0 | 3 (0.3)[e] |

Source: Created by the reviewer using MAED (MedDRA-based Adverse Event Diagnostic) tool (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')
[a] 302-337-80223 exfoliative rash (described further below)
[b] 302-395-80740 (BP decreased, rash), 304-005-00509 (dyspnea, flushing), 304-011-01115 (asthma, pruritus, rash), 304-307-30721 (cough, pruritus, sneezing)
[c] 304-953-95304 eye swelling, 304-113-11301 eyelid oedema, 304-049-04909 pharyngeal oedema
[d] 304-953-95306 dyskinesia, loss of consciousness, pyrexia (described in Section 7.3.5 of this review)
[e] 302-311-80277 (loss of consciousness, vision blurred, disorientation), 302-395-80739 (disorientation, dizziness, gait disturbance, somnolence), 302-392-80383 (confusional state, dizziness, tachycardia)

Additionally, in the Nonepilepsy Double-blind Pool, ESL subjects reported TEAEs in these SMQs at similar frequencies as placebo subjects except for the narrow search for the SMQ Angioedema (0.9% vs 0.4%). There were also 2 ESL subjects (vs 0 placebo) with TEAEs that were identified in the narrow search for the SMQ Severe cutaneous adverse reactions (subjects 207-168-168009 and 207-225-225001 with toxic skin eruption, described below).

In the next few paragraphs, I will discuss skin disorders, anaphylactic reactions, angioedema, and drug reaction with eosinophilia and systemic symptoms (DRESS) in more detail.

Skin and subcutaneous tissue disorders
A TEAE coded to the preferred term, Stevens-Johnson syndrome, was reported in 1 ESL subject (Phase 1 Study) in the entire safety database (along with 2 potential cases in the postmarketing database). However, there were no cases coded to toxic epidermal necrolysis. The following table summarizes the rash-related TEAEs along

with SAEs and TEAEs leading to discontinuation that were reported in ESL subjects more often than placebo subjects in the Phase 3 Epilepsy Controlled Pool. A higher frequency of ESL subjects discontinued due to rash-related TEAEs than placebo subjects.

**Table 53. Rash-related TEAEs in ESL Subjects > Placebo, Phase 3 Epilepsy Controlled Pool**

| MedDRA PT | Placebo (%) n=426 | ESL (%) n=1021 |
|---|---|---|
| **TEAEs** | | |
| Rash | 4 (0.9) | 19 (1.9) |
| Pruritus | 4 (0.9) | 12 (1.2) |
| Dermatitis contact | 1 (0.2) | 3 (0.3) |
| Dermatitis | 0 | 2 (0.2) |
| Drug eruption | 0 | 1 (0.1) |
| Exfoliative rash | 0 | 1 (0.1) |
| Leukocytoclastic vasculitis | 0 | 1 (0.1) |
| Rash pruritic | 0 | 1 (0.1) |
| Purpura | 0 | 1 (0.1) |
| Skin disorder | 0 | 1 (0.1) |

Source: ISS Table 7.1.4.1.s5 and created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

**Table 54. All SAEs and Discontinuations in SOC Skin Disorders in ESL Subjects > Placebo, Phase 3 Epilepsy Controlled Pool**

| MedDRA SOC Skin and Subcut. tissue disorders | Placebo n=426 | ESL n=1021 |
|---|---|---|
| **SAEs** | | |
| Rash | 0 | 1 (0.1)[a] |
| Leukocytoclastic vasculitis | 0 | 1 (0.1)[b] |
| **Discontinuation TEAEs** | | |
| Rash | 0 | 7 (0.7) |
| Pruritus | 0 | 3 (0.3) |
| Leukocytoclastic vasculitis | 0 | 1 (0.1)[b] |
| Drug eruption | 0 | 1 (0.1) |
| Purpura | 0 | 1 (0.1) |
| Skin disorder | 0 | 1 (0.1) |

Source: Created by the reviewer using JReview (ADEVENTX: DISC=1, AESER='Y', AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')
[a]301-111-90341 described below
[b]304-955-95501 described below

The following table summarizes the SAEs and TEAEs leading to discontinuation that were reported in ESL subjects more often than placebo subjects in the Nonepilepsy Double-blind Pool. A higher frequency of ESL subjects discontinued due to rash-related TEAEs than placebo subjects.

**Table 55. All SAEs and DCs in SOC Skin Disorders in ESL Subjects > Placebo, Nonepilepsy Double-blind Pool (includes Study 206)**

| MedDRA SOC Skin and Subcut. tissue disorders | Placebo n=507 | ESL n=1755 |
|---|---|---|
| **SAEs** | | |
| Rash | 0 | 2 (0.1) |
| Pruritus | 0 | 1 (0.1) |
| Rash generalised | 0 | 1 (0.1) |
| Rash maculo-papular | 0 | 1 (0.1) |
| Toxic skin eruption | 0 | 1 (0.1)* |
| Skin disorder | 0 | 1 (0.1) |
| **Discontinuation TEAEs** | | |
| Rash | 1 (0.2) | 21 (1.2) |
| Pruritus | 0 | 8 (0.5) |
| Dermatitis allergic | 0 | 3 (0.2) |
| Rash pruritic | 0 | 3 (0.2) |
| Rash generalised | 0 | 1 (0.1) |
| Rash erythematous | 0 | 1 (0.1) |
| Rash papular | 0 | 1 (0.1) |
| Rash maculo-papular | 0 | 1 (0.1) |
| Skin disorder | 0 | 1 (0.1) |
| Toxic skin eruption | 0 | 2 (0.1)* |

Source: Created by the reviewer using JReview (ADEVENTX: DISC=1, AESER='Y', AEDECOD and ADSL: TRTP1) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')
*subjects 207-168-168009 and 207-225-225001, described below

In the Phase I Study Pool, the incidence of AEs leading to discontinuation for ESL overall was 3.4% compared with 1.8% for placebo (ISS Table 7.5.4.1). There were a total of 2 ESL subjects with SAEs (119-000-00004 with SJS, skin exfoliation, swelling face and 114-000-00008 with rash macular likely DRESS, both described below).

In the All Studies Pool (including 303), there were 4 additional ESL subjects who developed the following SAEs in the SOC Skin and Subcutaneous Tissue Disorders (which were not rash-related): night sweats, skin haemorrhage, ecchymosis, skin lesion, skin nodule.

*Comment: I reviewed all of the narratives for the rash-related SAEs and TEAEs leading to discontinuation (in addition to TEAEs such as drug eruption, skin exfoliation) and further describe the relevant and notable cases below. Some of these other cases (not included in the table of narratives below) included information regarding skin exfoliation or mouth ulceration. However, from the limited information (limited descriptions) provided in the narratives, none of these other cases reported a biopsy- (or dermatologist-confirmed) diagnosis along with widespread, full-thickness denudation and mucocutaneous involvement with treatment in a burn unit.*

*Of note, the Sponsor reported that only one subject (304-955-95501) received HLA typing as a result of a serious allergic reaction. The results from the HLA-B*1502 test were negative.*

In the ongoing studies, the Sponsor reported that no cases of SJS have been identified. In the postmarketing database, the Sponsor reported a total of 2 cases of Stevens-Johnson syndrome (both SAEs). In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 6/27/13 to provide additional information regarding these 2 cases. The Sponsor confirmed that these 2 potential cases were the following:

BIAL 01037 with "skin dropping off hands, mouth, and feet" and oral ulceration on an "unknown date, during treatment with [ESL]" with positive dechallenge

BIAL-01249 with "life-threatening allergic exanthema with skin detachment on the entire body" a "few days" after starting ESL (and was also on concomitant lamotrigine). ESL was discontinued and the events are "recovering".

In both cases, the Sponsor stated that the "reporter declined repeated efforts to obtain further information." The Sponsor's estimated rate of Stevens-Johnson syndrome (based on prescription exposure of 12,279 patient-years) was 2 per 10,000 patient-years.

The following table summarizes the narratives of the ESL subjects with rash-related SAEs and TEAEs leading to discontinuation in the All Studies Pool (including 303).

**Table 56. Narratives for Rash-Related SAEs and TEAEs leading to discontinuation, All Studies Pool (including 303)**

| Subject # | Age,Sex, Race | Dose | Adverse event (Preferred Term) | Study day |
|---|---|---|---|---|
| 119-000-00004 | 30, M, W | 1200mg | Stevens Johnson syndrome, skin exfoliation, swelling face | Day 10 |
| Subject is a healthy male volunteer who developed "hypersensitivity" 10 days after starting ESL (and 18 days after starting lamotrigine). On Day 3, the subject c/o tongue numbness, lightheadedness, photophobia, and headache. On Day 10, a rash developed on his right wrist along with erythema of the back of the throat. Two days later, the subject experienced pain with eye movement, fever to 39.4 degrees C, "red spots all over his body," cervical lymphadenopathy, and nausea. Acetaminophen was started. Labs revealed leukopenia and elevated CRP. Two days later, the subject reported facial swelling and pruritus. Treatment during the hospitalization included diphenhydramine, methylprednisolone. Subject developed dysphagia, ulceration of the lower lip mucosa, lip/tongue swelling, and "peeling all over the body." Labs revealed elevated AST 62 U/L (14-42 U/L) and ALT 152 U/L (10-63 U/L). ESL was discontinued on Day 14. The subject recovered ~2 weeks later.<br>The Sponsor recoded this event from the non-serious event of hypersensitivity to the serious event of Stevens-Johnson syndrome.<br>*Comment: This case does not meet all of the criteria for probable Stevens-Johnson syndrome (with a biopsy- or dermatologist-confirmed diagnosis with full-thickness denudation). Although this case could also be DRESS, Stevens-Johnson syndrome is still a possibility. Because of the close temporal relationship with ESL initiation and positive dechallenge information, the causal role of ESL in this case of SJS cannot be ruled out. However, the concomitant treatment with lamotrigine is a significant confounder. The prescribing information for lamotrigine includes information regarding serious skin rashes (SJS/TEN) as a boxed warning.* | | | | |

| | | | | |
|---|---|---|---|---|
| 304-955-95501 | 35, M, A | 800mg | Leukocytoclastic vasculitis, Purpura | Day 29 |
| Subject with a history of epilepsy (and no history of allergies) developed an exanthematous rash "all over his body" on Day 29 of ESL. Systemic symptoms included "feeling feverish and restless." Vitals were WNL. Exam was negative for lymphadenopathy, purpura. Labs revealed elevated platelets, low monocytes, and slightly elevated CPK. Subject was diagnosed with "leukocytoclastic vasculitis." ESL was discontinued. Treatment included antihistamines and analgesics. Repeat examination on Day 42 revealed complete resolution of the rash.<br>HLA-B1502 test (performed prior to ESL dose) was negative.<br>Concomitant medications included levetiracetam (>1 yr) and clobazam (>6 months). | | | | |
| 207-168-168009 | 73, F, W | 1200mg | Toxic skin eruption, rash generalized, rash maculo-papular, rash | Day 10 |
| Subject with a history of post-herpetic neuralgia, asthma who developed severe rash on Day 10 of ESL. She developed a generalized maculopapular exanthema (worse on the arms, thighs, back, and low neck) and was hospitalized in the dermatology department. The rash consisted of small pink-colored maculae and papulae from 0.2 to 0.4 cm. Subject had normal vital signs and "no other symptoms other than the rash." Labs revealed a high total IgE. ESL was discontinued. Treatment included systemic corticosteroids and antihistamines. Subject recovered ~1 week later.<br>No recent concomitant medications. | | | | |
| 207-225-225001 | 74, F, W | 600mg | Toxic skin eruption | Day 14 |
| Subject with a history of post-herpetic neuralgia who developed "toxicoderma" of "mild intensity" on Day 14 of ESL. ESL was discontinued. Subject recovered 1 week later. Other adverse events included gastric pain treated with omeprazole. | | | | |
| 302-337-80223 | 34, F, B | 800mg | Exfoliative Rash | Day 163 |
| Subject with a history of epilepsy developed a rash on Day 163 of ESL. Physical examination revealed cutaneous erythematous rash and desquamative lesions on the torso and legs. About 1 month later, ESL was discontinued. The subject recovered from the event 7 days after ESL discontinuation.<br>Concomitant medications (>10 yrs) included carbamazepine and clobazam. | | | | |
| 203-334-203052 | 66, M, W | 800mg | Skin disorder | Day 26 |
| Subject with a history of bipolar disorder experienced the SAE of worsening mania on Day 26 of ESL. ESL was continued and subject recovered from the event 22 days later. In the narrative, the Sponsor noted that the subject also had "data review events of … pletoric skin (skin disorder)." No additional descriptions were provided. | | | | |
| 207-141-141001 | 70, M, W | 800mg | Rash | Day 3 |
| Subject with a history of post-herpetic neuralgia who was hospitalized on Day 3 of ESL with a herpetic rash that started 8 days prior to ESL initiation. The final diagnosis was acute herpes zoster. | | | | |
| 206-566-566007 | 75, M, W | 1600mg | Pruritus, hyperhidrosis | Day 18 |
| Subject with a history of diabetes who on Study Day 18 was hospitalized for dyspnea, "tickling behind the sternum" (coded to pruritus), fatigue, and sweating (coded to hyperhidrosis). Subject was diagnosed with a myocardial infarction and ESL was discontinued. | | | | |
| 301-111-90341 | 36, F, W | 800mg | Rash | Day 14 |
| Possible case of DRESS – discussed below. | | | | |
| 114-000-00008 | 21, F, W | 1200mg | Rash macular | Day 11 |
| Possible case of DRESS – discussed below. | | | | |

Source: Created by the reviewer using narratives provided by the Sponsor and JReview Graphical Patient Profile using ADLAB, ADSL, ADEVENTX, and ADVS datasets

In conclusion, ESL use is associated with an increased occurrence of rash and discontinuations due to rash compared with placebo use. Although there were some cases of serious rash-related adverse events with mucocutaneous involvement and skin

exfoliation/detachment requiring hospitalization, there were no biopsy- (or dermatologist-) confirmed cases of any severe cutaneous adverse reactions associated with ESL use. However, these events are currently included in the prescribing information for carbamazepine (in the Warnings section) and oxcarbazepine products (in Warnings and Precautions). Thus, I recommend that similar information regarding serious dermatologic events be included in the Warnings and Precautions section of ESL labeling due to the higher biologic plausibility for these reactions. Furthermore, I recommend a postmarketing requirement for the Sponsor to study the possible genetic risk factors for developing severe cutaneous adverse reactions, specifically the association with the presence of HLA alleles such as HLA-B*1502 and HLA-A*3101.

Anaphylactic reaction/Angioedema
The following tables summarize the hypersensitivity TEAEs along with SAEs and TEAEs leading to discontinuation that were reported in ESL subjects more often than placebo subjects in the Phase 3 Epilepsy Controlled Pool. Importantly, there were no adverse events coded to the PTs anaphylactic reaction or angioedema in the completed clinical trials (using the Sponsor's integrated adverse events dataset ADEVENTX). (There was 1 case each of angioedema and laryngospasm in the postmarketing database).

**Table 57. Hypersensitivity TEAEs in ESL Subjects > Placebo**

| MedDRA PT | Placebo (%) | ESL (%) |
|---|---|---|
| **Phase 3 Epilepsy Controlled Pool** | n=426 | n=1021 |
| Hypersensitivity | 1 (0.2) | 4 (0.4) |
| Drug hypersensitivity | 0 | 2 (0.2) |
| Eye swelling | 0 | 1 (0.1) |
| Eyelid oedema | 0 | 1 (0.1) |
| Pharyngeal oedema | 0 | 1 (0.1) |
| Swelling | 0 | 1 (0.1) |
| **Nonepilepsy Double-blind Pool** | n=507 | n=1755 |
| Hypersensitivity | 2 (0.4) | 8 (0.5) |
| Face oedema | 0 | 6 (0.3) |
| Eyelid oedema | 1 (0.2) | 5 (0.3) |
| Drug hypersensitivity | 1 (0.2) | 4 (0.2) |
| Local swelling | 0 | 1 (0.1) |
| Periorbital oedema | 0 | 1 (0.1) |
| Swelling face | 0 | 1 (0.1) |
| Tongue oedema | 0 | 1 (0.1) |

Source: ISS Table 7.1.4.1.s5 and created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

**Table 58. All SAEs and DCs in SOC Immune System Disorders in ESL Subjects > Placebo**

| MedDRA SOC Skin and Subcut. tissue disorders | Placebo n=426 | ESL n=1021 |
|---|---|---|
| **Phase 3 Epilepsy Controlled Pool** | | |
| Eye swelling | 0 | 1 (0.1) |
| Hypersensitivity | 0 | 1 (0.1) |
| **Nonepilepsy Double-blind Pool** | | |
| Hypersensitivity | 0 | 6 (0.3) |
| Face oedema | 0 | 4 (0.2) |
| Drug hypersensitivity | 0 | 3 (0.2) |
| Eyelid oedema | 0 | 3 (0.2) |
| Oedema | 0 | 2 (0.1) |
| Urticaria | 0 | 2 (0.1) |
| Tongue oedema | 0 | 1 (0.1) |

Source: Created by the reviewer using JReview ( ADEVENTX: DISC=1, AESER='Y', AEDECOD and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

The narratives for the SAEs (and notable DCs) are summarized below:
Subject 302-423-80744 developed an "allergic reaction" (no other details provided in the narrative) 2 days after the last dose of ESL. Events resolved 3 days later.
Subject 304-953-95304 developed "periorbital swelling" and redness on Day 9 of ESL. ESL was discontinued and events resolved 2 days later. Positive rechallenge 2 days later.
Subject 206-701-701017 developed "tongue edema" and burning of the tongue on Day 18 of ESL. ESL was continued for another 20 days. No respiratory events were reported in the narrative. Events resolved 3 days after the last dose of ESL. Patient had a history of hypersensitivity (no other details provided).

Many of the events coded to hypersensitivity or drug hypersensitivity were events of a rash. Typical onset of these TEAEs was within 1 month of ESL initiation (mode=12 days). Events resolved promptly after ESL discontinuation with typical time to resolution of <1 week (mode=3 days). None of the narratives reported any associated respiratory signs or symptoms such as difficulty breathing or stridor. None of the narratives reported the use of epinephrine as treatment.

In the ongoing studies, the Sponsor reported 1 ESL subject with the SAE drug hypersensitivity:
Subject 308-3107801 developed an "allergic reaction" (diffuse rash and pruritus) on Day 36 of ESL. The subject was hospitalized and treated with antihistamines and corticosteroids. ESL was discontinued and events resolved 6 days later. Labs revealed normal liver tests.

In the postmarketing database, the Sponsor reported 3 ESL subjects with the following SAEs hypersensitivity, laryngospasm, and angioedema:
BIAL 00309 developed an "allergic reaction" with urticaria, itching, dyspnea, and circulatory problems during the first hour after taking ESL. ESL was discontinued and the patient recovered. Patient had a prior history of allergy to oxcarbazepine (rash).
BIAL 00484 developed sore throat that progressed to pharyngospasm with complete anarthria on Day 17 of ESL. Pt was hospitalized. ESL was discontinued and the patient recovered the next day.

BIAL 01798 developed rash and Quincke's edema with tongue edema on an unknown date (but "quickly after treatment with ESL"). ESL was discontinued and the outcome was unknown.

*Comment: Additionally, we received information as a IND safety report (Mfr report # 2013SP002353) regarding a cumulative literature report from a post-authorization study from Spain (translated from original language) in which 2 cases of exanthematic skin reactions (one severe rash-angioedema and one mild pruritic erythema) were reported. Of note, these skin reactions were not included in the list of the 18 adverse event terms that were coded by the Sponsor. This is another example of a coding omission.*

In summary, ESL use is associated with hypersensitivity reactions such as localized angioedema (of the eyelid, face, tongue). Some of these events were serious and led to treatment discontinuation. Symptoms typically began quickly after initiation of ESL and resolved quickly after ESL discontinuation. Although there were no cases of anaphylactic reactions in the completed clinical trials, there were spontaneous reports of possible pharyngospasm and anaphylaxis in the postmarketing database. A prior history of an allergy to oxcarbazepine was reported in 1 patient and may be a risk factor. In conclusion, I recommend the addition of these events in the Warnings and Precautions section of ESL labeling.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
In response to the Division's information request, the Sponsor conducted a review of the entire ESL database for subjects who met the search criteria for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) using an extensive list of MedDRA PTs. Specifically, the search used the following European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) Project criteria for DRESS:

Reaction suspected to be drug related with at least 3 of the following:

1. Acute skin rash
2. Involvement of at least one internal organ
3. Enlarged lymph nodes
4. One of the following blood count abnormalities (lymphocytes > or < than the lab limits, eosinophils > than the lab limits in % or absolute count, platelets < lab limits)
5. Fever above 38°Celsius

This programmatic search identified a total of 3 subjects (all ESL subjects) as possible cases of DRESS (114-000-00008, 301-111-90341, and 301-174-90414, described below).
*Comment: I reviewed the narratives for these 3 subjects along with an independent review of each of the subject's laboratory and vital sign parameters. All of these subjects met the RegiSCAR criteria for DRESS criteria. However, for subject 301-174-90414, a significant confounder was present (recent use of antibiotics). The other 2 cases could be cases of DRESS associated with ESL use.*

In the ongoing studies, the Sponsor reported 2 ESL subjects with SAEs of DRESS (305-21109 and 046-6156-S0004, described below). Since the data cut-off date, the Sponsor reported 2 additional cases (311-1813-11 and 311-2901-01, described below). In the postmarketing database, the Sponsor reported no cases of DRESS. The following table summarizes the narratives of the ESL subjects with potential DRESS in the All Studies Pool (including 303) and ongoing studies.

**Table 59. Narratives of ESL Subjects with Potential DRESS**

| Subject # | Age,Sex, Race | Dose | Adverse events/Lab values that fit DRESS criteria | Study day (of ESL) |
|---|---|---|---|---|
| 114-000-00008 | 21, F, W | 1200mg | Rash macular<br>Fever<br>Lymphadenopathy<br>Decreased WBC | Day 11 |
| Subject is a healthy female (history of allergic rhinitis) who received ESL for 11 days and developed an erythematous macular rash on the face (with a "slapped cheek" appearance) which later spread to the feet and legs. Subject also c/o preceding oral paresthesias, dizziness, and somnolence. ESL was continued until the end of the study 4 days later. At this time, the subject experienced myalgia, "hyperthermia" to 38.9 degrees C, cervical lymphadenopathy, and headache. Labs revealed leukopenia (neutropenia), thrombocytopenia (with normal eosinophils, liver and kidney tests, normal titers of parvovirus, hepatitis B/C, HIV, EBV IgM, complements, ANA)). Treatment included paracetamol. The subject recovered 6 days after ESL discontinuation.<br>Subject was enrolled in this open-label DDI study in which the subject received a single dose of ethinylestradiol and levonorgestrel about 3 weeks prior to ESL initiation.<br>No other concomitant medications were reported.<br><br>*Comment: This case meets 4 of the RegiSCAR criteria for DRESS. These events could be due to ESL with close temporal relationship and positive dechallenge (along with a negative work up for alternative etiologies).*<br><br>*Of note, the narrative summary above includes information submitted by the Sponsor in response to the Division's information request, that included the adverse events that began on or after April 19, 2005 (Day 11 of ESL when the rash began) with updated corresponding laboratory values and vital signs that were not included in the ADLAB dataset or the initial narrative provided in the ISS. The Sponsor reported that an error was identified related to the subject identifier in the SAS programs that integrated data from study 2093-114 into the ISS data sets.*<br><br>*Additionally, the Sponsor reported that although the subject was "originally reported as experiencing 'erythema infectiosum' due to the appearance of the facial rash, parvovirus testing was negative. The rash was originally recorded as non-serious (treated as an outpatient with acetaminophen, full recovery) but was upgraded to an SAE after the subject recovered and after the clinical database was locked. The reason for upgrading this event to an SAE was not stated."* | | | | |
| 301-111-90341 | 36, F, W | 800mg | Rash<br>Fever to 39.8 degrees C<br>Increased AST<br>Leukopenia, thrombocytopenia | Day 8 |
| Subject with a history of epilepsy due to herpetic meningoencephalitis developed a fever up to 39.8° C on Day 8 of ESL. Treatment included paracetamol (Day 8-11) and diclofenac (Day 11-12). On Day 14, the subject developed a severe "generalized macular rash" and was hospitalized. Labs during the hospitalization revealed an elevated CRP/AST/LDH, leukopenia, anemia, and thrombocytopenia. | | | | |

Serologies of HbsAg, anti-HCV, anti-HIV, heterophile antibodies were negative. ESL was discontinued (last dose on Day 13). Treatment included azithromycin, antihistamines, and dexamethasone. The symptoms gradually improved with resolution on Day 20.
Concomitant AED medications included carbamazepine (>15 yrs), topiramate (~2 yrs), and oxazepam (~1 yr).
*Comment: This case meets 4 of the RegiSCAR criteria for DRESS. These events could be due to ESL with close temporal relationship and positive dechallenge (along with a negative work up for alternative etiologies).*

| | | | | |
|---|---|---|---|---|
| 301-174-90414 | 44, F, W | 800 mg | Rash<br>Increased ALT/AST<br>Leukopenia, thrombocytopenia | Day 93 |

Subject with a history of epilepsy developed a rash ("moderate") on Day 93 of ESL. The narrative reports that "there were no pertinent abnormal objective findings. There were no data on relevant findings on physical and neurologic exams." ESL was continued. On Study Day 105, labs revealed elevated ALT 3xULN and AST 5xULN with decreased platelet count and WBC. ESL was continued for >3 more years. Events resolved while on ESL.

Concomitant medications (chronic use) included clonazepam, valproic acid, furosemide, spironolactone, risperidone, diazepam.

*Comment: This case meets 3 of the RegiSCAR criteria for DRESS. However, this is unlikely due to ESL use as the events resolved with the continuation of ESL.*

| | | | | |
|---|---|---|---|---|
| 046-6156-S0004 | 40, F, W | ESL | Rash<br>Lymphadenopathy<br>Eosinophilia<br>Fever | Day 33 |

Subject with a history of epilepsy developed fever and lymphadenopathy (supraclavicular and cervical) on Day 21 of ESL. Treatment included "amoxiclav" on Day 22-26. On Day 27, medication was changed to clarithromycin (given for 1 day). The subject developed face erythema/edema and generalized pruritus. Antibiotics were discontinued and the subject was treated with dexamethasone. Three days later on Day 30, the rash spread to the "whole body." On Day 33, the subject developed diffuse erythema and papules on the legs. Subject was hospitalized and evaluated by a dermatologist who suspected DRESS due to eslicarbazepine. Recent labs (on Day 29) revealed elevated eosinophils (normal ALT/AST). ESL was discontinued. Treatment included systemic intravenous corticosteroids and antihistamines. Serologies were negative for infectious mononucleosis. The subject "recovered with sequelae" 15 days after last dose of ESL.

Concomitant medications included levetiracetam (Study Day 8 to Day 11).

*Comment: This could be a case of DRESS due to ESL with close temporal relationship and positive dechallenge. However this case is confounded by the recent use of antibiotics, "amoxiclav".*

| | | | | |
|---|---|---|---|---|
| 305-21109* | 5, F | Blinded (ESL or PBO) | Rash<br>Fever<br>Lymphadenopathy | Day 6 |

Subject with a history of epilepsy developed dysphagia and fever to 40.7 degrees C on Day 6 of study drug (ESL or PBO). Subject was evaluated by the general practitioner who diagnosed the subject with a throat infection and started treatment with amoxicillin/clavulanate. Two days later, the subject developed edema on upper eyelids, ears, and lips. Then started to have perioral macular skin changes that spread to the ears, neck, chest, and arms. Lymphadenopathy was also noted during physical examination. The subject was hospitalized. Study medication was discontinued. A chest xray revealed "pneumonia infiltration." Antibiotic therapy was modified to imipenem. Oxygen therapy was initiated. Labs revealed an elevated AST, ALT, GGT, LDH, and titers of EBV IgM/IgG, Coxsackie B IgM, Enterovirus B18 IgM. The subject slowly recovered and was discharged after a month long hospitalization. The Sponsor diagnosed this case as infectious mononucleosis with elevated EBV titers.

| | | | | |
|---|---|---|---|---|
| Concomitant medications included sodium valproate, clobazam, lamotrigine.<br>*Comment: Case confounded by concomitant use of amoxicillin/clavulanate which can also cause a rash in patients with infectious mononucleosis.* | | | | |
| 311-1813-11 | 49, F, W | Blinded (ESL or CBZ) | Rash<br>Fever<br>Increased ALT, eosinophils<br>Leukopenia, thrombocytopenia | Day 11 |
| Subject with a history of multiple environmental allergies developed a fever and rash on Day 11 of study medication. Labs revealed an elevated ALT 2xULN and eosinophils along with decreased WBC and platelets. Study medication was discontinued. The subject recovered 10 days later.<br>No concomitant medications were reported.<br>*Comment: Case confounded by subject's prior history of multiple allergies.* | | | | |
| **Cases with < 3 RegiSCAR Criteria:** | | | | |
| 311-2901-01 | 58, M,W | Blinded (ESL or CBZ) | Rash | Day 24 |
| Subject with a history of epilepsy developed a rash and pruritus on Day 24 of study medication. Physical examination revealed "skin exanthema." Study medication was discontinued. Subject recovered. Recent concomitant medications included amoxicillin (started 1 week prior to onset of rash).<br>*Comment: Case confounded by concomitant use of amoxicillin.* | | | | |
| 116-001-00034 | 32, F, W | 2400mg | Rash and Increased ALT<br>Rechallenge: Rash and Fever | Day 8 |
| Subject (healthy volunteer) developed rash 3 days after a 5 day treatment course of ESL. "No details regarding dermatologic examination and temperature were available." Labs revealed an elevated ALT <2xULN. The event resolved 7 days later. Ten days later, ESL was restarted at a lower dosage and the subject again experienced rash (along with a fever). ESL was discontinued. Treatment included antihistamines. Subject recovered 3 days later. | | | | |
| 121-000-00028 | 25, M, W | | Rash, lymphadenopathy, lip swelling | Day 5 |
| Subject (healthy volunteer) developed rash and swollen lips on Day 5 of ESL. ESL was continued and the subject recovered. Ten days later, the subject experienced "hypersensitivity syndrome" (recoded from DRESS by the Sponsor). ESL was discontinued (and treated with antihistamines). Events resolved 5 days later. | | | | |
| 210-603-603009 | 72, F, W | 800mg | Rash<br>Increased AST/ALT (high at baseline) | Day 10 |
| Subject with a history of fibromyalgia and diabetes mellitus developed pruritus and mild exanthema on arms, breast, and back on Day 10 of ESL. ESL was discontinued on Day 13. Three days later, the subject recovered from these events. Labs revealed elevated AST <2xULN and ALT <2xULN (however both elevated at baseline). | | | | |
| 209-125-90151 | 60, F, W | 600mg | Rash, eye lids oedema<br>Decreased WBC (low at baseline) | Day 56 |
| Subject with history of migraines developed an erythematous rash and eye lid edema on Day 56 of ESL. "No details regarding lymphadenopathy or temperature were available." "No pertinent abnormal objective findings." ESL was discontinued. Treatment included antihistamines. Subject recovered from the events 30 days later. Labs revealed lower WBC and neutrophils. Recent concomitant medications included clindamycin (stopped ~50 days prior to ESL). | | | | |
| 209-203-90112 | 41, F, W | 600 mg | Rash, face edema | Day 12 |
| Subject with a history of migraines developed edema of the lips and face, erythema (chest/back), and pruritus on Day 12 of ESL. "No details regarding lymphadenopathy were available." ESL was discontinued. Treatment included hydrocortisone and antihistamines. Subject recovered from these events within 1 week. | | | | |

| | | | | |
|---|---|---|---|---|
| 206-762-762005 | 50, F, W | 1600mg | Urticaria, edema | Day 12 |
| Subject with a history of diabetic neuropathy and autoimmune thyroiditis developed "hypersensitivity" with cough, edema, pruritus, urticaria on Day 12 of ESL. ESL was discontinued. Treatment included antihistamines. The event resolved the same day. | | | | |
| 210-642-642008 | 31, F, W | 1200mg | Rash<br>Increased ALT/AST | Day 12 |
| Subject with a history of fibromyalgia who developed a rash on Day 12 of ESL. "There were no other pertinent abnormal findings" on physical examination. ESL was discontinued. Treatment included antihistamines. Two days later, early discontinuation labs were notable for an elevation of ALT and AST to >2xULN and slightly decreased free T4 and T3 (and ?low WBC). Rash resolved the next day. Transaminitis reportedly resolved ~2 weeks later.<br>No new concomitant medications were reported. | | | | |

Source: Created by the reviewer using narratives provided by the Sponsor and JReview Graphical Patient Profile using ADLAB, ADSL, ADEVENTX, and ADVS datasets
*CIOMS form submitted by the Sponsor in the Safety Information Amendment dated 6/17/13 in response to the Division's request for additional information.

In conclusion, there were cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) associated with ESL use. I recommend that information regarding DRESS be included in the Warnings and Precautions section of ESL labeling (with language similar to the warning in the prescribing information for other AEDs).

7.3.4.3 Nervous System Disorders

A higher number of ESL subjects experienced TEAEs in the SOC Nervous System Disorders than placebo subjects in both the Phase 3 Epilepsy Controlled Pool (48.3% vs 31.2%) and the Nonepilepsy Double-blind Pool (22.8% vs 13.4%). Discontinuations due to these TEAEs occurred more often in ESL subjects than placebo in both the Phase 3 Epilepsy Controlled Pool (11.5% vs 3.8%) and the Nonepilepsy Double-blind Pool (4.6% vs 0.6%). Nervous system disorder SAEs occurred twice as often in ESL subjects than placebo in both pooled groups. The following table summarizes the adverse events in the SOC Nervous System Disorders for the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool.

**Table 60. Overview of TEAEs, SAEs, DCs in SOC Nervous System Disorders**

| SOC Nervous System Disorders | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=426 | n=1021 | n=507 | n=1755 |
| TEAEs | 133 (31.2%) | 493 (48.3%) | 68 (13.4%) | 401 (22.8%) |
| SAEs | 6 (1.4%) | 31 (3.0%) | 1 (0.2%) | 8 (0.5%) |
| Discontinuations (DCs) | 16 (3.8%) | 117 (11.5%) | 3 (0.6%) | 81 (4.6%) |

Source: ISS Tables 7.1.4.1.s5, 7.1.11.1.s2, 7.4.1.1.s2 and created by the reviewer using JReview (ADEVENTX: AESER='Y', DISC=1 and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

To further analyze these SAEs, I stratified the SAEs by the HLGTs in the SOC Nervous System Disorders (with ≥2 ESL subjects and >placebo), then by the PTs (with ≥1 ESL

subject and >placebo) (see table below). In both pooled groups, SAEs occurred in ESL subjects more than placebo in the HLGT Neurological disorders NEC (or "not elsewhere classified") and to a lesser degree in the HLGT Headaches. Many of these SAEs were related to coordination and balance disturbances.

*Comment: In the Phase 3 Epilepsy Controlled Pool, more ESL subjects reported SAEs in the HLGT Seizures (incl subtypes) than placebo (1.4% vs 0.5%). The reader is referred to Dr. Teresa Podruchny's review of efficacy for a detailed analysis of rebound epilepsy, worsening of seizures, and seizure-related TEAEs with ESL use.*

**Table 61. SAEs in Nervous System Disorders HLGTs in ≥2 ESL subjects and >Placebo (then PTs in ≥1 ESL subject and >Placebo)**

| **Nervous system disorders HLGT Preferred Term** | **Placebo** | **ESL** |
|---|---|---|
| **Phase 3 Epilepsy Controlled Pool** | n = 426 | n = 1021 |
| HLGT Neurological disorders NEC | 5 (1.2%) | 17 (1.7%) |
| Ataxia | 0 | 7 (0.7) |
| Dizziness | 0 | 2 (0.2) |
| Balance disorder | 0 | 2 (0.2) |
| Nystagmus | 0 | 2 (0.2) |
| Cerebellar syndrome | 0 | 1 (0.1) |
| Sensory disturbance | 0 | 1 (0.1) |
| Somnolence | 0 | 1 (0.1) |
| Tongue biting | 0 | 1 (0.1) |
| HLGT Seizures (incl subtypes)* | 2 (0.5%) | 14 (1.4%) |
| HLGT Headaches | 0 | 2 (0.2%) |
| | | |
| **Nonepilepsy Double-blind Pool** | n=507 | n=1755 |
| HLGT Neurological disorders NEC | 0 | 6 (0.3%) |
| Altered state of consciousness | 0 | 1 (0.1) |
| Balance disorder | 0 | 1 (0.1) |
| Dizziness | 0 | 1 (0.1) |
| Dizziness exertional | 0 | 1 (0.1) |
| Dysstasia | 0 | 1 (0.1) |
| Loss of consciousness | 0 | 1 (0.1)** |
| Postictal state | 0 | 1 (0.1) |
| Syncope | 0 | 1 (0.1)** |
| HLGT Headaches | 0 | 4 (0.2%) |

Source: ISS Table 7.1.11.1.s2 and created by the reviewer using JReview (ADEVENTX: AESER='Y', and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)
*See Dr. Teresa Podruchny's review of efficacy for an analysis of seizure-related TEAEs.
**SAEs of loss of consciousness and syncope discussed in Section 7.3.5 on Cardiac Disorders

In the Phase 2 Study 201, there was 1 ESL subject with the SAE ischaemic stroke. In the Phase 1 studies, there were no SAEs in the SOC Nervous System Disorders.

In the ongoing studies, the following SAEs occurred in at least 2 ESL subjects (which

were consistent with the SAEs listed above): seizure-related PTs, dizziness, and syncope (Safety Information Amendment 4/19/13 Table 2).

To further analyze the TEAEs leading to drug discontinuation in the SOC Nervous system disorders, I stratified these TEAEs by the HLGTs in the SOC Nervous System Disorders (with ≥2 ESL subjects and >placebo) then by the PTs (with ≥1 ESL subject and >placebo) (see table below). ESL subjects discontinued more frequently than placebo due to the TEAEs in the HLGT Neurological disorders NEC and to a lesser extent in the HLGTs Headaches, Movement disorders, Mental impairment disorders, and Sleep disturbances. Many of these TEAEs were related to coordination and balance disturbances (and somnolence/lethargy).

**Table 62. Discontinuations in Nervous System Disorders HLGTs in ≥2 ESL subjects and >Placebo (PTs in ≥1 ESL subject and >Placebo), Phase 3 Epilepsy Controlled Pool**

| Nervous system disorders SOC<br>Preferred Term | **Placebo** | **ESL** |
|---|---|---|
| **Phase 3 Epilepsy Controlled Pool** | n = 426 | n = 1021 |
| HLGT Neurological disorders NEC | 6 (1.4) | 104 (10.2) |
| Dizziness | 2 (0.5) | 62 (6.1) |
| Ataxia | 0 | 28 (2.7) |
| Somnolence | 2 (0.5) | 19 (1.9) |
| Dysarthria | 0 | 6 (0.6) |
| Nystagmus | 0 | 4 (0.4) |
| Balance disorder | 0 | 3 (0.3) |
| Aphasia | 0 | 2 (0.2) |
| Cerebellar syndrome | 0 | 2 (0.2) |
| Coordination abnormal | 0 | 2 (0.2) |
| Lethargy | 0 | 2 (0.2) |
| HLGT Seizures (incl subtypes)* | 9 (2.1) | 10 (1.0) |
| HLGT Headaches | 3 (0.7) | 9 (0.9) |
| Headache | 3 (0.7) | 9 (0.9) |
| HLGT Movement disorders | 1 (0.2) | 8 (0.8) |
| Tremor | 1 (0.2) | 5 (0.5) |
| HLGT Mental impairment disorders | 1 (0.2) | 6 (0.6) |
| Amnesia | 0 | 2 (0.2) |
| HLGT Sleep disturbances | 0 | 2 (0.2) |
| Hypersomnia | 0 | 2 (0.2) |

Source: Created by the reviewer using JReview (ADEVENTX: DISC=1 and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')
*See Dr. Teresa Podruchny's review of efficacy for an analysis of seizure-related TEAEs.

Similar results were noted in the Nonepilepsy Double-blind Pool. The following TEAEs leading to discontinuation occurred in at least 2 ESL subjects and greater than placebo: headache (1.3% versus 0), hemicephalalgia (0.1% versus 0), disturbance in attention (0.3% versus 0), memory impairment (0.1% versus 0), dizziness (1.8% versus 0.2%), dysaesthesia (0.1% versus 0), hypoaesthesia (0.1% versus 0), lethargy (0.1% versus

0), post herpetic neuralgia (0.2% versus 0), somnolence (0.7% versus 0), syncope (0.1% versus 0).

To address the issue of the splitting of potentially similar neurological events into multiple preferred terms, I performed additional analyses in order to pool together related events (please see Section 7.1.2 of this review for a detailed discussion regarding splitting). I reanalyzed the AEs in the following main groups: Dizziness and gait disturbance, Somnolence and fatigue, Cognitive dysfunction, and Paresthesia. The preferred terms for these groups were chosen after reviewing the AE dataset for relevant PTs but prior to analyzing the relative frequencies in the treatment groups. In this section, I will also further discuss neurologic events in the SOC Eye disorders and falls (in the context of injuries and seizures).

Dizziness and Gait disturbance
The following table summarizes the percentages of subjects who reported the following TEAEs (in the HLTs Gait disturbances, Coordination/balance disturbances, Vertigos NEC): dizziness, vertigo, acute vestibular syndrome, vestibular ataxia, vestibular disorder, nystagmus, abasia, ataxia, gait disturbance, balance disorder, coordination abnormal, cerebellar ataxia, cerebellar syndrome, and dysstasia. Subjects treated with ESL experienced these TEAEs (grouped together) at a higher frequency than placebo subjects. A dose response relationship was observed with the higher dose groups (800 mg and 1200 mg) with 2 and 3 times higher incidence than placebo, respectively.

**Table 63. Dizziness/Gait disturbance Group, Phase 3 Epilepsy Controlled Pool**

| MedDRA PT | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | 426 | 196 | 415 | 410 | 1021 |
| Dizziness | 40 (9.4%) | 31 (15.8%) | 82 (19.8%) | 116 (28.3%) | 229 (22.4%) |
| Ataxia | 9 (2.1%) | 7 (3.6%) | 18 (4.3%) | 25 (6.1%) | 50 (4.9%) |
| Vertigo | 2 (0.5%) | 6 (3.1%) | 10 (2.4%) | 26 (6.3%) | 42 (4.1%) |
| Balance disorder | 2 (0.5%) | 1 (0.5%) | 13 (3.1%) | 14 (3.4%) | 28 (2.7%) |
| Gait disturbance | 2 (0.5%) | 3 (1.5%) | 8 (1.9%) | 9 (2.2%) | 20 (2.0%) |
| Nystagmus | 1 (0.2%) | 2 (1.0%) | 3 (0.7%) | 7 (1.7%) | 12 (1.2%) |
| Coordination abnormal | 0 | 1 (0.5%) | 4 (1.0%) | 4 (1.0%) | 9 (0.9%) |
| Cerebellar syndrome | 0 | 0 | 1 (0.2%) | 2 (0.5%) | 3 (0.3%) |
| Dysstasia | 0 | 0 | 1 (0.2%) | 1 (0.2%) | 2 (0.2%) |
| Abasia | 1 (0.2%) | 0 | 1 (0.2%) | 0 | 1 (0.1%) |
| Cerebellar ataxia | 0 | 0 | 0 | 1 (0.2%) | 1 (0.1%) |
| Vestibular ataxia | 0 | 0 | 1 (0.2%) | 0 | 1 (0.1%) |
| Vestibular disorder | 0 | 0 | 0 | 1 (0.2%) | 1 (0.1%) |
| **Total subjects** | 52 (12.2%) | 43 (21.9%) | 107 (25.8%) | 155 (37.8%) | 305 (29.9%) |

Source: Created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

The Sponsor reported that the median time to the PT dizziness was shorter for the ESL 400 mg, 800 mg, and 1200 mg groups (14.5 days, 4.5 days, and 3.0 days, respectively) compared with the placebo group (15.0 days) (ISS Table 7.7.1.8.2). The median

duration of events was longer in the ESL 400 mg, 800 mg, and 1200 mg groups (8.0 days, 9.0 days, and 15.5 days, respectively) compared with the placebo group (4.0 days) (ISS Table 7.7.1.8.3).

The Sponsor reported that the median time to Ataxia events (PTs of ataxia, coordination abnormal, gait disturbance, balance disorder, tremor, cerebellar ataxia, or cerebellar syndrome) was shorter in each of the ESL 400 mg, 800 mg, and 1200 mg groups (19.0 days, 6.0 days, and 9.5 days, respectively) compared with the placebo group (94.0 days) (ISS Table 7.7.1.11.2). The median duration of Ataxia events in the ESL 400 mg, 800 mg, and 1200 mg groups were 14.0 days, 5.5 days, and 14.0 days, compared with 13.0 days in the placebo group (ISS Table 7.7.1.11.3).

The following table summarizes the incidence and relative risk of dizziness & gait disturbance TEAEs by sex, age, and period of the study. In the Phase 3 Epilepsy Controlled Pool, elderly subjects have a higher relative risk for developing dizziness & gait disturbance TEAEs than adults. There is also a higher relative risk for these TEAEs in the titration period than the maintenance period. Of note, the relative risk of dizziness TEAEs by concomitant AED use is discussed in Section 7.5 of this review.

**Table 64. Risk Factors, Dizziness Group, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo | | ESL | | Relative Risk | 95% CI | |
|---|---|---|---|---|---|---|---|
| | n (%) | total | n (%) | total | | LL | UL |
| **Any Dizziness TEAEs** | 52 | 426 | 305 | 1021 | 2.45 | 1.87 | 3.21 |
| **Sex:** | | | | | | | |
| Male | 23 | 212 | 132 | 504 | 2.41 | 1.60 | 3.65 |
| Female | 29 | 214 | 173 | 517 | 2.47 | 1.72 | 3.54 |
| **Age:** | | | | | | | |
| Adults (18-< 60 years) | 50 | 402 | 286 | 971 | 2.37 | 1.80 | 3.12 |
| Elderly (≥ 60 years) | 1 | 18 | 16 | 40 | 7.20 | 1.03 | 50.2 |
| **Age (nonepilepsy DB pool):** | | | | | | | |
| Adults (18-< 60 years) | 18 | 366 | 118 | 1059 | 2.27 | 1.40 | 3.67 |
| Elderly (≥ 60 years) | 12 | 141 | 99 | 696 | 1.67 | 0.94 | 2.96 |
| **Period/week of study:** | | | | | | | |
| Titration period | 22 | 426 | 217 | 1021 | 4.12 | 2.69 | 6.29 |
| Maintenance period | 34 | 410 | 149 | 939 | 1.91 | 1.34 | 2.73 |
| Tapering-off | 1 | 377 | 9 | 811 | 4.18 | 0.53 | 32.9 |

Source: Created by the reviewer using JReview (ADEVENTX and ADSL: SEX, AGEGRP, AEPERIOD) for studies 301, 302, 304 (PART='Part 1', DOSCATC)

Somnolence and Fatigue

The following table summarizes the percentages of subjects who reported the following TEAEs: somnolence, hypersomnia, sedation, along with PTs in the HLT Asthenic conditions (fatigue, asthenia, lethargy, decreased activity, listless, and malaise). Subjects treated with ESL experienced these TEAEs (grouped together) at a higher frequency than placebo subjects. A dose response relationship was observed.

**Table 65. Somnolence and Fatigue Group, Phase 3 Epilepsy Controlled Pool**

| MedDRA PT | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | 426 | 196 | 415 | 410 | 1021 |
| Somnolence | 36 (8.5%) | 26 (13.3%) | 46 (11.1%) | 74 (18.0%) | 146 (14.3%) |
| Fatigue | 16 (3.8%) | 6 (3.1%) | 18 (4.3%) | 28 (6.8%) | 52 (5.1%) |
| Asthenia | 7 (1.6%) | 4 (2.0%) | 8 (1.9%) | 14 (3.4%) | 26 (2.5%) |
| Malaise | 2 (0.5%) | 2 (1.0%) | 2 (0.5%) | 3 (0.7%) | 7 (0.7%) |
| Hypersomnia | 0 | 2 (1.0%) | 2 (0.5%) | 1 (0.2%) | 5 (0.5%) |
| Lethargy | 2 (0.5%) | 0 | 0 | 4 (1.0%) | 4 (0.4%) |
| Sedation | 0 | 0 | 1 (0.2%) | 2 (0.5%) | 3 (0.3%) |
| Decreased activity | 0 | 1 (0.5%) | 0 | 0 | 1 (0.1%) |
| **Total subjects** | 57 (13.4%) | 36 (18.4%) | 67 (16.1%) | 115 (28.0%) | 218 (21.4%) |

Source: Created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

The Sponsor reported that the median time to the onset of the PT somnolence was shorter in each of the ESL 400 mg, 800 mg, and 1200 mg groups (2.0 days, 3.5 days, and 3.0 days) compared with placebo (7.5 days) (ISS Table 7.7.1.10.2). The median duration in the ESL 400 mg, 800 mg, and 1200 mg groups was 42.0 days, 27.5 days, and 24.5 days, compared with 22.0 days in the placebo group (ISS Table 7.7.1.10.3).

The following table summarizes the incidence and relative risk of somnolence & fatigue TEAEs by sex, age, and period of the study. In both pooled groups, elderly subjects have a slightly higher relative risk for developing these TEAEs than adults. There is also a higher relative risk for these TEAEs in the titration period than the maintenance period. Of note, the relative risk of TEAEs by concomitant AED use is discussed in Section 7.5 of this review.

**Table 66. Risk Factors, Somnolence Group, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo | | ESL | | Relative Risk | 95% CI | |
|---|---|---|---|---|---|---|---|
| | n (%) | total | n (%) | total | | LL | UL |
| **Any Somnolence TEAEs** | 57 | 426 | 218 | 1021 | 1.60 | 1.22 | 2.09 |
| **Sex:** | | | | | | | |
| Male | 24 | 212 | 97 | 504 | 1.70 | 1.12 | 2.58 |
| Female | 33 | 214 | 121 | 517 | 1.52 | 1.07 | 2.15 |
| **Age:** | | | | | | | |
| Adults (18-< 60 years) | 54 | 402 | 203 | 971 | 1.56 | 1.18 | 2.05 |
| Elderly (≥ 60 years) | 3 | 18 | 12 | 40 | 1.80 | 0.58 | 5.61 |
| **Age (nonepilepsy DB pool):** | | | | | | | |
| Adults (18-< 60 years) | 17 | 366 | 120 | 1059 | 2.44 | 1.49 | 4.00 |
| Elderly (≥ 60 years) | 4 | 141 | 63 | 696 | 3.19 | 1.18 | 8.62 |
| **Period/week of study:** | | | | | | | |
| Titration period | 32 | 426 | 141 | 1021 | 1.84 | 1.27 | 2.65 |
| Maintenance period | 28 | 410 | 94 | 939 | 1.47 | 0.98 | 2.20 |
| Tapering-off | 1 | 377 | 4 | 811 | 1.86 | 0.21 | 16.6 |

Source: Created by the reviewer using JReview (ADEVENTX and ADSL: SEX, AGEGRP, AEPERIOD) for studies 301, 302, 304 (PART='Part 1', DOSCATC)

Cognitive dysfunction
Cognitive dysfunction is related to the neurological events of confusion, psychomotor slowing, difficulty with concentration and attention, difficulty with memory, and speech or language problems with word-finding difficulty. The following table summarizes the percentages of subjects who reported the following TEAEs (in the HLTs Memory loss [excl dementia], Mental impairment [excl dementia and memory loss], Cortical dysfunction NEC, and Speech and language abnormalities): dysarthria *(though it is noted that this is not a cognitive disability)*, speech disorder, aphasia, memory impairment, amnesia, confusional state, disturbance in attention, disorientation, cognitive disorder, psychomotor retardation, apraxia, mental impairment, and bradyphrenia. ESL subjects experienced these TEAEs (grouped together) 4 times more frequently than placebo subjects. A dose response relationship was observed with the higher dose groups (800 mg and 1200 mg) with 6 and 3 times higher incidence than placebo, respectively.

**Table 67. Cognitive Dysfunction Group, Phase 3 Epilepsy Controlled Pool**

| MedDRA PT | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | 426 | 196 | 415 | 410 | 1021 |
| Dysarthria | 0 | 0 | 3 (0.7%) | 10 (2.4%) | 13 (1.3%) |
| Memory Impairment | 1 (0.2%) | 2 (1.0%) | 4 (1.0%) | 7 (1.7%) | 13 (1.3%) |
| Disturbance in Attention | 2 (0.5%) | 2 (1.0%) | 3 (0.7%) | 6 (1.5%) | 11 (1.1%) |
| Amnesia | 1 (0.2%) | 0 | 4 (1.0%) | 3 (0.7%) | 7 (0.7%) |
| Confusional State | 2 (0.5%) | 2 (1.0%) | 2 (0.5%) | 3 (0.7%) | 7 (0.7%) |
| Aphasia | 0 | 0 | 1 (0.2%) | 5 (1.2%) | 6 (0.6%) |
| Speech Disorder | 0 | 2 (1.0%) | 0 | 3 (0.7%) | 5 (0.5%) |
| Bradyphrenia | 0 | 0 | 1 (0.2%) | 2 (0.5%) | 3 (0.3%) |
| Disorientation | 0 | 2 (1.0%) | 1 (0.2%) | 0 | 3 (0.3%) |
| Cognitive Disorder | 0 | 0 | 1 (0.2%) | 1 (0.2%) | 2 (0.2%) |
| Psychomotor retardation | 0 | 0 | 1 (0.2%) | 1 (0.2%) | 2 (0.2%) |
| **Total subjects** | 6 (1.4%) | 7 (3.6%) | 20 (4.8%) | 36 (8.8%) | 63 (6.2%) |

Source: Created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

Of note, I did not perform the analyses of the incidence and relative risk of these TEAEs by sex, age, and period of the study due to the small numbers.

The Sponsor reported that the two Phase 1 studies, Study 123 and 153, were conducted specifically to examine the effects of ESL on cognitive dysfunction in normal volunteers and recreational CNS depressant users, respectively. Study 123 evaluated the pharmacodynamics effects of a single oral dose (900 mg) and multiple oral doses (800 mg QD over 7 days and 1200 mg QD over 7 days) of ESL in 26 healthy volunteers (2093-123 CSR). The Sponsor concluded that the acute administration of ESL was not associated with differences in measures of cognitive performance as compared with placebo. However, the study revealed some conflicting results for the chronic administration of ESL compared with placebo: both improvements in cognitive

performance (ability to detect visual targets while executing a manual tracking task and ability to produce words for a given semantic category within 1 minute) and reductions (diminished psychomotor speed and word retrieval ability along with a reduction in the ability to detect digits) (2093-123 CSR Synopsis).

Study 153 evaluated the pharmacodynamic effects of ESL in otherwise healthy recreational CNS depressant users. The Sponsor concluded that ESL administration produced minimal effects on any of the cognitive assessments (alertness, recall/recognition, reaction time, attention) compared with placebo.

Paresthesia
The following table summarizes the percentages of subjects who reported the following TEAEs in the HLTs Sensory abnormalities NEC and Paraesthesias/dysaesthesia (paraesthesia, paraesthesia oral, hypoaesthesia, hypoaesthesia facial, hypoaesthesia oral, hypoaesthesia teeth, dysgeusia, dysaesthesia, oral dysaesthesia, sensory disturbance, sensory loss, hyperaesthesia, hypogeusia, allodynia). A slightly lower percentage of ESL subjects reported terms in this group, overall, than placebo (2.3% vs 2.8%). The percentages of subjects reporting terms in this group were small.

**Table 68. Paresthesia Group, Phase 3 Epilepsy Controlled Pool**

| MedDRA PT | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | 426 | 196 | 415 | 410 | 1021 |
| Paraesthesia | 4 (0.9%) | 1 (0.5%) | 2 (0.5%) | 6 (1.5%) | 9 (0.9%) |
| Hypoaesthesia | 6 (1.4%) | 1 (0.5%) | 3 (0.7%) | 1 (0.2%) | 5 (0.5%) |
| Hypoaesthesia Oral | 2 (0.5%) | 0 | 2 (0.5%) | 2 (0.5%) | 4 (0.4%) |
| Sensory disturbance | 0 | 2 (1.0%) | 1 (0.2%) | 0 | 3 (0.3%) |
| Dysgeusia | 1 (0.2%) | 1 (0.5%) | 1 (0.2%) | 0 | 2 (0.2%) |
| Paraesthesia Oral | 0 | 0 | 1 (0.2%) | 1 (0.2%) | 2 (0.2%) |
| Dysaesthesia | 0 | 0 | 1 (0.2%) | 0 | 1 (0.1%) |
| Oral Dysaesthesia | 0 | 0 | 0 | 1 (0.2%) | 1 (0.1%) |
| Sensory loss | 1 (0.2%) | 0 | 0 | 0 | 0 |
| **Total subjects** | 12 (2.8%) | 5 (2.6%) | 10 (2.4%) | 8 (2.0%) | 23 (2.3%) |

Source: Created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

Of note, I did not perform the analyses of the incidence and relative risk of these TEAEs by sex, age, and period of the study due to the small numbers.

Eye Disorders
A higher frequency of ESL subjects than placebo subjects experienced TEAEs in the SOC Eye Disorders in both the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool. A dose response relationship was observed. The following table summarizes the TEAEs in the SOC Eye Disorders that occurred in at least 2 ESL subjects and greater than placebo.

**Table 69. TEAEs in SOC Eye disorders in ≥2 ESL Subjects and > Placebo**

| MedDRA Preferred Term in SOC Eye disorders | Placebo | ESL |
|---|---|---|
| **Phase 3 Epilepsy DB Pool** | 25 (5.9%) | 160 (15.7%) |
| Diplopia | 10 (2.3) | 97 (9.5) |
| Vision blurred | 6 (1.4) | 52 (5.1) |
| Vision impairment | 3 (0.7) | 11 (1.1) |
| Eye pruritus | 0 | 3 (0.3) |
| Ocular hyperaemia | 0 | 3 (0.3) |
| Oscillopsia | 0 | 2 (0.2) |
| **Nonepilepsy DB Pool** | 7 (1.4%) | 46 (2.6%) |
| Vision blurred | 1 (0.2) | 17 (1.0) |
| Vision impairment | 0 | 6 (0.3) |
| Conjunctivitis | 0 | 3 (0.2) |
| Eyelid oedema | 1 (0.2) | 5 (0.3) |

Source: ISS Tables 7.1.4.1.s5 and created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

The Sponsor reported that the median time to the PTs of diplopia and vision blurred was shorter for each of the ESL 400 mg, 800 mg, and 1200 mg groups (15.0 days, 16.0 days, and 8.0 days) compared with the placebo group (91.0 days) (ISS Table 7.7.1.9.2). The median duration of events in the ESL 400 mg, 800 mg, and 1200 mg groups was 14.0 days, 7.0 days, and 18.5 days compared with 17.0 days in the placebo group (ISS Table 7.7.1.9.3).

The following table summarizes the incidence and relative risk of TEAEs in the SOC Eye disorders by sex, age, and period of the study. In the Phase 3 Epilepsy Controlled Pool, elderly subjects have a trend toward a higher relative risk for developing eye-related TEAEs than adults. There is also a higher relative risk for these TEAEs in the titration period than the maintenance period. Of note, the relative risk of eye-related TEAEs by concomitant AED use is discussed in Section 7.5 of this review.

**Table 70. Risk Factors, Eye Disorders, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo | | ESL | | Relative Risk | 95% CI | |
|---|---|---|---|---|---|---|---|
| | n (%) | total | n (%) | total | | LL | UL |
| **Any TEAEs in Eye SOC** | 25 | 426 | 160 | 1021 | 2.67 | 1.78 | 4.01 |
| **Sex:** | | | | | | | |
| Male | 13 | 212 | 77 | 504 | 2.49 | 1.42 | 4.39 |
| Female | 12 | 214 | 83 | 517 | 2.86 | 1.60 | 5.13 |
| **Age:** | | | | | | | |
| Adults (18-< 60 years) | 24 | 402 | 151 | 971 | 2.60 | 1.72 | 3.94 |
| Elderly (≥ 60 years) | 0 | 18 | 9 | 40 | 8.10 | 0.50 | 132 |
| **Age (nonepilepsy pool):** | | | | | | | |
| Adults (18-< 60 years) | 4 | 366 | 25 | 1059 | 2.16 | 0.76 | 6.17 |
| Elderly (≥ 60 years) | 3 | 141 | 21 | 696 | 1.42 | 0.43 | 4.69 |
| **Period/week of study:** | | | | | | | |
| Titration period | 4 | 426 | 80 | 1021 | 8.34 | 3.08 | 22.6 |
| Maintenance period | 21 | 410 | 96 | 939 | 2.00 | 1.26 | 3.15 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Tapering-off | 0 | 377 | 1 | 811 | 0.93 | 0.03 | 27.7 |

Source: Created by the reviewer using JReview (ADEVENTX and ADSL: SEX, AGEGRP, AEPERIOD) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

The following table summarizes the TEAEs, SAEs, and TEAEs that led to discontinuations in these groups of neurologic events by treatment group. ESL is associated with an increased incidence of SAEs and discontinuations related to dizziness/gait disturbance, somnolence/fatigue, cognitive dysfunction, and eye disorders. In the majority of these groups, there were no placebo subjects who developed SAEs in both the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool.

**Table 71. TEAEs, SAEs, DCs in Neurologic Groups**

| Groups of Neurologic Events | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool^ | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=426 | n=1021 | n=507 | n=1755 |
| Dizziness/gait disturbance | 52 (12.2) | 305 (29.9) | 30 (5.9) | 217 (12.4) |
| SAEs | 0 | 17 (1.7) | 0 | 3 (0.2) |
| Discontinuations (DCs) | 3 (0.7) | 96 (9.4) | 4 (0.8) | 50 (2.8) |
| Somnolence/fatigue group | 57 (13.4) | 218 (21.4) | 21 (4.1) | 183 (10.4) |
| SAEs | 0 | 3 (0.3)[a] | 0 | 1 (0.1)[a] |
| Discontinuations | 3 (0.7) | 34 (3.3) | 2 (0.4) | 25 (1.4) |
| Cognitive dysfunction group | 6 (1.4) | 63 (6.2) | 0 | 21 (1.2) |
| SAEs | 1 (0.2) | 2 (0.2)[b] | 0 | 2 (0.1)[b] |
| Discontinuations | 2 (0.5) | 15 (1.5) | 0 | 9 (0.5) |
| Paresthesia group | 12 (2.8) | 23 (2.3) | 7 (1.4) | 32 (1.8) |
| SAEs | 2 (0.5) | 2 (0.2)[c] | 0 | 0 |
| Discontinuations | 1 (0.2) | 4 (0.4) | 1 (0.2) | 6 (0.3) |
| Eye disorders | 25 (5.9) | 160 (15.7) | 7 (1.4) | 46 (2.6) |
| SAEs | 0 | 7 (0.7)[d] | 0 | 0 |
| Discontinuations | 1 (0.2) | 37 (3.6) | 0 | 8 (0.5) |

Source: Created by the reviewer using JReview and Epilepsy ADEVENTX and ADSL datasets
[a]Phase III ESL SAEs: asthenia, malaise, fatigue, somnolence; Nonepilepsy SAE: fatigue
[b]Phase III ESL SAEs: confusional state, amnesia; Nonepilepsy SAEs: disorientation, mental impairment
[c]hypoaesthesia, sensory disturbance
[d]diplopia (6), blindness (1)
^includes Study 206

I reviewed all of the PT terms for the neurologic-related TEAEs, SAEs, and TEAEs leading to DC. Notable adverse events are further described below (using the information provided in the narratives by the Sponsor along with data provided in the analysis datasets):

Blindness (SAE): subject 301-122-90387 on Day 18 of ESL was hospitalized with "intermittent loss of vision" *(no other details were provided in the narrative)*, vertigo, loss of memory, and headache. Events resolved 1 day after ESL discontinuation.

Blindness (TEAE): subject 303-703-70210 with "loss of the vision" and photophobia on Day 190 of the OLE study. Events resolved 1 day later while ESL was continued for more than 200 days without any recurrence. *(Narrative was not included in the ISS by the Sponsor).*
Deafness (DC): subject 210-612-612036 on Day 10 of ESL developed "severe acute hearing loss." ESL was discontinued and treatment was initiated with prednisone. The events resolved 17 days later.
Deafness (TEAE): subject 304-301-30115 with "hearing loss" along with dizziness on Day 80 of ESL that resolved within 1 day. ESL was continued until the study was completed 15 days later. *(Narrative was not included in the ISS by the Sponsor).*
Iritis (DC): subject 207-202-202010 (80 year-old WF with history of post-herpetic neuralgia, HTN, DM) who developed iritis *(no other details were provided in the narrative)* and facial swelling on Day 6 of ESL. ESL was discontinued. Prednisolone, cetirizine, and hyoscine hydrobromide were administered. Events resolved 11 days later.

*Comment: This isolated event of iritis is difficult to attribute to ESL in an 80 yo with comorbidities*.

Visual field defect (TEAE) in a placebo subject
Visual acuity reduced (DC): subject 206-566-566019 on Day 9 of ESL developed "bad visual acuity" and nausea/vertigo. The subject underwent an eye examination and "there were no pertinent abnormal objective findings" *(no other details were provided in the narrative)*. ESL was discontinued. Events resolved 1 day later.
Visual acuity reduced (DC): subject 207-211-211005 on Day 2 of ESL developed dizziness and "reduction of visual faculty" *(no other details were provided in the narrative)*. ESL was discontinued. Eight days later, the subject experienced worsening of arterial HTN. Visual changes resolved 14 days later.
Visual impairment (DC): subject 209-103-90302 on Day 3 of ESL developed "decreased visus" *(no other details were provided in the narrative)*. On Day 5, subject developed agitation, insomnia, and nervousness. ESL was discontinued and events resolved 7 days later.
Visual impairment (DC): subject 210-606-606003 on Day 1 of ESL developed "reduction of sight" *(no other details were provided in the narrative)*. ESL was discontinued due to nausea and worsening of headache on Day 11. Events resolved.
Oscillopsia (DC) subject 302-315-80254 on Day 2 of ESL developed vertical oscillopsia, "vision-difficulty shifting gaze," and ataxia. ESL was discontinued. Events resolved 2 days later.
Oscillopsia (TEAE) subject 302-301-80667 on Day 56 of ESL developed oscillopsia, diplopia, and dizziness. ESL was continued for another 400 days into the OLE study.
Oscillopsia (TEAE) subject 302-301-80671 (no narrative provided by the Sponsor).
Metamorphopsia (TEAE) subjects 304-016-01603 and 045-0066-S001

*Comment: Of note, metamorphopsia is a visual defect in which a grid of straight lines appears wavy and parts of the grid may appear blank. In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 6/27/13 to provide narratives for these subjects. The verbatim terms were "distorted vision" on Day 2 of ESL associated with horizontal nystagmus and "distorted vision" on Day 14 of ESL along with blurred vision, unstable balance/coordination, and confusional state. In both cases, ESL was continued with resolution of symptoms within 2 days.*

Falls and Injuries

In both the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool, the incidence of adverse events coded to the PT fall was low and only slightly higher in ESL subjects compared to placebo. While the incidence of SAEs coded to fall were similar in both ESL and placebo subjects, fall PTs leading to discontinuation were slightly higher in ESL subjects.

To assess for the sequelae of the falls, an analysis was performed for fall-related adverse events in the SOC Injury, Poisoning, and Procedural Complications and the SMQ Accidents and Injury. The following table summarizes the incidence of the PT fall

and TEAEs in the Injury SOC and SMQ by treatment group and DB pooled group. The results of the SMQ analyses were similar to the SOC. ESL subjects experienced slightly higher frequencies of these injury-related TEAEs than placebo. The Sponsor performed additional analyses for fractures, head injuries, and all injuries (and noted that rates were similar in the ESL and placebo groups).

**Table 72. Falls and TEAEs in SOC Injury and SMQ Accidents/Injury**

| | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=426 | n=1021 | n=507 | n=1755 |
| PT Fall | 6 (1.4) | 19 (1.9) | 1 (0.2) | 7 (0.4) |
| SAEs | 2 (0.5) | 5 (0.5) | 0 | 2 (0.1) |
| TEAEs leading to DC | 0 | 5 (0.5) | 0 | 1 (0.1) |
| SOC Injury, Poisoning/Procedural Complic. | 28 (6.6) | 76 (7.4) | 4 (0.8) | 34 (1.9) |
| SMQ Accidents and Injury (narrow) | 25 (5.9) | 61 (6.0) | 3 (0.6) | 27 (1.5) |
| Sponsor's analysis – all events | 26 (6.1) | 70 (6.9) | 2 (0.5) | 27 (2.1) |
| Falls | 6 (1.4) | 19 (1.9) | 1 (0.2) | 7 (0.5) |
| Fractures | 6 (1.4) | 11 (1.1) | 0 | 3 (0.2) |
| Head injuries | 7 (1.6) | 14 (1.4) | 1 (0.2) | 2 (0.2) |
| Injuries | 26 (6.1) | 69 (6.8) | 2 (0.5) | 27 (2.1) |

Source: ISS Tables 7.1.4.1.s5, 7.4.1.1.s2, 59.1, 59.b and SMQs created by reviewer using MAED tool (ADEVENTX: AEDECOD and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

To further analyze these SAEs, I stratified the SAEs by the HLGTs in the SOC Injury, Poisoning and Procedural Complications (with ≥2 ESL subjects and >placebo), then by the PTs (with ≥1 ESL subject and >placebo) (see table below). There was no common pattern of HLGTs (or PTs) between the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool.

**Table 73. SAEs in Injury HLGTs in ≥2 ESL subjects and >Placebo (then PTs in ≥1 ESL subject and >Placebo)**

| Injury, Poisoning, Procedural Complications HLGTs<br>Preferred Term | Placebo | ESL |
|---|---|---|
| **Phase 3 Epilepsy Controlled Pool** | n = 426 | n = 1021 |
| HLGT Bone and Joint Injuries | 1 (0.2) | 4 (0.4) |
| Jaw fracture | 0 | 1 (0.1) |
| Radius fracture | 0 | 1 (0.1) |
| Foot fracture | 0 | 1 (0.1) |
| HLGT Chemical Injury and Poisoning | 0 | 4 (0.4) |
| Drug toxicity | 0 | 3 (0.3) |
| Therapeutic agent toxicity | 0 | 1 (0.1) |
| | | |
| **Nonepilepsy Double-blind Pool** | n=507 | n=1755 |
| HLGT Injuries NEC | | 3 (0.2) |
| Fall | 0 | 2 (0.1) |
| Concussion | 0 | 1 (0.1) |
| Neck injury | 0 | 1 (0.1) |
| Arthropod sting | 0 | 1 (0.1) |

Source: ISS Tables 7.1.11.1.s2 and created by the reviewer using JReview (ADEVENTX: AESER='Y', and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

To assess whether these falls and injuries were occurring with seizures, the Sponsor performed further analyses in the NDA resubmission (Section 2.1.5.21) in response to the Division's comments in the November 2012 Acknowledge Incomplete Response letter. In order to determine the cause of falls, fractures, and head injuries, the Sponsor stated that multiple data sources were reviewed for each event, including the clinical database (CRF data), safety narratives (CIOMS reports), and seizure diaries for all studies. The Sponsor considered a seizure related to the fall/fracture/head injury event if it was a major seizure (e.g., either a complex partial, secondarily generalized or unclassified seizure, but not a simple partial seizure) and occurred within 3 days prior to the fall/fracture/head injury event. The Sponsor reported that the majority of fall events occurred in close temporal relationship (<3 days) to major seizures for both ESL and placebo subjects.

There were more falls that occurred without seizure events in ESL subjects than placebo (15.8% vs 0%). Furthermore, there were both more fractures in ESL subjects than placebo (45.5% vs 16.7%) and more injuries in ESL subjects than placebo (29% vs 23.1%) that occurred without seizure events. Therefore, there is an association between ESL use and falls/fractures/injuries that are not confounded by seizures.

*Comment: There may have been a stronger association between ESL use and falls, fractures, injuries that were not confounded by seizures if the Sponsor used a shorter interval of 1 day (instead of 3 days) between the seizure and the fall, fracture, or injury.*

**Table 74. Falls and Injuries by Seizures, Phase 3 Epilepsy Controlled Pool**

| | Placebo | | ESL | |
|---|---|---|---|---|
| | n (%) | total | n (%) | total |
| # subjects with falls | 6 (1.4) | 426 | 19 (1.9) | 1021 |
| Falls related to seizure | 5 (83.3) | 6 | 11 (57.9) | 19 |
| Falls not related to seizure | 0 | 6 | 3 (15.8) | 19 |
| | | | | |
| # subjects with fractures | 6 (1.4) | 426 | 11 (1.1) | 1021 |
| Fractures related to seizure | 5 (83.3) | 6 | 7 (63.6) | 11 |
| Fractures not related to seizure | 1 (16.7) | 6 | 5 (45.5) | 11 |
| Fractures related to a fall | 2 (33.3) | 6 | 3 (27.3) | 11 |
| Fractures not related to a fall | 4 (66.7) | 6 | 8 (72.7) | 11 |
| | | | | |
| # subjects with head injuries | 7 (1.6) | 426 | 14 (1.4) | 1021 |
| Head injuries related to seizure | 5 (71.4) | 7 | 9 (64.3) | 14 |
| Head injuries not related to seizure | 2 (28.6) | 7 | 4 (28.6) | 14 |
| | | | | |
| # subjects with injuries | 26 (6.1) | 426 | 69 (6.8) | 1021 |
| Injuries related to seizure | 20 (76.9) | 26 | 41 (59.4) | 69 |
| Injuries not related to seizure | 6 (23.1) | 26 | 20 (29.0) | 69 |

Source: ISS Table 59.a

The following table summarizes the incidence and relative risk of the PT fall by age group. Elderly subjects have a trend toward a higher relative risk for experiencing TEAEs coded to the PT fall than adults in both pooled groups. However, the small numbers preclude any definite conclusions.

**Table 75. PT Fall by Age Group**

| Category | Placebo | | ESL | | Relative Risk | 95% CI | |
|---|---|---|---|---|---|---|---|
| | n (%) | total | n (%) | total | | LL | UL |
| **PT Fall** | | | | | | | |
| **Age (epilepsy pool):** | 6 | 426 | 19 | 1021 | 1.32 | 0.53 | 3.29 |
| Adults (18-< 60 years) | 6 | 402 | 16 | 971 | 1.10 | 0.44 | 2.80 |
| Elderly (≥ 60 years) | 0 | 18 | 3 | 40 | 2.70 | 0.14 | 51.2 |
| **Age (nonepilepsy pool):** | 1 | 507 | 7 | 1755 | 2.02 | 0.25 | 16.4 |
| Adults (18-< 60 years) | 1 | 366 | 3 | 1059 | 1.04 | 0.11 | 9.94 |
| Elderly (≥ 60 years) | 0 | 141 | 4 | 696 | 1.62 | 0.09 | 30.5 |

Source: Created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL: AGEGRP) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)
*Using zero event correction of 0.5

In conclusion, there is reasonable evidence of a causal relationship between ESL use and dizziness/gait disturbance, somnolence/fatigue, cognitive dysfunction, visual changes, and falls/injuries. These are all clinically significant adverse reactions: serious (all associated with SAEs), and could be mitigated through the appropriate use of the drug (closer monitoring during the titration period and with high risk subgroups such as the elderly). Therefore, I recommend that these adverse reactions be included in the Warnings and Precautions section of ESL labeling.

7.3.4.4 Psychiatric Disorders

A slightly higher number of ESL subjects experienced TEAEs in the SOC Psychiatric Disorders than placebo subjects in both the Phase 3 Epilepsy Controlled Pool (10.8% vs 10.3%) and the Nonepilepsy Double-blind Pool (5.1% vs 4.1%). Discontinuations due to these TEAEs occurred slightly more often in ESL subjects than placebo in both the Phase 3 Epilepsy Controlled Pool (1.9% vs 0.7%) and the Nonepilepsy Double-blind Pool (1.1% vs 0.8%). Psychiatric disorder SAEs occurred at similar rates in ESL and placebo subjects in both pooled groups. The following table summarizes the adverse events in the SOC Psychiatric Disorders for the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool.

**Table 76. Overview of TEAEs, SAEs, DCs in the SOC Psychiatric Disorders**

| SOC Psychiatric Disorders | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=426 | n=1021 | n=507 | n=1755 |
| TEAEs | 44 (10.3%) | 110 (10.8%) | 21 (4.1%) | 89 (5.1%) |
| SAEs | 2 (0.5%) | 6 (0.6%) | 2 (0.4%) | 10 (0.6%) |
| Discontinuations (DCs) | 3 (0.7%) | 19 (1.9%) | 4 (0.8%) | 19 (1.1%) |

Source: ISS Tables 7.1.4.1.s5, 7.1.11.1.s2, 7.4.1.1.s2 and created by the reviewer using JReview (ADEVENTX: AESER='Y', DISC=1 and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

*Comment: Of note, I performed stratified analyses by the different indications in the Nonepilepsy Double-blind Pool. In the bipolar studies (Studies 203 and 204), ESL subjects (13.5%) had a greater incidence of TEAEs in the SOC Psychiatric Disorders than placebo subjects (9.8%) driven by the PTs insomnia, anxiety, and logorrhoea. This was also seen in the fibromyalgia Study 210 (9.1% vs 6.1%, driven by the PT anxiety) and in the migraine Study 209 (5.5% vs 2.9%, driven by the PT anxiety). However, opposite results were seen in the neuropathy Studies 206 and 207 with ESL subjects having a slightly lower incidence of psychiatric TEAEs than placebo subjects (1.9% vs 2.1%).*

I performed additional analyses using the psychiatric-related SMQs. The following tables summarize the percentages of subjects reporting TEAEs in the 4 psychiatric SMQs. In the Phase 3 Epilepsy Controlled Pool, ESL subjects had a similar or lower incidence compared to placebo of TEAEs in all of these psychiatric SMQs: Depression and suicide/self-injury, Hostility and aggression, Psychosis and Psychotic disorders, and Drug abuse, dependence and withdrawal. Similar SMQ results were obtained for the Nonepilepsy Double-blind Pool.

**Table 77. Psychiatric Disorders SOC and SMQs (Narrow PTs), Phase 3 Epilepsy Controlled Pool**

| MedDRA SOC, SMQ | Placebo n = 426 | ESL n = 1021 |
|---|---|---|
| SOC Psychiatric disorders | 44 (10.3%) | 110 (10.8%) |
| SMQ Depression and suicide/self-injury | 12 (2.8) | 35 (3.4) |
| (2) Depression (excl suicide and self-injury) | 12 (2.8) | 33 (3.2) |
| (2) Suicide and self-injury | 1 (0.2) | 3 (0.3) |
| SMQ Hostility and Aggression | 4 (0.9) | 1 (0.1) |
| SMQ Psychosis and Psychotic disorders | 4 (0.9) | 2 (0.2) |
| SMQ Drug abuse, dependence and withdrawal | 0 | 1 (0.1) |

Source: Created by the reviewer using the MAED tool (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

**Table 78. Psychiatric Disorders SOC and SMQs (Narrow PTs), Nonepilepsy Double-blind Pool (includes Study 206)**

| MedDRA SOC, SMQ | Placebo n = 507 | ESL n = 1755 |
|---|---|---|
| SOC Psychiatric disorders | 21 (4.1%) | 89 (5.1%) |
| SMQ Depression and suicide/self-injury | 5 (1.0) | 15 (0.9) |
| (2) Depression (excl suicide and self-injury) | 5 (1.0) | 14 (0.8) |
| (2) Suicide and self-injury | 1 (0.2) | 2 (0.1) |
| SMQ Hostility and Aggression | 1 (0.2) | 4 (0.2) |
| SMQ Psychosis and Psychotic disorders | 0 | 1 (0.1) |
| SMQ Drug abuse, dependence and withdrawal | 0 | 1 (0.1) |

Source: Created by the reviewer using the MAED tool (ADEVENTX: AEDECOD and ADSL: TRTP1) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')

The following table summarizes the psychiatric-related TEAEs (including those in the SOC General disorders and social circumstances) that occurred in at least 2 ESL subjects (and greater than placebo) in the Phase 3 Epilepsy Controlled Pool.

**Table 79. Psychiatric-Related TEAEs in ≥ 2 ESL Subjects > Placebo, Phase 3 Epilepsy Controlled Pool**

| Psychiatric-related PT | Placebo n = 426 | ESL n = 1021 |
|---|---|---|
| SOC General disorders | | |
| Irritability | 2 (0.5) | 15 (1.5) |
| Feeling drunk | 0 | 2 (0.2) |
| SOC Psychiatric disorders | | |
| Depression | 9 (2.1) | 24 (2.4) |
| Insomnia | 5 (1.2) | 20 (2.0) |
| Nervousness | 1 (0.2) | 8 (0.8) |
| Confusional state | 2 (0.5) | 7 (0.7) |
| Apathy | 0 | 6 (0.6) |
| Agitation | 1 (0.2) | 5 (0.5) |
| Mood swings | 1 (0.2) | 4 (0.4) |
| Restlessness | 0 | 4 (0.4) |
| Bradyphrenia | 0 | 3 (0.3) |
| Disorientation | 0 | 3 (0.3) |
| Suicidal ideation | 1 (0.2) | 3 (0.3) |
| Abnormal behaviour | 0 | 2 (0.2) |
| Emotional disorder | 0 | 2 (0.2) |
| Fear | 0 | 2 (0.2) |
| Mood altered | 0 | 2 (0.2) |
| Nightmare | 0 | 2 (0.2) |
| Panic attack | 0 | 2 (0.2) |
| Psychomotor retardation | 0 | 2 (0.2) |

Source: ISS Table 7.1.4.1.s5

The TEAEs, confusional state, psychomotor retardation, bradyphrenia, and disorientation, are discussed in more detail in Section 7.3.4.3 on cognitive dysfunction.

For the TEAEs feeling drunk, the reader is also referred to the Controlled Substance Staff review by Dr. Alicja Lerner for further details on drug abuse potential, withdrawal, and rebound effects of ESL.

The Sponsor reported that the median time to Psychiatric Events was shorter for ESL overall (22.0 days) compared with the placebo group (26.0 days) (ISS Table 7.7.1.20.2). The median duration of Psychiatric Events was longer for ESL subjects (27.0 days) overall compared with placebo (13.0 days) (ISS Table 7.7.1.20.3).

To further analyze the psychiatric-related SAEs, the following table summarizes those that occurred in the ESL group greater than in the placebo group in the Phase 3 Epilepsy Controlled Pool.

**Table 80. SAEs in the SOC Psychiatric Disorders in ESL Subjects > Placebo***

| **Psychiatric disorders SOC Preferred Term** | **Placebo** | **ESL** |
|---|---|---|
| **Phase 3 Epilepsy DB Pool** | n = 426 | n = 1021 |
| Psychiatric disorders SOC | 2 (0.5%) | 6 (0.6%) |
| Restlessness | 0 | 2 (0.2) |
| Abnormal behavior | 0 | 1 (0.1) |
| Aggression | 0 | 1 (0.1) |
| Depression | 0 | 1 (0.1) |
| Eating disorder | 0 | 1 (0.1) |
| Logorrhoea | 0 | 1 (0.1) |
| Nervousness | 0 | 1 (0.1) |
| Paranoia | 0 | 1 (0.1) |
| Psychotic disorder | 0 | 1 (0.1) |
| Suicidal ideation | 0 | 1 (0.1) |
| Suicide attempt | 0 | 1 (0.1) |
| Thinking abnormal | 0 | 1 (0.1) |

Source: ISS Tables 7.1.11.1.s2
*There were no psychiatric-related SAEs in the SOCs General disorders and Social circumstances

The TEAEs that led to discontinuations in ESL subjects (>placebo) in the Phase 3 Epilepsy Controlled Pool included irritability (3), abnormal behavior (1), apathy (1), bradyphrenia (2), depressed mood (1), depression (4), insomnia (3), logorrhoea (1), mental disorder (1), mental status changes (1), mood swings (1), nervousness (2), nightmare (1), paranoia (1), postictal psychosis (1), restlessness (1), stress (1), thinking abnormal (1).

Additional psychiatric-related SAEs in the Nonepilepsy Double-blind Pool in ESL subjects greater than placebo subjects included 1 PT each of affect lability, affective disorder, agitation, bipolar disorder, completed suicide, disorientation, disturbance in social behavior, euphoric mood, fear, grandiosity, hostility, hyposomnia, insomnia, mental disorder, social avoidant behavior, stress, tachyphrenia.

The Sponsor reported that there were no psychiatric-related SAEs in Study 201, Study 303, or the Phase 1 Study Pool,

In the ongoing studies, the Sponsor reported the following psychiatric SAEs in ESL subjects: irritability, anxiety, conduct disorder, 2 depression, 1 drug abuse, 2 suicidal ideation, 1 suicide attempt (Safety Information Amendment 4/19/13 Table 2).

In the postmarketing database, the Sponsor reported the following psychiatric SAEs (1 patient each): completed suicide, suicidal ideation, suicide attempt, depression, anger, aggression (Safety Information Amendment 4/19/13).

Suicidal Behavior and Ideation
In this section, I will further discuss and analyze the adverse events of suicidality (suicidal behavior and ideation). The Sponsor identified suicidality as an adverse event of special interest and included subjects in the Depression and Suicidality group with the following TEAEs and scores:

- TEAEs contained in MedDRA SMQ of “depression (excl suicide and self-injury)”
- TEAEs contained in MedDRA SMQ of “suicide/self-injury”
- C-SSRS scores (only in Studies 2093-304, -153, -150, and -155)
  - suicidality was assessed prospectively
  - for any suicidal behavior postbaseline
  - for any worsening in suicidal ideation postbaseline
- C-CASA codes of 1, 2, 3, 4, or 7 (in all studies)
  - suicidality assessed retrospectively
  - database was searched electronically for the following:
    - PTs with text strings of "suic" or "overdos"
    - AE verbatim terms and investigator comments with text strings of "attempt", "cut", "gas", "hang", "hung", "jump", "mutilat", "overdos", "self damage", "self harm", "self inflict", "self injur", "shoot", "slash", "suic", "poison", "asphyxiation", "suffocation", "firearm"; events were screened for false positives
    - All deaths and other SAEs
    - All AEs coded as accidental injury
  - cases classified by a panel of blinded experts to the following categories:
    0: No event
    1: Completed suicide
    2: Suicide attempt
    3: Preparatory actions toward imminent suicidal behavior
    4: Suicidal ideation
    5: Self-injurious behavior, intent unknown
    6: Not enough information, fatal
    7: Nonsuicidal self injurious behavior
    8: Other
    9: Not enough information, nonfatal

*Comment: A Warning for Suicidal Behavior and Ideation is required by the Division for all antiepileptic medications. Of note, for this warning, the primary endpoint of suicidal behavior or ideation was defined by the C-CASA categories of 1, 2, 3, or 4 (Dr. Evelyn*

*Mentari's Review of Antieplieptic Drugs and Suicidality, 6/12/08). Therefore, the Sponsor's classification of these suicidality events for ESL is broader with the inclusion of the C-CASA category of 7 (in addition to 1, 2, 3, or 4).*

In the Phase 3 Epilepsy Controlled Pool, the Sponsor reported that the incidence of events in the Depression and Suicidality group were slightly greater in ESL-treated subjects (7.7%, 7.0%, and 8.3% in the ESL 400 mg, 800 mg, and 1200 mg groups, respectively) compared with the placebo group (6.1%) (see table below). In ESL subjects, the most frequently reported event was depression. Suicidal behavior identified by C-SSRS was seen in similar percentages of ESL and placebo subjects. Suicidal ideation identified by C-SSRS was seen in a lower percentage of ESL subjects (1.5%) compared with placebo (2.3%). However, using C-CASA classification, events were seen only in ESL subjects (0.7%) and not in placebo.

**Table 81. Depression and Suicidality, Phase 3 Epilepsy Controlled Pool**

| | Placebo (N=426) | ESL 400 mg (N=196) | ESL 800 mg (N=415) | ESL 1200 mg (N=410) | Total ESL (N=1021) |
|---|---|---|---|---|---|
| Source/ Preferred Term or Lab Value | Subjects # (%) | Subjects # (%) | Subjects # (%) | Subjects # (%) | Subjects # (%) |
| Any Depression and Suicidality Events | 26 (6.1%) | 15 (7.7%) | 29 (7.0%) | 34 (8.3%) | 78 (7.6%) |
| Source: Adverse Events | 14 (3.3%) | 14 (7.1%) | 20 (4.8%) | 27 (6.6%) | 61 (6.0%) |
| APATHY | 0 | 1 (0.5%) | 0 | 4 (1.0%) | 5 (0.5%) |
| CRYING | 0 | 0 | 0 | 1 (0.2%) | 1 (<0.1%) |
| DEPRESSED MOOD | 4 (0.9%) | 2 (1.0%) | 2 (0.5%) | 1 (0.2%) | 5 (0.5%) |
| DEPRESSION | 7 (1.6%) | 6 (3.1%) | 6 (1.4%) | 9 (2.2%) | 21 (2.1%) |
| DISTURBANCE IN ATTENTION | 2 (0.5%) | 1 (0.5%) | 3 (0.7%) | 6 (1.5%) | 10 (1.0%) |
| HYPERSOMNIA | 0 | 2 (1.0%) | 1 (0.2%) | 1 (0.2%) | 4 (0.4%) |
| INITIAL INSOMNIA | 1 (0.2%) | 0 | 0 | 1 (0.2%) | 1 (<0.1%) |
| MEMORY IMPAIRMENT | 1 (0.2%) | 1 (0.5%) | 4 (1.0%) | 6 (1.5%) | 11 (1.1%) |
| MOOD ALTERED | 0 | 0 | 1 (0.2%) | 1 (0.2%) | 2 (0.2%) |
| MOOD SWINGS | 0 | 1 (0.5%) | 2 (0.5%) | 1 (0.2%) | 4 (0.4%) |
| NEGATIVE THOUGHTS | 0 | 0 | 0 | 1 (0.2%) | 1 (<0.1%) |
| PSYCHOMOTOR RETARDATION | 0 | 0 | 1 (0.2%) | 0 | 1 (<0.1%) |
| SELF ESTEEM DECREASED | 1 (0.2%) | 0 | 0 | 0 | 0 |
| SUICIDE ATTEMPT | 0 | 0 | 1 (0.2%) | 0 | 1 (<0.1%) |
| Source: C-SSRS | 12 (2.8%) | 0 | 10 (2.4%) | 7 (1.7%) | 17 (1.7%) |
| C-SSRS Suicidal Behavior | 2 (0.5%) | 0 | 2 (0.5%) | 2 (0.5%) | 4 (0.4%) |
| C-SSRS Suicidal Ideation | 10 (2.3%) | 0 | 10 (2.4%) | 5 (1.2%) | 15 (1.5%) |
| Source: C-CASA | 0 | 1 (0.5%) | 5 (1.2%) | 1 (0.2%) | 7 (0.7%) |
| C-CASA | 0 | 1 (0.5%) | 5 (1.2%) | 1 (0.2%) | 7 (0.7%) |

Note: Subjects may have more than one event per source and preferred term/lab value. At each level of summarization (global, source, preferred term/lab value), a subject was counted once if he/she reported more than one event at that level.
Source: ISS Table 7.7.1.6.1

In the Nonepilepsy Controlled Pool, the Sponsor reported that the incidence of Depression and Suicidality events was slightly greater in ESL subjects overall (2.6%)

compared with placebo subjects (1.5%) (see table below). The most frequently reported event within this special interest category was disturbance in attention.

**Table 82. Overview of Suicidality TEAEs and SMQ Suicide & Self-Injury**

| | Phase 3 Epilepsy DB | | Nonepilepsy Pool | |
|---|---|---|---|---|
| | **Placebo** | **ESL** | **Placebo** | **ESL** |
| | n=426 | n=1021 | n=411 | n=1294 |
| Depression/suicidality events (Sponsor) | 26 (6.1) | 78 (7.6) | 6 (1.5) | 33 (2.6) |
| C-SSRS Suicidal Behavior | 2 (0.5) | 4 (0.4) | -- | -- |
| C-SSRS Suicidal Ideation | 10 (2.3) | 15 (1.5) | -- | -- |
| C-CASA | 0 | 7 (0.7) | 1 (0.2) | 3 (0.2) |
| SMQ Depression & Suicide/self-injury | | | | |
| SMQ Suicide and self-injury | 1 (0.2) | 3 (0.3) | 1 (0.2) | 2 (0.2)* |

Source: ISS Tables 53, 7.7.4.19.1 and SMQs created by reviewer using MAED tool (ADEVENTX: AEDECOD and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

*Comment: In the Warning for Suicidal Behavior and Ideation required by the Division for all antiepileptic medications, the following table summarizes the risk of suicidal thoughts or behavior by indication for antiepileptic drugs. For this pooled analysis, the primary endpoint of suicidal behavior or ideation was defined by the C-CASA categories of 1, 2, 3, or 4 (Dr. Evelyn Mentari's Review of Antieplieptic Drugs and Suicidality, 6/12/08). Of note, the Sponsor's classification of these suicidality events for ESL is broader with the inclusion of the C-CASA category of 7 "nonsuicidal self injurious behavior" (in addition to 1, 2, 3, or 4).*

*Of the 7 ESL subjects identified by the Sponsor using the C-CASA search strategy in the Phase 3 Epilepsy Controlled Pool, there was 1 ESL subject (304-307-30720) who was classified as C-CASA category 7 and 3 ESL subjects (302-336-80077, 302-336-80795, 302-332-80177) classified as C-CASA category 2 or 4 because of a history of prior suicidal attempt without any suicidal ideations or attempts reported during the study (described further below). Therefore, there were a total of 3 ESL subjects in the C-CASA categories of 1, 2, 3, or 4 for suicidality events that occurred during the study in the Phase 3 Epilepsy Controlled Pool (vs 0 placebo).*

**Table 83. Risk of Suicidal Thoughts or Behavior by Indication for Antiepileptic Drugs in the Pooled Analysis**

| Indication | Placebo Patients with Events Per 1000 Patients | Drug Patients with Events Per 1000 Patients | Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients | Risk Differences: Additional Drug Patients with Events Per 1000 Patients |
|---|---|---|---|---|
| Epilepsy | 1 | 3.4 | 3.5 | 2.4 |
| Psychiatric | 5.7 | 8.5 | 1.5 | 2.9 |
| Other | 1 | 1.8 | 1.9 | 0.9 |
| Total | 2.4 | 4.3 | 1.8 | 1.9 |

*For the nonepilepsy controlled pool (that includes both psychiatric and other indications), the incidence of suicidal thoughts or behavior (using the C-CASA categorization) in ESL subjects (2.3 per 1000) was similar to the meta-analysis for "other" and psychiatric indications (1.8-8.5 per 1000). For the Phase 3 Epilepsy Controlled Pool, the incidence of suicidal thoughts or behavior (C-CASA categories of 1, 2, 3, or 4 without 7) in ESL subjects (3/1021 or 2.9 per 1000) was slightly lower than in the meta-analysis for epilepsy patients (3.4 per 1000).*

*Using the SMQ Suicide and self-injury, the incidence of suicidality in ESL subjects in both of the double-blind groups (1.5 and 2.9 per 1000) was less than in the meta-analysis (1.8 and 3.4 per 1000, respectively).*

In the Phase 3 Epilepsy Controlled Pool, the Sponsor reported that the median time to Depression and Suicidality TEAEs was shorter in the ESL 400 mg, 800 mg, and 1200 mg groups (19.0 days, 16.0 days, and 17.0 days, respectively) compared with placebo (40.0 days). The median duration of events was longer in the ESL 400 mg, 800 mg, and 1200 mg groups (40.0 days, 35.0 days, and 44.0 days, respectively) compared with placebo (14.0 days). The median time to depression in the total ESL group was 22.0 days. Similarly, in the Nonepilepsy Controlled Pool, the Sponsor reported that the median time to Depression and Suicidality events was 16.0 days for ESL overall and 23.5 days for placebo, and the median duration of events was 16.0 days for ESL overall compared with 21.0 days for placebo (ISS Tables 7.7.4.19.2 and 7.7.4.19.3).

No additional events of suicidal behavior or ideation were identified by the Sponsor in Study 201, Study 202, or the Phase 1 studies.

For the All Studies Pool (including 303), the Sponsor reported that the incidence of Depression and Suicidality events was 4.7% (see table below). The most frequently reported events within this special interest category were depression (1.4%) and disturbance in attention (1.2%) (ISS Table 7.7.6.6.1). The Sponsor identified a small percentage of ESL subjects with suicidality using C-CASA (n=11, 0.3%), C-SSRS suicidal behavior (n=4, <0.1%), and C-SSRS suicidal ideation (n=15, 0.3%) (ISS Table 7.7.6.6.1).

I performed a search of the All Studies Pool (including Study 303 using the ADEVENTX dataset) for all of the ESL subjects with adverse events coded to suicidal ideation or behavior (completed suicide, intentional overdose, suicidal ideation, or suicide attempt). There were a total of 8 ESL subjects (0.2%) with AEs coded to suicidal ideation or behavior (see table below). These events resulted in SAEs (n=5 including 2 deaths) and discontinuation of treatment (n=4).

*Comment: Of note, the Sponsor reported a total of only 4 SAEs in ESL treated subjects along with 3 SAEs in non-ESL treated subjects (2 occurred pre-dose and 1 was in*

*placebo) (ISS Table 55). The Sponsor's search did not include the ESL subject with an SAE of suicidal ideation (302-306-80604).*

**Table 84. Suicidal Thoughts or Behavior, All Studies Pool (including Study 303)**

| | **Total ESL** |
|---|---|
| | n = 4307 |
| Depression/suicidality events (Sponsor) | 202 (4.7) |
| C-SSRS Suicidal Behavior | 4 (<0.1) |
| C-SSRS Suicidal Ideation | 15 (0.3) |
| C-CASA | 11 (0.3) |
| SMQ Suicide and self-injury | 8 (0.2)* |
| Completed suicide | 2 (<0.1) |
| Intentional overdose | 1 (<0.1)* |
| Suicidal ideation | 5 (0.1) |
| Suicide attempt | 2 (<0.1) |

Source: ISS Table 7.7.6.6.1 and created by the reviewer using the MAED tool (ADEVENTX: AEDECOD and ADSL: DOSCATH)
*subject with 2 unique subject IDs (204-476-204137 and 205-576-204137) only counted once

The narratives for the 8 ESL subjects with suicidality events (in the SMQ Suicide and self-injury) are summarized below (the first 5 subjects with SAEs):

Subjects 205-543-203154 & 210-589-589001 with completed suicides, described in Section 7.3.1 Deaths
Subject 302-306-80604 developed suicidal ideation on Day 211 of ESL and was hospitalized with depression with psychotic symptoms (emotional liability, excitation, auditory hallucinations with voices telling her to kill herself). ESL was discontinued. Risperidone and lorazepam were initiated. Events resolved 3 days later. Final diagnosis was schizoaffective disorder.
Subject 304-301-30118 with history of depression with prior suicidal ideations ingested several tablets of phenytoin in a suicide attempt on Day 77 of ESL. Subject was not hospitalized because she was asymptomatic and family members were not aware of the event. ESL was continued and the subject completed the study ~1 month later without any recurrence of events.
Subject 207-210-21001 drank a "significant amount of alcohol in a suicide attempt due to worsening of chronic post-herpetic pain" on Day 252 of ESL. ESL was discontinued. Events resolved the next day.
Subject 302-336-80710 with history of suicidal ideation developed suicidal ideation (unknown date).
Subject 204-476-204137 (same as 205-576-204137) with history of bipolar disorder intentionally overdosed on clonazepam on Day 34 of ESL. ESL was discontinued and events resolved the same day.
Subject 304-005-00508 developed suicidal ideation on Day 1 of ESL. ESL was continued and the subject completed the study ~3 months later.

*Comment: Of note, although this was an adverse event of special interest, this narrative was not provided by the Sponsor in the ISS.*

*Comment: The Sponsor reported 11 ESL subjects who had suicidal thoughts or behavior defined by the C-CASA codes of 1, 2, 3, 4, or 7. I identified these subjects using the ADSIEVTX dataset with the variable SIEVENT="C-CASA". All of the 8 subjects listed above (in the SMQ Suicide and self-injury) should have been identified by the Sponsor as cases of suicidality using the C-CASA search strategy. However, interestingly, only 4 of these 8 subjects were identified by the Sponsor after the database was searched electronically for the text strings of "suic" and "overdos": subjects 304-301-30118, 207-210-21001, 302-336-80710, and 204-476-204137. The*

*other 4 subjects who were not identified by the Sponsor included the 2 completed suicides (which should have been classified as C-CASA category 1: completed suicide). Therefore, the search for cases of suicidality that was performed by the Sponsor was inadequate and not comprehensive.*

*Furthermore, there were 7 ESL subjects who were identified by the Sponsor using the C-CASA search strategy but did not have TEAEs coded to the suicidality PTs (in the SMQ Suicide and self-injury). I describe these subjects below using the narratives provided by the Sponsor in the ISS. Most of these subjects (n=6) had events referring to a previous history of suicidality (before the study) and did not have any suicidal thoughts or behavior during the study. There was 1 subject (301-112-90394) with suicidal thoughts that was not recorded as a TEAE in the dataset. This is a coding omission. Of note, even after including this 1 subject, the incidence of suicidal thoughts and behavior during the study (9/4225 or 2.1 per 1000) in the All Studies Pool (including 303) remains lower than the meta-analysis for all AEDs (3.4 per 1000).*

*Subject 301-112-90394 classified as C-CASA category 4 based on the following investigator comments: "although patient expressed suicidal thoughts, she is not suicidal. Her behavior and appearance is definitely not depressive."*
*Subject 302-336-80795 classified as C-CASA category 4 based on the following investigator comments: "suicidal thoughts with no suicide attempt" (and listed as past medical history 6 years prior to the study). No suicidal ideations or attempts were reported during the study.*
*Subject 302-332-80177 classified as C-CASA category 2 based on the following investigator comments: "patient tried suicide" (and listed as past medical history 1 year prior to the study). No suicidal ideations or attempts were reported during the study.*
*Subject 302-336-80077 classified as C-CASA category 2 because of a history of prior suicidal attempt. No suicidal ideations or attempts were reported during the study.*
*Subject 210-816-816005 classified as C-CASA category 2 because of a history of prior suicidal attempts. No suicidal ideations or attempts were reported during the study.*
*Subject 303-518-70003 classified as C-CASA category 7 based on the following investigator comments: "one year ago, she took 5 tablets of phenobarbital. No suicidal thoughts now."*
*Subject 304-307-30720 classified as C-CASA category 7 based on the accidental overdose.*

In the ongoing studies, TEAEs of suicidal ideations occurred in 5 ESL subjects and 2 blinded subjects. SAEs of suicidal ideations occurred in 2 ESL subjects while suicidal attempt was reported in 1 ESL subject and 1 blinded subject.

In the postmarketing database, the Sponsor reported 3 cases with suicidal ideation or behavior: BIAL-00632 ("suicidal thoughts"), BIAL-01172 ("suicide attempt with a mixture of several drugs including Zebinix"), and BIAL-01616 (committed suicide) along with 36 AEs indicating potential suicidality (including 18 cases of "overdose"). The Sponsor concluded that the 3 suicidality events reflected a low reporting rate of 2.4 per 10,000 patient-years.

*Comment: An additional case was reported by the Sponsor on July 30, 2013, of a subject (BIAL 02122) who was hospitalized "following an overdose of Zebinix which was*

*suspected to be intentional." Of note, this adverse event was coded as "toxicity to various agents" rather than intentional overdose.*

In conclusion, there 8 ESL subjects with suicidality (suicidal behavior or ideation) identified in the integrated adverse event dataset (ADEVENTX). There were 2 completed suicides: 1 subject with a history of bipolar disorder and the other case occurred 73 days after discontinuing ESL. The remaining 6 suicidality cases were in subjects with prior history of depression or bipolar disorder (n=3), in OLE studies after more than 200 days of ESL use (n=2), or ESL was continued without recurrence of symptoms (n=1). Therefore, it is difficult to establish the causal role of ESL in these suicidality cases. Furthermore, the incidence of suicidal thoughts or behavior (C-CASA categories of 1, 2, 3, or 4 without 7) in ESL subjects was similar to or lower than the results from the meta-analysis performed for all antiepileptics drugs. However, it is important to note that the exclusion criteria in the epilepsy studies listed major psychiatric disorders and schizophrenia with acute psychosis episode (within 2 years) or suicide attempt. Therefore, the results from the epilepsy studies may not represent the effects of ESL in the general population. Even though ESL was studied in subjects with bipolar disorder (Studies 203, 204, 205), the number of ESL subjects in these trials comprised only a small percentage (8.4%) of the subjects in the Nonepilepsy Double-blind Pool. Thus, the above analyses for psychiatric disorders may represent less severe cases than in the general population.

7.3.4.5 Endocrine Disorders

A similar percentage of ESL and placebo subjects experienced TEAEs in the SOC Endocrine Disorders in both the Phase 3 Epilepsy Controlled Pool (1.3% vs 0.9%) and the Nonepilepsy Double-blind Pool (0.6% vs 0.6%). There were no SAEs in this SOC. There was 1 ESL subject who discontinued due to the PT hypothyroidism:

> Subject 304-421-42102: developed hypothyroidism on Day 99 of ESL. Free T4 values of 0.89 ng/dL were just below the lower limit of normal (0.93 ng/dL) with high TSH value of 4.93 µU/mL (ULN 4.20 µU/mL). "There were no pertinent abnormal objective findings suggestive of clinical hypothyroidism." The subject did not receive treatment for this event. ESL was discontinued. Events were ongoing at last report. Baseline TFTs and on Day 58 were WNL.

**Table 85. Overview of TEAEs, SAEs, DCs in the SOC Endocrine Disorders**

| SOC Endocrine Disorders | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=426 | n=1021 | n=507 | n=1755 |
| TEAEs | 4 (0.9%) | 13 (1.3%) | 3 (0.6%) | 11 (0.6%) |
| SAEs | 0 | 0 | 0 | 0 |
| Discontinuations (DCs) | 0 | 1 (0.1%)* | 0 | 0 |

Source: ISS Tables 7.1.4.1.s5, 7.1.11.1.s2, 7.4.1.1.s2 and created by the reviewer using JReview (ADEVENTX: AESER='Y', DISC=1 and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)
*PT hypothyroidism (304-421-42102, described above)

The following table summarizes the potentially clinically significant changes (for subjects with normal values at baseline) in thyroid parameters for the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Controlled Pool. In both of the DB pools, the incidences of PCS changes to low free T3 and low free T4 were higher in ESL subjects than placebo (while the PCS changes to high free T3 and T4 values were similar or lower than placebo).

**Table 86. PCS Thyroid Values (for Subjects Normal at Baseline)**

| | **Phase 3 Epilepsy Controlled Pool** | | | | **Nonepilepsy Controlled Pool^** | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| **Parameter** | n | #PCS (%) | n | #PCS (%) | n | #PCS (%) | n | #PCS (%) |
| Free T3 <200 pg/dL | 363 | 4 (1.1) | 819 | 18 (2.2) | 247 | 1 (0.4) | 616 | 16 (2.6) |
| Free T3 >415 pg/dL | 363 | 18 (5.0) | 819 | 28 (3.4) | 247 | 0 | 616 | 3 (0.5) |
| Free T4 <0.75 ng/dL | 362 | 15 (4.1) | 832 | 110 (13) | 249 | 0 | 622 | 9 (1.4) |
| Free T4 >1.75 ng/dL | 362 | 1 (0.3) | 832 | 3 (0.4) | 249 | 1 (0.4) | 622 | 2 (0.3) |

Source: ISS Tables 9.1.8, 9.4.7.1, Safety Information Amendment 5/20/13 Tables 9.1.12.1.r1, 9.4.10.1.r1, 9.1.8.r1
^excludes Study 206

The following table summarizes the mean changes from baseline to the end of treatment for the thyroid parameters. For all of the thyroid parameters (except for thyrotropin), the mean values decreased more during the study for ESL subjects than placebo in both controlled pools.

*Comment: In the Phase 3 Epilepsy Controlled Pool, thyrotropin (TSH) values were measured only in Study 304. These values were drawn at baseline and at the end of the study (at Visit 5) along with T3 and T4 values. Typically, changes in TSH lag changes in T3/T4 by 4 weeks. Therefore, additional measurements of TSH (after study completion) may have provided more complete information regarding changes in TSH resulting from changes in T3/T4.*

**Table 87. Mean Change from Baseline to End of Treatment, Thyroid Parameters**

| | **Phase 3 Epilepsy Controlled Pool** | | | | **Nonepilepsy Controlled Pool^** | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| **Parameter** | n | mean Δ | n | mean Δ | n | mean Δ | n | mean Δ |
| Free T3 (pg/dL) | 382 | 1.438 | 894 | -12.856 | 253 | -6.92 | 628 | -22.32 |
| Total T3 (ng/dL) | 183 | 2.1 | 315 | -11.6 | 253 | -4.46 | 628 | -13.73 |
| Free T4 (ng/dL) | 384 | -0.0 | 895 | -0.1 | 253 | -0.03 | 628 | -0.13 |
| Total T4 (µg/dL) | 183 | -0.1 | 317 | -1.1 | 253 | 0.07 | 628 | -0.95 |
| Thyrotropin (µU/mL) | 183 | 0.1 | 318 | 0.0 | 253 | 0.06 | 628 | 0.05 |

Source: ISS Tables 9.1.4.1.s1, 9.4.4.s1, 9.1.2, 9.4.2 and Safety Information Amendment 5/20/13 Table 9.1.2.r1
^excludes Study 206

The following table summarizes the percentages of subjects who shifted from normal at baseline to low and high values for all of the thyroid parameters. Incidences of shifts to low values of free T3/T4 and total T3/T4 were much higher in ESL subjects than

placebo. A dose-response relationship was observed. Furthermore, there was an associated increased incidence of shifts to high thyrotropin in ESL subjects than placebo. Conversely, incidences of shifts to high values of free T3/T4 and total T3/T4 (and low values of thyrotropin) were similar or lower in ESL subjects than placebo.

**Table 88. Shift Results (from normal) for Thyroid Parameters**

| | Phase 3 Epilepsy Controlled Pool | | | | Nonepilepsy Controlled Pool^ | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| **Parameter** | n | # shift (%) | n | # shift (%) | n | # shift (%) | n | # shift (%) |
| Free T3 Low | 350 | 6 (1.7) | 794 | 49 (6.2)* | 200 | 36 (18.0) | 499 | 169 (34) |
| Free T4 Low | 334 | 22 (6.6) | 779 | 129 (17)* | 235 | 19 (8.1) | 567 | 180 (32) |
| Total T3 Low | 164 | 3 (1.8) | 292 | 20 (6.8)* | 236 | 12 (5.1) | 598 | 86 (14) |
| Total T4 Low | 180 | 5 (2.8) | 304 | 15 (4.9)* | 250 | 0 | 622 | 36 (5.8) |
| Thyrotropin High | 162 | 7 (4.3) | 282 | 14 (5.0) | 235 | 5 (2.1) | 591 | 20 (3.4) |
| | | | | | | | | |
| Free T3 High | 350 | 13 (3.7) | 794 | 19 (2.4) | 200 | 0 | 499 | 2 (0.4) |
| Free T4 High | 334 | 1 (0.3) | 779 | 2 (0.3) | 235 | 1 (0.4) | 567 | 2 (0.4) |
| Total T3 High | 164 | 1 (0.6) | 292 | 0 | 236 | 1 (0.4) | 598 | 2 (0.3) |
| Total T4 High | 180 | 2 (1.1) | 304 | 0 | 250 | 1 (0.4) | 622 | 1 (0.2) |
| Thyrotropin Low | 162 | 0 | 282 | 1 (0.4) | 235 | 5 (2.1) | 591 | 5 (0.8) |

Source: ISS Tables 9.1.6.2.s1, 9.1.6.4.s1, 9.4.5.4.s1 and Safety Information Amendment 5/20/13 Table 9.1.6.2.r1
*Dose-related increase from 400 mg to 800 mg to 1200 mg randomized dose groups
^excludes Study 206

In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 5/20/13 to analyze the correlation between thyrotropin and T3/T4 values. The following table summarizes the incidences of concurrent thyroid parameters in the Phase 3 Epilepsy Controlled Pool. Of subjects with a high TSH, ESL subjects had a higher incidence than placebo of low free T4 values (34% vs 25%) and low free T3 values (17% and 10%). The strongest correlation occurred between TSH and free T4 values. No ESL subjects had both low TSH and high free T4 values. Similarly in the Nonepilepsy Controlled Pool, in subjects with a high TSH, a slightly higher incidence of the ESL subjects had high TSH and low free T4 values compared to placebo (43%vs 40%) (Safety Information Amendment 5/20/13 Table 9.4.10.7.r1).

**Table 89. Concurrent Thyroid Function Tests, Phase 3 Epilepsy Controlled Pool**

| **Category** | **Placebo n (%)** | **ESL n (%)** | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=426 | n=196 | n=415 | n=410 | n=1021 |
| Thyrotropin >ULN and | n=20 | n=0 | n=18 | n=15 | n=53 |
| Free T3 <LLN | 2 (10) | 0 | 4 (22) | 5 (33) | 9 (17) |
| Free T4 <LLN | 5 (25) | 0 | 8 (44) | 10 (67) | 18 (34) |
| Total T3 <LLN | 2 (10) | 0 | 0 | 1 (6.7) | 1 (1.9) |
| Total T4 <LLN | 1 (5.0) | 0 | 0 | 0 | 0 |
| | | | | | |
| Thyrotropin <LLN and | n=2 | n=0 | n=2 | n=0 | n=4 |
| Free T3 >ULN | 1 (50) | 0 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| Free T4 >ULN | 1 (50) | 0 | 0 | 0 | 0 |
| Total T3 >ULN | 1 (50) | 0 | 0 | 0 | 0 |
| Total T4 >ULN | 1 (50) | 0 | 0 | 0 | 0 |

Source: Safety Information Amendment 5/20/13 Table 9.1.12.5.r1
*concurrent values do not have to be at the same lab visit
ULN= upper limit of normal; LLN= lower limit of normal

Hypothyroidism signs and symptoms may include fatigue, cold intolerance, constipation, dry skin, weight gain, muscle weakness/aches, myxedema, hoarseness, joint pain/stiffness, alopecia, paresthesia, bradycardia, depression, and impaired memory/concentration. Hypothyroidism can be associated with other abnormal labs such as hyponatremia, hypercholesterolemia, hypertriglyceridemia, and increased CPK.[3]

The following table (submitted by the Sponsor upon the Division's request) summarizes the concurrent PCS values in the Phase 3 Epilepsy Controlled Pool. Of the subjects with PCS low values of free T4, a higher percentage of ESL subjects than placebo have concurrent PCS low values of sodium and chloride and concurrent PCS high values of CPK, cholesterol, and triglycerides.

**Table 90. Concurrent PCS Values, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=426 | n=196 | n=415 | n=410 | n=1021 |
| Free T4<0.75 ng/dL and | n=29 | n=33 | n=55 | n=60 | n=148 |
| Sodium ≤130 meq/L | 0 | 2 (6.1) | 2 (3.6) | 4 (6.7) | 8 (5.4) |
| Chloride ≤90 meq/L | 0 | 0 | 1 (1.8) | 0 | 1 (0.7) |
| CPK >2.5xULN | 0 | 0 | 0 | 2 (3.3) | 2 (1.4) |
| Cholesterol >300 mg/dL | 1 (3.4) | 1 (3.0) | 3 (5.5) | 2 (3.3) | 6 (4.1) |
| LDL >160 mg/dL | 4 (13.8) | 3 (9.1) | 9 (16.4) | 8 (13.3) | 20 (13.5) |
| HDL <30 mg/dL | 0 | 0 | 0 | 1 (1.7) | 1 (0.7) |
| Triglycerides >300 mg/dL | 1 (3.4) | 2 (6.1) | 3 (5.5) | 3 (5.0) | 8 (5.4) |

Source: Safety Information Amendment 5/20/13
*concurrent values at the same lab visit

The Sponsor submitted tables comparing AE incidence in subjects with normal T4 to the incidence in subjects with low T4 assessed at any time on treatment (Safety Information Amendment 5/20/13). I have summarized the risk differences (incidence rates in the total ESL group minus the placebo group) in the table below for the low T4 subjects and the normal T4 subjects in the Phase 3 Epilepsy Controlled Pool.

[3] Weetman AP, Jameson JL. Chapter 341. Disorders of the Thyroid Gland. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=9140510. Accessed August 22, 2013.

*Comment: The Sponsor reported that the differences in AE incidence between the "low" and "normal" T4 groups of subjects were small, and ESL-associated treatment differences were overall similar between the "low T4" and "normal T4" subjects. The Sponsor concluded that subjects with abnormal thyroid function laboratory tests were generally not symptomatic, and that symptomatic hypothyroidism is not associated with ESL therapy. However, I noted that there were larger differences between ESL and placebo subjects for vertigo, diplopia, dizziness, and fall in subjects with low T4 compared to subjects with normal T4. Interestingly, these symptoms are not typically associated with hypothyroidism and are instead the common adverse events for ESL.*

*However, I did notice that the TEAE alopecia was reported in 0.6% (27/4334) of ESL subjects. Some of those subjects (n=8) also had low free T4 or free T3 values (<LLN).*

**Table 91. Risk difference of TEAEs for subjects with low free T4 levels (<LLN) compared to subjects with normal free T4 levels, Phase 3 Epilepsy DB Pool**

| MedDRA SOC<br>PT | Low free T4:<br>Total ESL - PBO | Normal free T4:<br>Total ESL - PBO |
|---|---|---|
| Any TEAE | 11% | 15% |
| | | |
| Blood and Lymphatic System Disorders | -0.5 | 0.1 |
| Cardiac Disorders | 0.3 | 0.8 |
| Congenital, Familial and Genetic Disorders | 0 | 0.3 |
| Ear and Labyrinth Disorders | 6.3 | 3.3 |
| Vertigo | 4.7 | 3.0 |
| Endocrine Disorders | -4.7 | 1.1 |
| Hypothyroidism | -3.0 | 0.6 |
| Eye Disorders | 13.5 | 8.7 |
| Diplopia | 8.8 | 6.4 |
| Gastrointestinal Disorders | 0.9 | 9.4 |
| Nausea | 0.9 | 6.0 |
| General Disorders and Administration Site | -2.9 | 2.6 |
| Fatigue | 0.1 | 1.3 |
| Hepatobiliary Disorders | 0 | 0.2 |
| Immune System Disorders | 0.4 | 0.3 |
| Infections and Infestations | -5.0 | -0.7 |
| Injury, Poisoning & Procedural Complications | 5.7 | -0.3 |
| Fall | 2.0 | 0.2 |
| Investigations | 8.3 | 1.5 |
| Metabolism and Nutrition Disorders | -0.2 | 2.4 |
| Musculoskeletal/Connective Tissue Disorders | 0.7 | -0.2 |
| Neoplasms Benign, Malignant and Unspecified | 0 | 0 |
| Nervous System Disorders | 21.0 | 15.5 |
| Dizziness | 12.7 | 10.1 |
| Psychiatric Disorders | -2.0 | 1.4 |
| Depression | -0.6 | 0.2 |
| Renal and Urinary Disorders | 2.3 | -1.2 |
| Reproductive System and Breast Disorders | -2.3 | -0.1 |
| Respiratory, Thoracic & Mediastinal Disorders | -1.6 | -0.4 |
| Skin and Subcutaneous Tissue Disorders | 4.9 | -1.7 |

| | | |
|---|---|---|
| Pruritus | 1.6 | -0.1 |
| Social circumstances | 0.4 | 0.2 |
| Surgical and Medical Procedures | 0.8 | 0.2 |
| Vascular Disorders | 0.2 | 1.2 |

Source: Safety Information Amendment 5/20/13 Tables 9.1.12.6.r1, 9.1.12.7.r1

In conclusion, ESL use is associated with dose-dependent decreases in T3 and T4 values. These changes were associated with concurrent increases in TSH and signs and symptoms of hypothyroidism. Therefore, I recommend the addition of this information regarding thyroid parameters (and the need for monitoring) in Warnings and Precautions of ESL labeling.

## 7.3.5 Submission Specific Primary Safety Concerns

In the next three subsections (7.3.5.1 to 7.3.5.3), I will discuss my analyses along with the Sponsor's analyses of the following major organ systems: cardiac disorders, gastrointestinal disorders, and other organ systems.

### 7.3.5.1 Cardiac Disorders

A similar number of ESL subjects experienced TEAEs in the SOC Cardiac Disorders than placebo subjects in the Phase 3 Epilepsy Controlled Pool (2.3% vs 1.6%) and slightly higher in the Nonepilepsy Double-blind Pool (3.1% vs 1.6%). Cardiac SAEs occurred at higher rates in ESL subjects than placebo in both pooled groups. Discontinuations due to these TEAEs occurred more often in ESL subjects than placebo in only the Nonepilepsy Double-blind Pool (0.6% vs 0). There were no cardiac-related deaths during the controlled trials. The following table summarizes the adverse events in the SOC Cardiac Disorders for the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool.

**Table 92. Overview of TEAEs, SAEs, DCs in the SOC Cardiac Disorders**

| SOC Cardiac Disorders | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=426 | n=1021 | n=507 | n=1755 |
| Deaths | 0 | 0 | 0 | 0 |
| TEAEs | 7 (1.6%) | 23 (2.3%) | 8 (1.6%) | 54 (3.1%) |
| SAEs | 0 | 2 (0.2%) | 0 | 12 (0.7%) |
| Discontinuations (DCs) | 1 (0.2%) | 1 (0.1%) | 0 | 11 (0.6%) |

Source: ISS Tables 7.1.4.1.s5, 7.1.11.1.s2, 7.4.1.1.s2 and created by the reviewer using JReview (ADEVENTX: AESER='Y', DISC=1 and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

*Comment: Of note, I performed stratified analyses by the different indications in the Nonepilepsy Double-blind Pool. In the peripheral neuropathy studies (Studies 206 and 207), ESL subjects (4.1%) had a greater incidence of TEAEs in the SOC Cardiac Disorders than placebo subjects (1.1%). This was also seen in the migraine Study 209*

*(1.5% vs 0, driven by the PT tachycardia). However, opposite results were seen in the bipolar disorder Studies 203 and 206 and fibromyalgia Study 210 with ESL subjects having a lower incidence of cardiac TEAEs than placebo subjects (1.4% vs 3.9% and 2.5% vs 3.1%, respectively).*

A slightly higher number of ESL subjects experienced TEAEs in the SOC Vascular Disorders than placebo subjects in both the Phase 3 Epilepsy Controlled Pool (4.0% vs 2.8%) and the Nonepilepsy Double-blind Pool (3.0% vs 1.8%). Cardiac SAEs and discontinuations occurred at higher rates in ESL subjects than placebo in both pooled groups. There were no vascular-related deaths during the controlled trials. The following table summarizes the adverse events in the SOC Vascular Disorders for the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool.

**Table 93. Overview of TEAEs, SAEs, DCs in the SOC Vascular Disorders**

| SOC Vascular Disorders | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=426 | n=1021 | n=507 | n=1755 |
| Deaths | 0 | 0 | 0 | 0 |
| TEAEs | 12 (2.8%) | 41 (4.0%) | 9 (1.8%) | 52 (3.0%) |
| SAEs | 0 | 4 (0.4%)[a] | 0 | 1 (0.1%)[c] |
| Discontinuations (DCs) | 0 | 6 (0.6%)[b] | 1 (0.2%) | 9 (0.5%)[d] |

Source: ISS Tables 7.1.4.1.s5, 7.1.11.1.s2, 7.4.1.1.s2 and created by the reviewer using JReview (ADEVENTX: AESER='Y', DISC=1 and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)
[a]PTs aortic aneurysm, aortic dilatation, hypertension, arterial haemorrhage, pallor
[b]PTs aortic aneurysm, aortic dilatation, hypertension, hypotension, orthostatic hypotension, flushing,pallor
[c]PT haemorrhage
[d]PTs accelerated hypertension (1), hypertension (3), hypertensive crisis (1), hypotension (2), haematoma (1), hot flush (1)

To further analyze all of these cardiac adverse events across SOCs, I stratified the TEAEs by the HLGTs in the 4 SOCs with cardiac-related PTs (with ≥2 ESL subjects and >placebo) then by the PTs (with ≥1 ESL subject and >placebo) (see tables below). Furthermore, I performed an analysis of all of the cardiac-related SMQs.

**Table 94. TEAEs in Cardiac-related HLGTs in ≥ 2 ESL Subjects > Placebo (then PTs in ≥1 ESL subject and >Placebo), Phase 3 Epilepsy Controlled Pool**

| Phase 3 Epilepsy Controlled Pool | Placebo | ESL |
|---|---|---|
| | n=426 | n=1021 |
| **SOC Cardiac disorders** | 7 (1.6%) | 23 (2.3%) |
| HLGT Cardiac arrhythmias | 4 (0.9) | 19 (1.9) |
| PT Tachycardia | 1 (0.2) | 7 (0.7) |
| PT Sinus bradycardia | 0 | 6 (0.6) |
| PT Bradycardia | 0 | 5 (0.5) |
| PT Arrhythmia | 0 | 1 (0.1) |
| PT Bundle branch block right | 0 | 1 (0.1) |
| PT Conduction disorder | 0 | 1 (0.1) |
| **SOC Investigations** | | |
| HLGT Cardiac and vascular investigations | 12 (2.8) | 33 (3.2) |
| PT Blood pressure decreased | 1 (0.2) | 6 (0.6) |
| PT Blood pressure diastolic decreased | 3 (0.7) | 9 (0.9) |
| PT Blood pressure diastolic increased | 1 (0.2) | 6 (0.6) |
| PT Blood pressure diastolic abnormal | 0 | 1 (0.1) |
| PT Blood pressure systolic decreased | 0 | 5 (0.5) |
| PT Heart rate increased | 1 (0.2) | 4 (0.4) |
| PT Angiogram | 0 | 1 (0.1) |
| PT Electrocardiogram T wave abnormal | 0 | 1 (0.1) |
| PT Pulse abnormal | 0 | 1 (0.1) |
| **SOC Nervous system disorders** | | |
| HLGT Central nervous system vascular disorders | 1 (0.2) | 4 (0.4) |
| PT Cerebral haemorrhage | 0 | 1 (0.1) |
| PT Cerebral infarction | 0 | 1 (0.1) |
| PT Vasculitis cerebral | 0 | 1 (0.1) |
| PT Vertebrobasilar insufficiency | 0 | 1 (0.1) |
| **SOC Vascular disorders** | | |
| HLGT Vascular hypertension disorders | 5 (1.2) | 19 (1.9) |
| PT Hypertension | 5 (1.2) | 18 (1.8) |
| PT Hypertensive crisis | 0 | 1 (0.1) |
| HLGT Decreased & nonspecific BP disorders and shock | 2 (0.5) | 9 (0.9) |
| PT Hypotension | 1 (0.2) | 7 (0.7) |
| HLGT Arteriosclerosis, stenosis, vascular insufficiency | 0 | 2 (0.2) |
| PT Peripheral coldness | 0 | 2 (0.2) |
| | | |
| **SMQ Cardiac arrhythmias** - narrow | 3 (0.7) | 8 (0.8) |
| **SMQ Cardiac failure** – narrow | 0 | 1 (0.1) |
| **SMQ Cardiomyopathy** - narrow | 0 | 1 (0.1) |
| **SMQ Cerebrovascular disorders** - narrow | 1 (0.2) | 5 (0.5) |
| **SMQ Embolic and Thrombotic events** - narrow | 1 (0.2) | 0 |
| **SMQ Hypertension** - narrow | 10 (2.3) | 28 (2.7) |
| **SMQ Ischaemic heart disease** - narrow | 0 | 2 (0.2) |
| **SMQ Torsade/QT prolongation** - narrow | 0 | 0 |

Source: ISS Table 7.1.4.1.s5 and SMQs created by the reviewer using MAED tool (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

In the Phase 3 Epilepsy Controlled Pool, the risk differences between the ESL and placebo subjects for all of the HLGTs were small (≤1.0%) and even smaller for the SMQs (<0.5%). The largest risk differences in HLGT between ESL and placebo subjects occurred in the HLGT Cardiac arrhythmias (1.0%) and Vascular hypertension disorders (0.7%). These differences were driven by tachycardia, bradycardia/sinus bradycardia, and hypertension rather than any malignant arrhythmias. Furthermore, there were conflicting results of both increased and decreased heart rate as well as increased and decreased blood pressure. Importantly, the HLGTs of coronary artery disorders and heart failures had only 1 ESL subject each (versus 0 placebo subjects), and there were no TEAEs coded to any ventricular arrhythmias or electrocardiogram QT interval prolonged/abnormal in the Phase 3 Epilepsy Controlled Pool. Loss of consciousness was experience in fewer ESL subjects (0.4%) than placebo (0.5%) while no subjects experienced syncope. Additionally, both atrioventricular block first degree and second degree were only experienced in placebo subjects (2) and no ESL subjects.

In the Nonepilepsy Double-blind Pool, the risk differences between the ESL and placebo subjects for all of the HLGTs were small (≤1.0%) and even smaller for the SMQs (≤0.5% except for the SMQ Hypertension 1.4%). The largest risk difference in HLGT between ESL and placebo subjects occurred in the HLGT Vascular hypertension disorders (1.0%). This may be due to the baseline differences in medical history (particularly hypertension) between the ESL and placebo subjects (described in Section 7.2.1.2 of this review).

**Table 95. TEAEs in Cardiac-related HLGTs and PTs in ≥ 2 ESL Subjects > Placebo, Nonepilepsy Double-blind Pool (includes Study 206)**

| Nonepilepsy Double-blind Pool | Placebo | ESL |
|---|---|---|
| | n=507 | n=1755 |
| **SOC Cardiac disorders** | 8 (1.6%) | 54 (3.1%) |
| HLGT Cardiac arrhythmias | 5 (1.0) | 30 (1.7) |
| HLT Cardiac conduction disorders | 1 (0.2) | 10 (0.6) |
| PT Bundle branch block right | 0 | 4 (0.2) |
| PT Bundle branch block left | 0 | 3 (0.2) |
| PT Atrioventricular block (first, second) | 0 | 3 (0.2) |
| HLT Rate and rhythm disorders NEC | 3 (0.6) | 12 (0.7) |
| PT Tachycardia | 2 (0.4) | 8 (0.5) |
| PT Bradycardia | 0 | 3 (0.2) |
| HLT Supraventricular arrhythmias | 1 (0.2) | 7 (0.4) |
| PT Atrial fibrillation | 0 | 2 (0.1) |
| PT Atrial flutter | 0 | 2 (0.1) |
| PT Sinus bradycardia | 0 | 2 (0.1) |
| HLT Ventricular arrhythmias and cardiac arrest | 0 | 3 (0.2) |
| PT Ventricular extrasystoles | 0 | 3 (0.2) |
| HLGT Cardiac disorder signs and symptoms | 3 (0.6) | 14 (0.8) |
| PT Cyanosis | 0 | 2 (0.1) |
| HLGT Coronary artery disorders | 1 (0.2) | 12 (0.7) |
| PT Acute myocardial infarction | 0 | 2 (0.1) |
| PT Coronary artery disease | 0 | 2 (0.1) |

| | | |
|---|---|---|
| PT Myocardial infarction | 0 | 3 (0.2) |
| PT Myocardial ischaemia | 0 | 2 (0.1) |
| HLGT Heart failures | 0 | 6 (0.3) |
| PT Cardiac failure | 0 | 5 (0.3) |
| HLGT Myocardial disorders | 0 | 6 (0.3) |
| **SOC Investigations** | | |
| HLGT Cardiac and vascular investigations | 9 (1.8) | 34 (1.9) |
| PT Blood pressure increased | 4 (0.8) | 26 (1.5) |
| PT Electrocardiogram ST-T segment abnormal | 0 | 2 (0.1) |
| PT Troponin | 0 | 1 (0.1) |
| PT Troponin increased | 0 | 1 (0.1) |
| **SOC Nervous system disorders** | | |
| PT Loss of consciousness | 0 | 2 (0.1) |
| PT Syncope | 0 | 7 (0.4) |
| **SOC Vascular disorders** | | |
| HLGT Vascular hypertension disorders | 5 (1.0) | 35 (2.0) |
| PT Hypertension | 5 (1.0) | 29 (1.7) |
| PT Hypertensive crisis | 0 | 4 (0.2) |
| | | |
| **SMQ Cardiac arrhythmias** - narrow | 3 (0.6%) | 20 (1.1%) |
| **SMQ Cardiac failure** – narrow | 0 | 8 (0.5%) |
| **SMQ Cardiomyopathy** - narrow | 0 | 2 (0.1%) |
| **SMQ Cerebrovascular disorders** - narrow | 1 (0.2%) | 2 (0.1%) |
| **SMQ Embolic and Thrombotic events** - narrow | 2 (0.4%) | 7 (0.4%) |
| **SMQ Hypertension** - narrow | 10 (2.0%) | 60 (3.4%) |
| **SMQ Ischaemic heart disease** - narrow | 1 (0.2%) | 12 (0.7%) |
| **SMQ Torsade/QT prolongation** - narrow | 0 | 0 |

Source: ISS Table 20.5-54 and SMQs created by the reviewer using MAED tool (ADEVENTX: AEDECOD and ADSL: TRTP1) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')

The following table summarizes the cardiac-related SAEs for both the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool. The SAEs in the Phase 3 Epilepsy Controlled Pool were disparate events. Most of the SAEs in the Nonepilepsy Double-blind Pool occurred in the peripheral neuropathy Studies 206 and 207 where the following SAEs in the SOC cardiac disorders occurred in 10 (1.1%) ESL subjects (vs 0 placebo): acute myocardial infarction (2), myocardial infarction (2), angina pectoris (2), bradyarrhythmia, bundle branch block left, cardiac failure (3), cardiac failure congestive, and congestive cardiomyopathy. These differences are difficult to attribute to ESL alone in the setting of baseline differences between the ESL and placebo groups in prior cardiac history (myocardial ischeamia) and cardiac risk factors (hypertension, hypercholesterolaemia) (described in Section 7.2.1.2 of this review). The SAEs of ventricular arrhythmia, cyanosis, loss of consciousness, and syncope are described in more detail below.

**Table 96. Cardiac-related SAEs in ≥1 ESL subject and >Placebo**

| **Cardiac Disorders SOC<br>Preferred Term** | **Placebo** | **ESL** |
|---|---|---|
| **Phase 3 Epilepsy Controlled Pool** | n = 426 | n = 1021 |
| **SOC Cardiac Disorders** | | |
| Heart valve incompetence | 0 | 1 (0.1) |
| Angina pectoris | 0 | 1 (0.1) |
| **SOC Nervous System Disorders** | | |
| Cerebral haemorrhage | 0 | 1 (0.1) |
| Vasculitis cerebral | 0 | 1 (0.1) |
| **SOC Vascular Disorders** | | |
| Aortic aneurysm | 0 | 1 (0.1) |
| Aortic dilatation | 0 | 1 (0.1) |
| Hypertension | 0 | 1 (0.1) |
| | | |
| **Nonepilepsy Double-blind Pool** | n=507 | n=1755 |
| **SOC Cardiac Disorders** | 0 | 12 (0.7%) |
| HLGT Coronary artery disorders | 0 | 6 (0.3) |
| Acute myocardial infarction | 0 | 2 (0.1) |
| Angina pectoris | 0 | 2 (0.1) |
| Myocardial infarction | 0 | 2 (0.1) |
| HLGT Cardiac arrhythmias | 0 | 6 (0.3) |
| Atrioventricular block second degree | 0 | 1 (0.1) |
| Bradyarrhythmia | 0 | 1 (0.1) |
| Bradycardia | 0 | 1 (0.1) |
| Bundle branch block left | 0 | 1 (0.1) |
| Tachycardia | 0 | 1 (0.1) |
| Ventricular arrhythmia | 0 | 1 (0.1) |
| Ventricular extrasystoles | 0 | 1 (0.1) |
| HLGT Heart failures | 0 | 4 (0.2) |
| Cardiac failure | 0 | 3 (0.2) |
| Cardiac failure congestive | 0 | 1 (0.1) |
| HLGT Myocardial disorders | 0 | 2 (0.1) |
| Congestive cardiomyopathy | 0 | 1 (0.1) |
| Left ventricular hypertrophy | 0 | 1 (0.1) |
| HLGT Cardiac disorders signs and symptoms | 0 | 1 (0.1) |
| Cyanosis | 0 | 1 (0.1) |
| **SOC Investigations** | | |
| Heart sounds | 0 | 1 (0.1) |
| Blood pressure abnormal | 0 | 1 (0.1) |
| Troponin | 0 | 1 (0.1) |
| **SOC Nervous System Disorders** | | |
| Loss of consciousness | 0 | 1 (0.1) |
| Syncope | 0 | 1 (0.1) |

Source: ISS Table 7.1.11.1.s2 and created by the reviewer using JReview (ADEVENTX: AEDECOD, AESER='Y' and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

In the Phase 1 Study Pool, there were 2 ESL subjects (vs 0 placebo) who reported the following cardiac-related SAEs: cardiac failure (subject 105-000-00005 described in Section 7.3.1 Deaths) and hypertension.
Subject 107-000-00011 developed asymptomatic hypertension (200/130 mmHg) on Day 5 of ESL. No action was taken and 3 days later, blood pressure was 150/100 mmHg. Baseline BP was elevated at 165/100 mmHg. Fourteen days after last dose of ESL (after crossing over to the placebo group), BP was again elevated at 240/130 mmHg. Subject was hospitalized and captopril was initiated.

I performed a search of all cardiac-related SAEs in ESL subjects in the All Studies Pool (including 303 using the ADEVENTX dataset). I identified only 1 ESL subject with the SAE of ventricular arrhythmia (subject 209-164-90336 with premature ventricular contractions). Furthermore, I identified 6 ESL subjects with the SAE loss of consciousness and 2 ESL subjects with the SAE syncope. The 6 SAEs of loss of consciousness were related to seizures (n=4), hypoglycemia (n=1), or occurred 3 days after ESL discontinuation in a subject with a past history of heart failure (n=1). The 2 SAEs of syncope were in the setting of hyponatremia or abdominal pain (possibly due to a vasovagal reaction on Day 82 of ESL). The narratives for other cardiac-related SAEs (and notable TEAEs) are summarized below:
Subject 302-313-80267 died due to "severe coronary atherosclerosis" on OLE Study Day 259. The subject had significant cardiac risk factors (hypertension, hyperlipidemia, obesity, atrioventricular block). Described in more detail in Section 7.3.1 of this review.
Subject 206-562-562004 developed atrioventricular block second degree (from 1st degree atrioventricular block in the setting of a myocardial infarction).
Subject 206-604-604002 developed bundle branch block left (history of myocardial infarction).
Subject 206-543-543001 developed cyanosis during episode of CHF (history of cardiac risk factors).
Subject 206-583-583022 developed cyanosis during episode of hypoglycemia and loss of consciousness.
Subject 206-701-701023 with an ECG at OLE Visit 5 that revealed complete left bundle branch block and delay of AV conduction (ECG s at DB Visits V 1 and V 6 were normal). Based on abnormal ECG findings, TEAE of atrioventricular block first degree was reported. No action was taken and the patient recovered.

*Comment: I also identified subject 302-301-80637 who was discontinued to the adverse event of "worsening Wolff Parkinson White syndrome" on Day 100 of ESL. In the narrative, it is reported that the subject first experienced "worsening Wolff Parkinson White syndrome" prior to the first dose of ESL. Therefore, this adverse event was not considered a treatment-emergent adverse event by the Sponsor.*

In the ongoing studies, the Sponsor reported 8 ESL subjects with the following SAEs: acute coronary syndrome, angina pectoris, atrial fibrillation, cardiogenic shock, myocardial infarction, supraventricular tachycardia, ventricular extrasystoles, and cardiac arrest/ventricular tachycardia (subject 307-1809701 with history of myocardial ischemia, described in more detail in Section 7.3.1 Deaths of this review) (Safety Information Amendment 4/19/13 Table 2).

In the postmarketing database, the Sponsor reported the following SAEs (1 each unless otherwise noted): syncope (case report not submitted by the Sponsor), cardiac arrest (case report submitted by the Sponsor on 6/10/13 and described below), circulatory

collapse, cardiomyopathy, cardiopulmonary failure, hypertension crisis (2), hypertension, heart rate increased, orthostatic hypotension, and palpitations (Safety Information Amendment 4/19/13). The Sponsor did not report any cases of ventricular arrhythmias or QT prolongation.

Subject BIAL 00504 who after receiving 1600 mg ESL for 2 months, was admitted to the hospital for seizures. Found to have hyponatremia (Na=128 mmol/L). Eight days later, the patient experienced an event of "asystole with a duration of 77 seconds." A permanent pacemaker was inserted. ESL was continued. The patient had no "cardiologic events in the past." Concomitant medications included clobazam (started at the same time as ESL), valproic acid, and levetiracetam.
*Comment: Ictal cardiac asystole has been reported in patients with refractory epilepsy.*[4,5]

In conclusion, although there were differences in cardiac-related TEAEs seen in ESL subjects compared to placebo subjects, these differences were small and difficult to attribute to ESL (especially in light of the baseline differences in prior cardiac history and cardiac risk factors in the nonepilepsy population).
In terms of the clinical events that can signal proarrhythmic potential per the ICH E14 guidelines, none of the following were reported with ESL use in the completed trials: torsade de pointes, ventricular tachycardia, ventricular fibrillation and flutter. However, there was a cardiac-related death (1) and loss of consciousness due to cardiac events (1) reported in ESL subjects. Additionally in the ongoing studies and postmarketing database, the following clinical events occurred in ESL subjects: cardiac death/ventricular tachycardia (1), cardiac arrest (1), and syncope (1). However, these clinical events (that can signal proarrhythmic potential per the ICH E14 guidelines) were rare and confounded by the presence of significant cardiac risk factors and/or baseline risk of cardiac arrhythmias in patients with epilepsy.[6]

7.3.5.2 Gastrointestinal Disorders

A higher number of ESL subjects experienced TEAEs in the SOC Gastrointestinal Disorders than placebo subjects in both the Phase 3 Epilepsy Controlled Pool (25.2% vs 16.0%) and the Nonepilepsy Double-blind Pool (20.5% vs 15.4%). The TEAEs in this SOC were driven by PTs in the HLGT Gastrointestinal signs and symptoms (specifically the PTs nausea and vomiting). A dose response relationship was observed for the HLGT GI signs and symptoms (15.8%, 18.1%, 22.4% versus placebo 10.6%) and the PTs nausea and vomiting (11.2%, 13.3%, 19.0% versus placebo 6.3%) for the ESL 400 mg, 800 mg, 1200 mg dose groups, respectively, in the Phase 3 Epilepsy Controlled Pool. SAEs and discontinuations due to these GI TEAEs occurred more often in ESL subjects than placebo in both pooled groups. Similarly, the TEAEs leading to discontinuation were also driven by the HLGT GI signs and symptoms with the majority due to nausea and vomiting. The following table summarizes the adverse

[4] Carvalho KS et al. Cardiac asystole during a temporal lobe seizure. Seizure. Dec 2004; 13(8): 595-599.
[5] Rugg-Gunn FJ et al. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. Lancet 2004; 364: 2212-19.
[6] Rugg-Gunn FJ et al. Cardiac arrhythmias in focal epilepsy: a prospective long-term study. Lancet 2004; 364: 2212-19.

events in the SOC Gastrointestinal Disorders for the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool.

**Table 97. Overview of TEAEs, SAEs, DCs in SOC Gastrointestinal Disorders**

| SOC Gastrointestinal Disorders | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=426 | n=1021 | n=507 | n=1755 |
| SOC Gastrointestinal Disorders (TEAEs) | 68 (16.0%) | 257 (25.2%) | 78 (15.4%) | 360 (20.5%) |
| HLGT GI signs and symptoms | 45 (10.6) | 198 (19.4) | 53 (10.5) | 273 (15.6) |
| PTs Nausea + vomiting | 27 (6.3) | 155 (15.2) | 31 (6.1) | 192 (10.9) |
| SAEs | 1 (0.2%) | 16 (1.6%) | 0 | 14 (0.8%) |
| Discontinuations (DCs) | 3 (0.7%) | 55 (5.4%) | 14 (2.8%) | 87 (5.0%) |

Source: ISS Tables 7.1.4.1.s5, 7.1.11.1.s2, 7.4.1.1.s2 and created by the reviewer using JReview (ADEVENTX: AEDECOD, AESER='Y', DISC=1 and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

The Sponsor reported that the median time to events in the ESL 400 mg, 800 mg, and 1200 mg groups was 49.0 days, 10.5 days, and 5.0 days, compared with 14.5 days for the placebo group (ISS Table 7.7.1.14.2). The median duration of events in the ESL 400 mg, 800 mg, and 1200 mg groups (9.0 days, 4.0 days, and 5.0 days) was similar to the placebo group (4.0 days) (ISS Table 7.7.1.14.3).

To further analyze these SAEs, I stratified the SAEs by the HLGTs in the SOC Gastrointestinal Disorders (with ≥2 ESL subjects and >placebo) then by the PTs (with ≥1 ESL subject and >placebo) (see table below). In both pooled groups, SAEs occurred in ESL subjects more than placebo in the HLGT Gastrointestinal signs and symptoms. Many of these SAEs were due to nausea, vomiting, and abdominal pain/dyspepsia.

**Table 98. SAEs in Gastrointestinal Disorders HLGTs in ≥2 ESL subjects and >Placebo (then PTs in ≥1 ESL subject and >Placebo)**

| Gastrointestinal disorders HLGT<br>Preferred Term | Placebo | ESL |
|---|---|---|
| **Phase 3 Epilepsy Controlled Pool** | n = 426 | n = 1021 |
| HLGT Gastrointestinal signs and symptoms | 1 (0.2) | 12 (1.2) |
| Vomiting | 1 (0.2) | 7 (0.7) |
| Nausea | 1 (0.2) | 7 (0.7) |
| Abdominal pain upper | 0 | 1 (0.1) |
| Flatulence | 0 | 1 (0.1) |
| | | |
| **Nonepilepsy Double-blind Pool** | n=507 | n=1755 |
| HLGT Gastrointestinal signs and symptoms | 0 | 8 (0.5%) |
| Vomiting | 0 | 4 (0.2)* |
| Nausea | 0 | 3 (0.2)* |
| Abdominal pain | 0 | 3 (0.2) |
| Abdominal pain lower | 0 | 1 (0.1) |
| Dyspepsia | 0 | 1 (0.1) |
| Dysphagia | 0 | 1 (0.1) |
| HLGT Abdominal hernias and other wall conditions | 0 | 3 (0.2) |

| | | |
|---|---|---|
| Abdominal hernia | 0 | 1 (0.1) |
| Hiatus hernia | 0 | 1 (0.1) |
| Inguinal hernia | 0 | 1 (0.1) |
| HLGT Gastrointestinal inflammatory conditions | 0 | 2 (0.1) |
| Duodenitis | 0 | 2 (0.1) |
| Gastritis | 0 | 2 (0.1) |

Source: ISS Tables 7.1.11.1.s2 and created by the reviewer using JReview (ADEVENTX: AEDECOD, AESER='Y' and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)
*subjects 206-683-683001, 207-285-285001, 207-287-287004, 210-583-583001, 210-612-612015

I reviewed the narratives for the SAEs in the SOC Gastrointestinal Disorders. Out of a total of 15 ESL subjects in epilepsy (n=10) and nonepilepsy studies (n=5) with SAEs of nausea and vomiting, the majority occurred during episodes of vertigo/dizziness/ataxia (n=8, typically within 1-2 weeks of ESL initiation) and hyponatremia (n=2). Few events occurred during episodes of hypertensive crisis (n=1), acute pyelonephritis (n=1), biliary tract infection (n=1), gastroenteritis (n=1), and inguinal hernia (n=1). There was significant sequelae in 1 ESL subject (subject 302-312-80299) who developed acute on chronic renal failure (baseline GFR <30 ml/min) as a result of severe nausea and vomiting.

7.3.5.3 Other Organ Systems

Renal Disorders
In the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool, a slightly lower percentage of ESL subjects than placebo experienced TEAEs in the SOC Renal and Urinary disorders (1.5% vs 1.9% and 1.3% vs 1.6%, respectively). In the Phase 3 Epilepsy Controlled Pool, there were 2 ESL subjects (vs 0 placebo subjects) with SAEs (1 urinary retention and 1 acute renal failure/GFR decreased in subject 302-312-80299 due to volume depletion, described above). In the Nonepilepsy Double-blind Pool, there were 4 ESL subjects with SAEs of hydronephrosis/renal colic, microalbuminuria, albuminuria/proteinuria, dysuria/polyuria/renal pain (vs 0 placebo subjects).

For the All Studies Pool (including 303), I reviewed all of the PTs included in the ADEVENTX dataset. While there were no other TEAEs coded to "renal failure acute", I identified the following notable adverse events:

"Blood creatinine increased" (SAE) during myocardial infarction and drowning death on Day 580.
"Asterixis" coded in a subject with a tremor and normal Cr.
"Azotaemia" on Day 5 with Cr increased from 1.50 to 2.08. ESL continued (>1 year) with resolution.
"Haemodialysis" in a subject with a history of Grade IV chronic renal failure who had an AV shunt operation performed in preparation for hemodialysis.

In the ongoing studies, the Sponsor reported 2 ESL subjects with SAEs renal failure and renal failure acute (Safety Information Amendment 4/19/13 Table 1).

Subject 307-3107702 was hospitalized for diabetic foot ulcer and cellulitis on Day 48 of ESL.
*Comment: No details regarding event of renal failure were provided in the Sponsor's narrative*.
Subject 307-3107703 developed diarrhea then acute renal failure, urosepsis, hyponatremia, and

hypokalemia on Day 171 of ESL. ESL was continued and events resolved 2 weeks later)
In the postmarketing database, the Sponsor reported 1 ESL subject with the SAE oliguria (ISS Table 116).

In conclusion, ESL is not associated with any renal or urinary disorders in this database. ESL use was not associated with an increase in TEAEs in the renal and urinary SOC. There were only rare SAEs with most cases not related to a decrease in renal function. Furthermore, ESL was not associated with an increase in renal laboratory parameters (creatinine PCS changes, mean changes, or shifts to high values) (see Section 7.4.2.2).

Respiratory Disorders
In the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool, a similar percentage of ESL subjects than placebo experienced TEAEs in the SOC Respiratory, Thoracic and Mediastinal Disorders (4.5% vs 4.9% and 2.6% vs 2.8%, respectively). In the Phase 3 Epilepsy Controlled Pool, there was 1 ESL subject with SAE of dyspnea (vs 2 placebo subjects with SAEs of lung infiltration, respiratory distress, and acute respiratory failure). In the Nonepilepsy Double-blind Pool, there were 6 ESL subjects with SAEs of haemoptysis, dyspnoea (n=2), pulmonary oedema, orthopnoea/dyspnoea, acute respiratory failure/bronchial obstruction/tachypnoea (vs 0 placebo subjects). In the All Studies Pool (including 303), there was 1 ESL subject with the SAE “cyanosis” during an episode of CHF in a subject with cardiac risk factors.

Infectious Diseases
In the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Double-blind Pool, a similar or slightly lower percentage of ESL subjects than placebo experienced TEAEs in the SOC Infections and Infestations (11.5% vs 12.7% and 9.5% vs 9.5%, respectively). In the Phase 3 Epilepsy Controlled Pool, there were 3 ESL subjects with the SAEs gastroenteritis, malaria, and sinusitis (vs 2 placebo subjects with the SAEs bronchitis, bronchopneumonia, pneumonia, and septic shock). In the Nonepilepsy Double-blind Pool, there were 8 (0.5%) ESL subjects with disparate SAEs of biliary tract infection, gastroenteritis, herpes virus infection, herpes zoster, infection, lung infection, pneumonia Klebsiella, pyelonephritis acute, septic shock, tracheobronchitis, viral infection (vs 1 or 0.2% placebo subjects with SAE viral infection).

Other Organ Systems
In the All Studies Pool (including 303 using the ADEVENTX dataset), there was a total of 1 ESL subject coded to pancreatitis (subject with history of “surgery of pancreas” developed pancreatitis on Day 394 after ESL discontinued for 20 days) along with 1 placebo subject coded to pancreatitis acute (304-038-03803). Additionally, there was 1 ESL subject (subject 206-743-743013) with the PT “pancreatic disorder” (without any further descriptions or enzyme values reported in the narrative) on Day 252 of ESL (diagnosed on the same day as the nonserious event of nonalcoholic steatohepatitis). In the ongoing studies, the Sponsor reported 1 ESL subject with the SAE pancreatitis (subject 050-6041-S001 who also had the SAEs of cholelithiasis obstructive, fallopian

tube cancer, ovarian cancer) (Safety Information Amendment 4/19/13 Table 1). The Sponsor did not report any SAEs of pancreatitis in the postmarketing database (Safety Information Amendment 4/19/13).

*Comment: Of note, there was 1 patient (BIAL 01654) with adverse events coded to abdominal pain and increased urine amylase who was reported to have an episode of acute pancreatitis in the case report (but lacked details on date of ESL initiation, concomitant medications, medical history, or outcome of the event).*

In the All Studies Pool (including 303 using the ADEVENTX dataset), there was a total of 1 ESL subject coded to the PT hyperthermia (for the event of fever in subject 114-000-00008).

In the All Studies Pool (including 303 using the ADEVENTX dataset), there was a total of 1 ESL subject (304-503-50304) coded to the PT Sjogren's syndrome and 1 ESL subject (302-351-80013) coded to the PTs vasculitis/vasculitis cerebral (along with 1 ESL subject, #304-955-95501, coded to leukocytoclastic vasculitis and purpura, described in Section 7.3.4 of this review). In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 6/27/13 that provided a narrative for subject 304-503-50304. Additionally, the Sponsor searched the clinical, ongoing studies and postmarketing databases and did not find any additional cases of Sjogren's syndrome.

> Subject 304-503-50304 was a 50 year-old male with a prior history of hand arthralgia who was diagnosed with "rheumatoid polyarthritis with Gougerot Sjogren" on Day 57 of ESL. No other information was reported or available (including signs and symptoms or serologic markers). Treatment included prednisone, methotrexate, and celecoxib. ESL was continued and the subject completed the study 6 weeks later.
>
> Subject 302-351-80013 was a 38 year-old male who was hospitalized due to worsening of headache on Day 78 of ESL. Brain MRI revealed cerebral vasculitis (new from MRI 10 months prior). Treatment included prednisolone. ESL was discontinued 8 days later due to ataxia and cerebral vasculitis. Past medical history included hypercholesterolemia, headache, positive antinuclear antibody, and MRI findings of high intensity foci in white matter. Event outcome was reported as ongoing *(However, there is no additional follow up information reported after 2005).*

In the Phase 3 Epilepsy Controlled Pool, there were slightly more ESL subjects (1.0%) than placebo subjects (0.7%) who developed the TEAE alopecia. Some (30%) of the ESL subjects who developed alopecia also experienced low free T4 or T3 levels. There were no SAEs. One of these ESL subjects discontinued due to alopecia:

> Subject 301-174-90449 with a history of hypothyroidism who developed hair loss on Day 58 of ESL along with dizziness, tremor, and gait disturbance. ESL was discontinued. Alopecia remained ongoing at last report. Thyroid function tests (free T4 and free T3) were WNL.

In conclusion, ESL use is not associated with any significant respiratory, infectious, or pancreatic disorders in this database. Furthermore, it is difficult to attribute the rare cases of hyperthermia, Sjogren's syndrome, and cerebral vasculitis (confounded by prior history of positive anti-nuclear antibodies) to ESL use. Alopecia may be associated with ESL-induced hypothyroidism.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The Sponsor submitted multiple datasets for the integrated adverse events data. In the August 31, 2012 resubmission, the Sponsor submitted the following integrated adverse event datasets:

- ADAE (main integrated adverse event dataset)
  - ADAE_EPI (adverse events for epilepsy studies)
  - ADAE_OTH (adverse events for nonepilepsy studies)
  - SDAEDTH (adverse events leading to deaths)
  - SDAEDTHC (adverse events leading to death – controlled data)
  - SDAEDTHU (adverse events leading to deaths- uncontrolled data)
  - SDAESAE (serious adverse events)
  - SDAESAEC (serious adverse events – controlled data)
  - SDAESAEU (serious adverse events-uncontrolled data)
  - SDDCAE (discontinuations due to adverse event)
  - SDDCAEC (discontinuations due to adverse event – controlled data)
  - SDDCAEU (discontinuations due to adverse event – uncontrolled data)
- ADAE_AU (adverse events with audit findings)
- ADSI (adverse events of special interest)
- ADAL (abuse liability events)
- ADAL_AU (abuse liability events including audit findings)

The ADAE_AU dataset included additional adverse events identified during the audits of all of the clinical sites of Studies 301 and 302. None of these events were adjudicated by site investigators. The Sponsor reported that inclusion of the audit-discovered potential events in the analyses as a conservative assumption that all were valid AEs did not result in an increase in the incidence rates of ≥2% for any TEAE (ISS Table 7.1.4.1). The auditors noted 2 sites from Poland in Study 2093-301 (Sites 301-174 and 301-175) to have significant GCP deficiencies related to recording of seizure diary information. The Sponsor reported that analysis of TEAEs reported at these 2 sites were conducted separately and revealed a similar adverse event profile and incidence rates for ESL overall (ISS Table 7.1.1.17).

In order to address the deficiencies in the above integrated adverse event datasets submitted in August 31, 2012 (listed in the Acknowledge Incomplete Response letter dated November 2, 2012), the Sponsor performed a comprehensive search to identify additional adverse events that were missing from the clinical database (referred to as the “2012 data review”). The Sponsor labeled these additional adverse events as “review events” if they were identified during the review of the narratives, case report forms, and Council for International Organizations of Medical Sciences (CIOMS) forms.

The Sponsor labeled the additional adverse events as “signs and symptoms” if they were separate adverse event terms originally subsumed under umbrella diagnoses. Of note, the Sponsor reports that signs and symptoms had already been identified during the conduct of Study 304 (and did not need to be added retrospectively). The 2012 data review also included “crossed out events” that were adverse events from the case report forms that were originally crossed out by the investigator.

Review events (excluding adverse event terms already present in the clinical database and excluding signs and symptoms or crossed out events) generated 243 new events in the 132 ESL treated subjects (12.9%) versus 98 in 47 placebo treated subjects (11.0%) (ISS Table 7.1.1.1.s1). TEAEs that increased by ≥1% in any ESL group (and > placebo) due to review events not already included in the previous database were nausea, fall, and menorrhagia (ISS Table 7.1.1.1.s1). Signs and symptoms generated 313 new events in 84 ESL treated subjects (8.2%) versus 89 in 32 placebo treated subjects (7.5%) (ISS Table 7.1.1.1.s3). TEAEs that increased by ≥1% in either the 800 mg or 1200 mg ESL group compared with the previous database included nausea, pyrexia, fall, balance disorder, and rhinorrhea (ISS Table 7.1.1.1.s3).

*Comment: I reviewed all of these “crossed out events” in the Sponsor’s listing of all new or changed records for the All Studies Pool (ISS Table 7.6.4.4.s1). A total of 59 ESL subjects had crossed out terms. The following table summarizes the terms that were crossed out in ≥2 ESL subjects in the All Studies Pool (including 303). I also reviewed all of the terms that were crossed out in 1 ESL subject and no significant new events were identified.*

**Table 99. Crossed-out Events in ≥2 ESL Subjects, All Studies Pool (including 303)**

| Dictionary-Derived Term | Total ESL |
|---|---|
| DIZZINESS | 5 ( 0.12%) |
| HEADACHE | 3 ( 0.07%) |
| COUGH | 3 ( 0.07%) |
| PYREXIA | 2 ( 0.05%) |
| SOMNOLENCE | 2 ( 0.05%) |
| INSOMNIA | 2 ( 0.05%) |
| VERTIGO | 2 ( 0.05%) |
| UNEVALUABLE EVENT | 2 ( 0.05%) |
| NAUSEA | 2 ( 0.05%) |
| ATRIOVENTRICULAR BLOCK FIRST DEGREE | 2 ( 0.05%) |
| DEPRESSION | 2 ( 0.05%) |
| ABDOMINAL PAIN UPPER | 2 ( 0.05%) |

Source: Created by the reviewer using JReview (ADEVENTS: AETYPE= “Crossed out AE", AEREMOV≠ “Y”, AEDECOD and ADSL: DOSCATH)

The Sponsor reported that inclusion of the findings of the 2012 data review (review events, signs and symptoms, and crossed out events) as a conservative assumption that all were valid AEs did not result in any clinical meaningful increase in the incidence rates for any TEAE when compared to the confirmed AEs plus the audit findings. The Sponsor reported that the only TEAE that increased by ≥2% in any treatment group was nausea compared with the original data (including the audit findings) (ISS Table 7.1.4.1.s2). Overall, the 2012 data review resulted in addition of a small number of new events: 1.0%, 2.2% and 2.6% for the ESL 400 mg, 800 mg, and 1200 mg groups, respectively, and 2.8% for the placebo group (ISS Table 7.1.4.1.s5). Of note, some of these events were in subjects who already had other adverse events reported.

New integrated adverse event datasets that included these "review events," "signs and symptoms," and "crossed out events" identified during the 2012 data review were submitted by the Sponsor when this NDA was resubmitted on February 10, 2013.

- ADEVENTS (includes all additional events identified during the 2012 data review and previous audit findings)
  - ADEV_EPI (adverse events for epilepsy studies)
  - ADEV_OTH (adverse events for nonepilepsy studies)
  - SDEVDTH (adverse events leading to deaths)
  - SDEVDTHC (adverse events leading to death – controlled data)
  - SDEVDTHU (adverse events leading to deaths- uncontrolled data)
  - SDEVSAE (serious adverse events)
  - SDEVSAEC (serious adverse events – controlled data)
  - SDEVSAEU (serious adverse events-uncontrolled data)
  - SDDCEV (discontinuations due to adverse event)
  - SDDCEVC (discontinuations due to adverse event – controlled data)
  - SDDCEVU (discontinuations due to adverse event – uncontrolled data)
- ADEVENTX (ADEVENTS excluding crossed out events)
- ADSIEVNT (adverse events of special interest)
- ADSIEVTX (adverse events of special interest – excluding crossed out events)
- ADALEVNT (abuse liability events)
- ADALEVTX (abuse liability events- excluding crossed out events)

*Comment: The Sponsor reports that the "review events" and "signs and symptoms" were not adjudicated by site investigators. However, the "crossed out events" were adjudicated by site investigators to not be considered AEs. Therefore, in this review, I will mainly use the integrated adverse event dataset (ADEVENTX) that includes the "review events" and "signs and symptoms" but excludes the "crossed out events."*

*It is important to report that there was an extremely large number of variables in every integrated dataset that the Sponsor submitted with this NDA. As an example, the ADEVENTX dataset contained over 400 variables. These datasets were not formulated according to the CDISC standards. In order to be able to accurately review these datasets (and choose the correct variables), the Sponsor was requested to provide the*

*algorithms and variables that were used to create all of the tables in the ISS. The Sponsor prepared and submitted a Reviewer Guide for Tables dated 2/3/13. I analyzed these datasets using the variables delineated by the Sponsor in this Reviewer Guide. Specifically, for all of the analyses performed in this review, I used the following variables: SAFETY='Y' to subset the dataset to the safety population and AETRTEM='Y' to subset the adverse events to the treatment-emergent events (along with AEREMOV≠Y for the analyses performed using the ADEVENTX dataset). The additional variables that I used are listed below the tables in the review.*

Phase 3 Epilepsy Controlled Pool
The following table summarizes the number of subjects with TEAEs for the Phase 3 Epilepsy Controlled Pool and the individual Phase 3 epilepsy studies. A dose-response relationship is present with the number of TEAEs increasing with increasing ESL dose (except for Study 302). There were fewer TEAEs reported in Study 301 (and 303) than in Study 302 or 304 for every treatment group.

**Table 100. TEAEs, Phase 3 Epilepsy Controlled Pool**

| Subjects with any TEAE | **Placebo n (%)** | **ESL n (%)** | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=426 | n=196 | n=415 | n=410 | n=1021 |
| Using ADAE dataset | 226 (53.1) | 120 (61.2) | 281 (67.7) | 303 (73.9) | 704 (69.0) |
| Study 301 Part 1 | 32 (31.4) | 45 (45.0) | 51 (52.0) | 62 (60.8) | 158 (52.7) |
| Study 302 Part 1 | 70 (70.0) | 75 (78.1) | 85 (84.2) | 78 (79.6) | 238 (80.7) |
| Study 304 Part 1 | 124 (55.4) | | 145 (67.1) | 163 (77.6) | 308 (72.3) |
| (Study 303 Part 1) | 36 (41.1) | | 46 (54.1) | 49 (61.3) | 95 (57.6) |
| Using ADEVENTX | 246 (57.7) | 131 (66.8) | 295 (71.1) | 320 (78.0) | 746 (73.1) |

Source: ISS Table 7.1.1.1 and 7.1.4.1.s1

*Comment: After analyzing the TEAEs using the different ISS adverse event datasets, there were similar risk differences (15.4%) between the total ESL group and the placebo group using the ADEVENTX dataset (that included audit findings of potential events, review events, and signs and symptoms, but excluded crossed out events) and the ADAE dataset (15.9%).*

In terms of severity, most of the TEAEs in the Phase 3 Epilepsy Controlled Pool were considered mild or moderate. Mild TEAEs occurred more frequently in the placebo group than the total ESL group. Moderate and severe TEAEs occurred more frequently in the higher dose groups (800 mg and 1200 mg) than the placebo group.

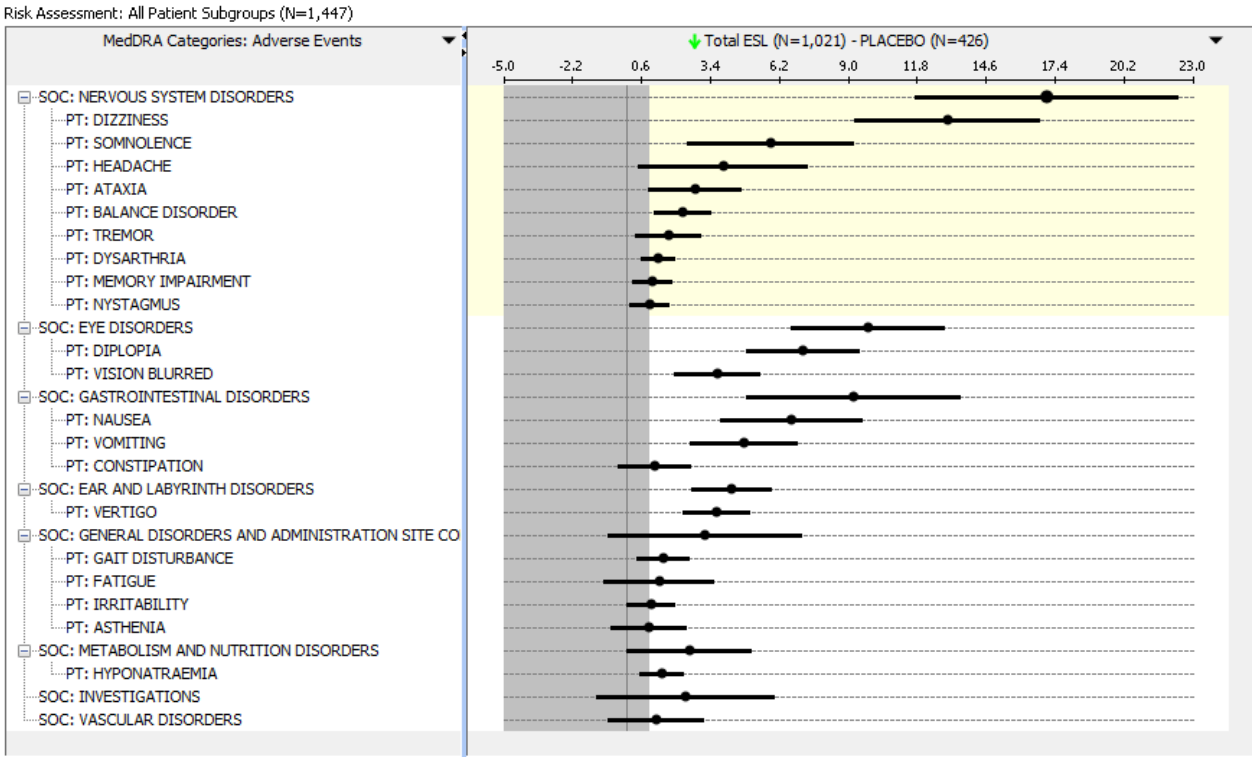
**Table 101. Severity of TEAEs, Phase 3 Epilepsy Controlled Pool**

| **Severity of TEAE** | **Placebo n (%)** | **ESL n (%)** | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| Subjects with any TEAEs | 226 (100) | 120 (100) | 281 (100) | 303 (100) | 704 (100) |
| Mild | 98 (43) | 56 (47) | 112 (40) | 103 (34) | 271 (38) |
| Moderate | 106 (47) | 46 (38) | 131 (47) | 146 (48) | 323 (46) |
| Severe | 21 (9.3) | 18 (15) | 37 (13) | 54 (18) | 109 15 |
| Missing | 5 (2.2) | 8 (6.7) | 5 (1.8) | 5 (1.7) | 18 (2.6) |

Source: ISS Table 7.1.8

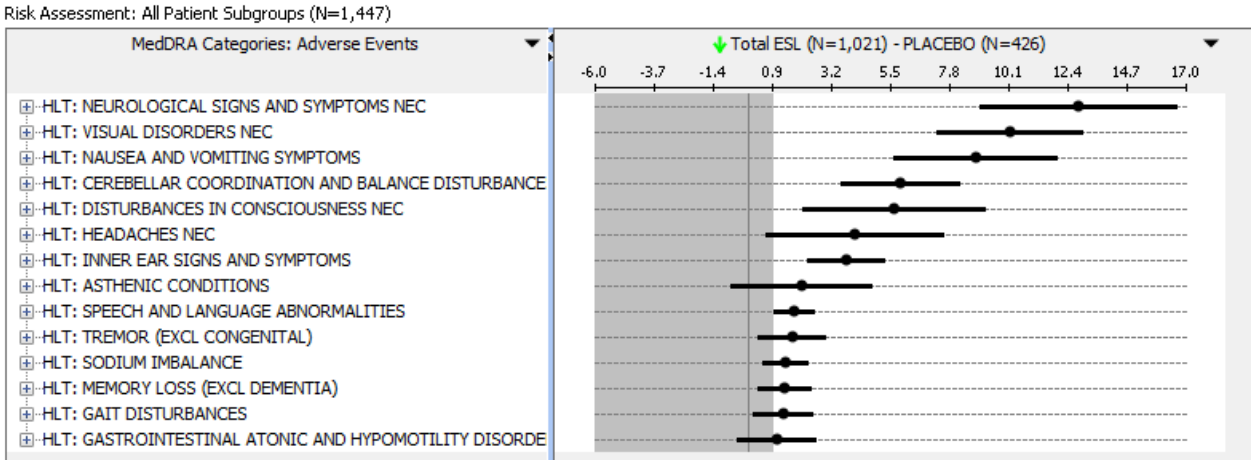
The following forest plots summarize the TEAEs by SOC, HLT, and PT with a risk difference of ≥ 1% between the total ESL group and placebo (>0.5% for PTs). The following SOCs had the largest risk differences between the total ESL and placebo groups: Nervous system, Eye, Gastrointestinal, Ear/Labyrinth, and General disorders.

**Figure 16. TEAE by SOC with Risk Difference ≥ 1.0% (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool**




Source: Created by the reviewer using JReview (ADEVENTX: AEHLT and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

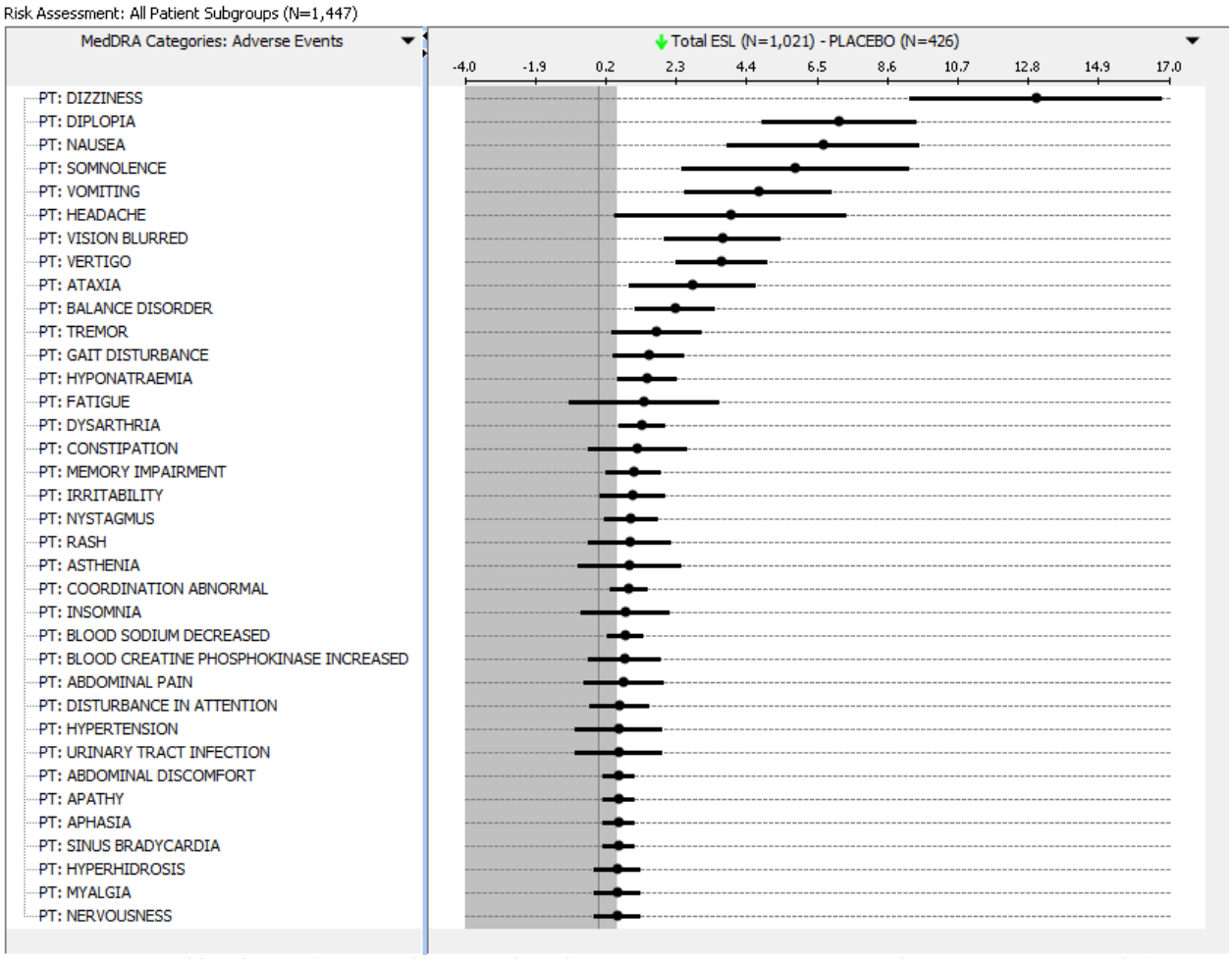
**Figure 17. TEAEs by HLT with Risk Difference ≥1.0% (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool**



Source: Created by the reviewer using JReview (ADEVENTX: AEHLT and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

The largest differences between the total ESL and placebo groups were in the incidences of the following PTs: dizziness, diplopia, nausea, somnolence, vomiting, headache, vision blurred, vertigo, ataxia, balance disorder, tremor, gait disturbance, hyponatremia, fatigue, dysarthria, constipation, memory impairment, irritability, nystagmus, and rash.

**Figure 18. TEAEs by PT with Risk Difference >0.5% (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool**

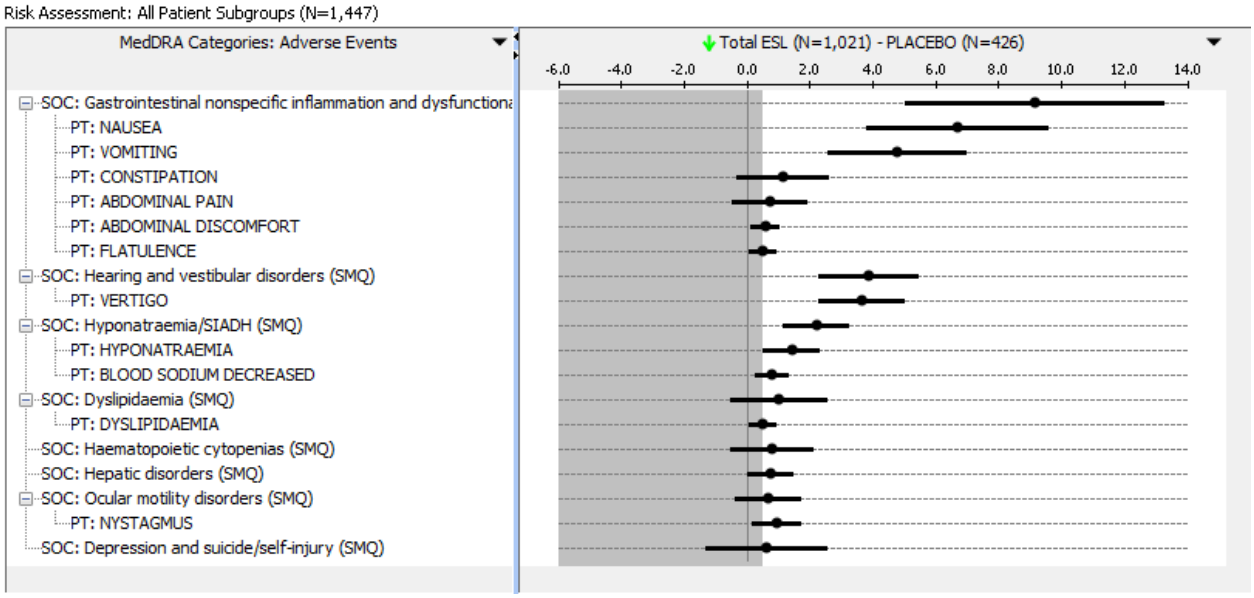



Source: Created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

The following forest plot summarizes the TEAEs by Standardized MedDRA Query (SMQ) with a risk difference of ≥0.5% between the total ESL group and placebo in the Phase 3 Epilepsy Controlled Pool. The following SMQs had the largest risk differences between the total ESL and placebo groups: Gastrointestinal nonspecific inflammation

and dysfunctional conditions (nausea/vomiting), Hearing and vestibular disorders (vertigo), and Hyponatraemia/SIADH. All of the algorithmic SMQs had risk differences <0.25% between the total ESL group and placebo.

**Figure 19. SMQs (Narrow PTs) with Risk Difference ≥ 0.5% (Total ESL-Placebo), Phase 3 Epilepsy Controlled Pool**




Source: Created by the reviewer using MAED tool (ADEVENTX: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')

The following table summarizes the TEAEs that occurred in at least 2% of the subjects and more frequently than placebo in any dose group for the Phase 3 Epilepsy Controlled Pool. The events that the Sponsor considered to be associated with ESL treatment (based on notably greater incidences at higher ESL doses and greater than placebo) included dizziness, somnolence, headache, ataxia, tremor, balance disorder, dysarthria, nausea, vomiting, diplopia, vision blurred, fatigue, asthenia, hyponatraemia, rash, and vertigo (ISS Table 15).

*Comment: I agree with these adverse drug reactions. However, I would also include the following PTs with dose-response relationships with ESL treatment: memory impairment and nystagmus.*

**Table 102. Adverse Reactions, Phase 3 Epilepsy Controlled Pool (Events ≥ 2% of subjects and more frequent than placebo in any dose group)**

| MedDRA System Organ Class<br>Preferred Term | Placebo<br>n=426<br>% | ESL % | | | |
|---|---|---|---|---|---|
| | | 400 mg<br>n=196 | 800 mg<br>n=415 | 1200 mg<br>n=410 | Total ESL<br>n=1021 |
| Subjects with any TEAE | 58 | 67 | 71 | 78 | 73 |
| | | | | | |
| Cardiac disorders | | | | | |
| Bradycardia | 0 | 2 | 0 | <1 | <1 |
| Ear and Labyrinth disorders | | | | | |
| Vertigo | <1 | 3 | 2 | 6 | 4 |
| Eye disorders | | | | | |
| Diplopia | 2 | 7 | 9 | 11 | 10 |
| Vision blurred | 1 | 5 | 6 | 5 | 5 |
| Visual impairment | 1 | 0 | 2 | 1 | 1 |
| Gastrointestinal disorders | | | | | |
| Nausea | 5 | 9 | 10 | 16 | 12 |
| Vomiting | 3 | 5 | 6 | 10 | 7 |
| Diarrhea | 3 | 2 | 4 | 2 | 3 |
| Constipation | 1 | 4 | 2 | 2 | 3 |
| Abdominal pain | 1 | 2 | 2 | 2 | 2 |
| Toothache | 1 | 2 | <1 | 2 | 1 |
| Gastritis | <1 | 0 | 2 | <1 | 1 |
| General disorders/administration site conditions | | | | | |
| Fatigue | 4 | 3 | 4 | 7 | 5 |
| Asthenia | 2 | 2 | 2 | 3 | 3 |
| Gait disturbance | <1 | 2 | 2 | 2 | 2 |
| Irritability | <1 | 4 | 1 | 1 | 1 |
| Edema peripheral | 1 | 0 | 2 | 1 | 1 |
| Infections and Infestations | | | | | |
| Influenza | 2 | 4 | 2 | 2 | 3 |
| Urinary tract infection | 1 | 1 | 2 | 2 | 2 |
| Injury, poisoning and procedural complications | | | | | |
| Fall | 1 | 2 | 3 | 1 | 2 |
| Contusion | 1 | 2 | 1 | 1 | 1 |
| Investigations | | | | | |
| Weight increased | 2 | 4 | 1 | 2 | 2 |
| Blood CPK increased | 1 | 4 | 1 | 1 | 1 |
| Blood cholesterol increased | <1 | 2 | 1 | <1 | 1 |
| Blood pressure decreased | <1 | 2 | <1 | <1 | 1 |
| Blood pressure systolic decreased | 0 | 2 | 0 | <1 | <1 |
| Metabolism and nutrition disorders | | | | | |
| Hyponatremia | <1 | 1 | 2 | 2 | 2 |
| Musculoskeletal & connective tissue disorders | | | | | |
| Arthralgia | 1 | 2 | 2 | 0 | 1 |
| Nervous system disorders | | | | | |
| Dizziness | 9 | 16 | 20 | 28 | 22 |
| Somnolence | 8 | 13 | 11 | 18 | 14 |
| Headache | 9 | 12 | 13 | 15 | 13 |
| Ataxia | 2 | 4 | 4 | 6 | 5 |

| | | | | | |
|---|---|---|---|---|---|
| Balance disorder | <1 | 1 | 3 | 3 | 3 |
| Tremor | <1 | 1 | 2 | 4 | 3 |
| Dysarthria | 0 | 0 | 1 | 2 | 1 |
| Memory impairment | <1 | 1 | 1 | 2 | 1 |
| Nystagmus | <1 | 1 | 1 | 2 | 1 |
| Psychiatric disorders | | | | | |
| Depression | 2 | 3 | 1 | 3 | 2 |
| Insomnia | 1 | 2 | 2 | 2 | 2 |
| Nervousness | <1 | 2 | <1 | 1 | 1 |
| Reproductive system/breast disorders | | | | | |
| Menorrhagia | <1 | 2 | <1 | 0 | <1 |
| Respiratory, thoracic & mediastinal disorders | | | | | |
| Cough | 1 | 0 | 2 | 1 | 1 |
| Skin & subcutaneous tissue disorders | | | | | |
| Rash | 1 | 1 | 1 | 3 | 2 |
| Pruritus | 1 | 2 | 1 | 1 | 1 |
| Alopecia | 1 | 2 | <1 | 1 | 1 |
| Hyperhidrosis | <1 | 2 | <1 | <1 | 1 |
| Vascular disorders | | | | | |
| Hypertension | 1 | 2 | 1 | 2 | 2 |

Source: Safety Amendment 2/27/13 Table 7.1.2.1a.s1

Phase 3 Epilepsy Uncontrolled and Controlled Pool

The following tables summarize the TEAEs by SOC and by PT in the Phase 3 Epilepsy Controlled and Uncontrolled Pool. The MedDRA SOC for which ESL subjects most frequently reported a TEAE was Nervous System Disorders (56.6%), followed by Gastrointestinal disorders (29.9%), Infections and Infestations (21.6%), General disorders and administration site conditions (20.4%), Investigations (19.8%), and Eye Disorders (19.1%). These TEAEs reported by ESL subjects after pooling together the open-label extension trials are similar to those reported in the double-blind trials except for mainly the TEAEs in the SOC Infections and Infestations (nasopharyngitis, influenza, upper respiratory infection).

**Table 103. TEAEs by SOC, Phase 3 Epilepsy Uncontrolled and Controlled Pool**

| Body System or Organ Class | Total ESL |
|---|---|
| NERVOUS SYSTEM DISORDERS | 676 (56.6%) |
| GASTROINTESTINAL DISORDERS | 357 (29.9%) |
| INFECTIONS AND INFESTATIONS | 258 (21.6%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 243 (20.4%) |
| INVESTIGATIONS | 237 (19.8%) |
| EYE DISORDERS | 228 (19.1%) |
| PSYCHIATRIC DISORDERS | 174 (14.6%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 139 (11.6%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 125 (10.5%) |
| METABOLISM AND NUTRITION DISORDERS | 107 (9.0%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 103 (8.6%) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 81 (6.8%) |
| VASCULAR DISORDERS | 76 (6.4%) |
| EAR AND LABYRINTH DISORDERS | 74 (6.2%) |
| CARDIAC DISORDERS | 43 (3.6%) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 40 (3.4%) |
| RENAL AND URINARY DISORDERS | 36 (3.0%) |

| | |
|---|---|
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 31 (2.6%) |
| SURGICAL AND MEDICAL PROCEDURES | 21 (1.8%) |
| ENDOCRINE DISORDERS | 17 (1.4%) |
| IMMUNE SYSTEM DISORDERS | 12 (1.0%) |
| HEPATOBILIARY DISORDERS | 8 (0.7%) |
| SOCIAL CIRCUMSTANCES | 6 (0.5%) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED | 6 (0.5%) |
| CONGENITAL, FAMILIAL AND GENETIC DISORDERS | 2 (0.2%) |
| Subjects with TEAEs | 955 (80.0%) |
| Total # of Subjects | 1194 (100.0%) |

Source: Created by reviewer using JReview (ADEVENTX: AEBODSYS and ADSL: DOSCATH) for studies 301, 302, 304

**Table 104. TEAEs by PT (in ≥2% of ESL subjects), Phase 3 Epilepsy Uncontrolled and Controlled Pool**

| Dictionary-Derived Term | Total ESL |
|---|---|
| DIZZINESS | 328 (27.5%) |
| HEADACHE | 220 (18.4%) |
| SOMNOLENCE | 210 (17.6%) |
| NAUSEA | 155 (13.0%) |
| DIPLOPIA | 133 (11.1%) |
| VOMITING | 105 (8.8%) |
| ATAXIA | 76 (6.4%) |
| PARTIAL SEIZURES | 71 (5.9%) |
| VISION BLURRED | 70 (5.9%) |
| FATIGUE | 67 (5.6%) |
| NASOPHARYNGITIS | 65 (5.4%) |
| VERTIGO | 63 (5.3%) |
| INFLUENZA | 55 (4.6%) |
| DIARRHOEA | 53 (4.4%) |
| ABDOMINAL PAIN UPPER | 45 (3.8%) |
| ASTHENIA | 40 (3.4%) |
| BACK PAIN | 39 (3.3%) |
| CONSTIPATION | 39 (3.3%) |
| DEPRESSION | 39 (3.3%) |
| TREMOR | 38 (3.2%) |
| ANXIETY | 36 (3.0%) |
| BLOOD PRESSURE DIASTOLIC DECREASED | 35 (2.9%) |
| PYREXIA | 35 (2.9%) |
| WEIGHT INCREASED | 35 (2.9%) |
| INSOMNIA | 33 (2.8%) |
| DECREASED APPETITE | 33 (2.8%) |
| FALL | 32 (2.7%) |
| HYPERTENSION | 31 (2.6%) |
| BALANCE DISORDER | 30 (2.5%) |
| ABDOMINAL PAIN | 30 (2.5%) |
| RASH | 27 (2.3%) |
| URINARY TRACT INFECTION | 25 (2.1%) |
| HEAD INJURY | 25 (2.1%) |
| UPPER RESPIRATORY TRACT INFECTION | 24 (2.0%) |
| TOOTHACHE | 24 (2.0%) |

Source: Created by reviewer using JReview (ADEVENTX: AEDECOD and ADSL: DOSCATH) for studies 301, 302, 304

In Study 201, TEAEs occurred in ≥ 2 ESL subjects and > placebo subjects in the following SOCs: Ear and labyrinth disorders (vertigo, ear buzzing), Gastrointestinal disorders (diarrhea, dry mouth, dyspepsia, nausea, vomiting, stomach discomfort), Nervous system disorders (concentration impaired, dizziness, headache, incoordination,

somnolence), Skin and subcutaneous tissue disorders (hair loss), and Vascular (hypertension) (Study 201 CSR Table S02).

In Study 202, the most frequent reported TEAEs were upper respiratory tract infection and somnolence (2093-202 CSR Tables 52-59). Of note, aggressive behavior, aggression aggravated, and psychomotor agitation were seen in 1 ESL subject each (in the 7-11 year-old group and were not SAEs).

Nonepilepsy Double-blind Pool
In the Nonepilepsy Double-blind Pool, the incidence of developing TEAEs was higher in the ESL subjects than in the placebo subjects. The following table summarizes the incidence of TEAEs leading to discontinuation by randomized dose group and indication.

*Comment: After analyzing the SAEs using different ISS adverse event datasets, there were similar risk differences between the total ESL group and the placebo group using the ADEVENTX dataset (that included audit findings of potential events, review events, and signs and symptoms, but excluded crossed out events) and the ADAE dataset.*

**Table 105. TEAEs, Nonepilepsy Pooled Groups**

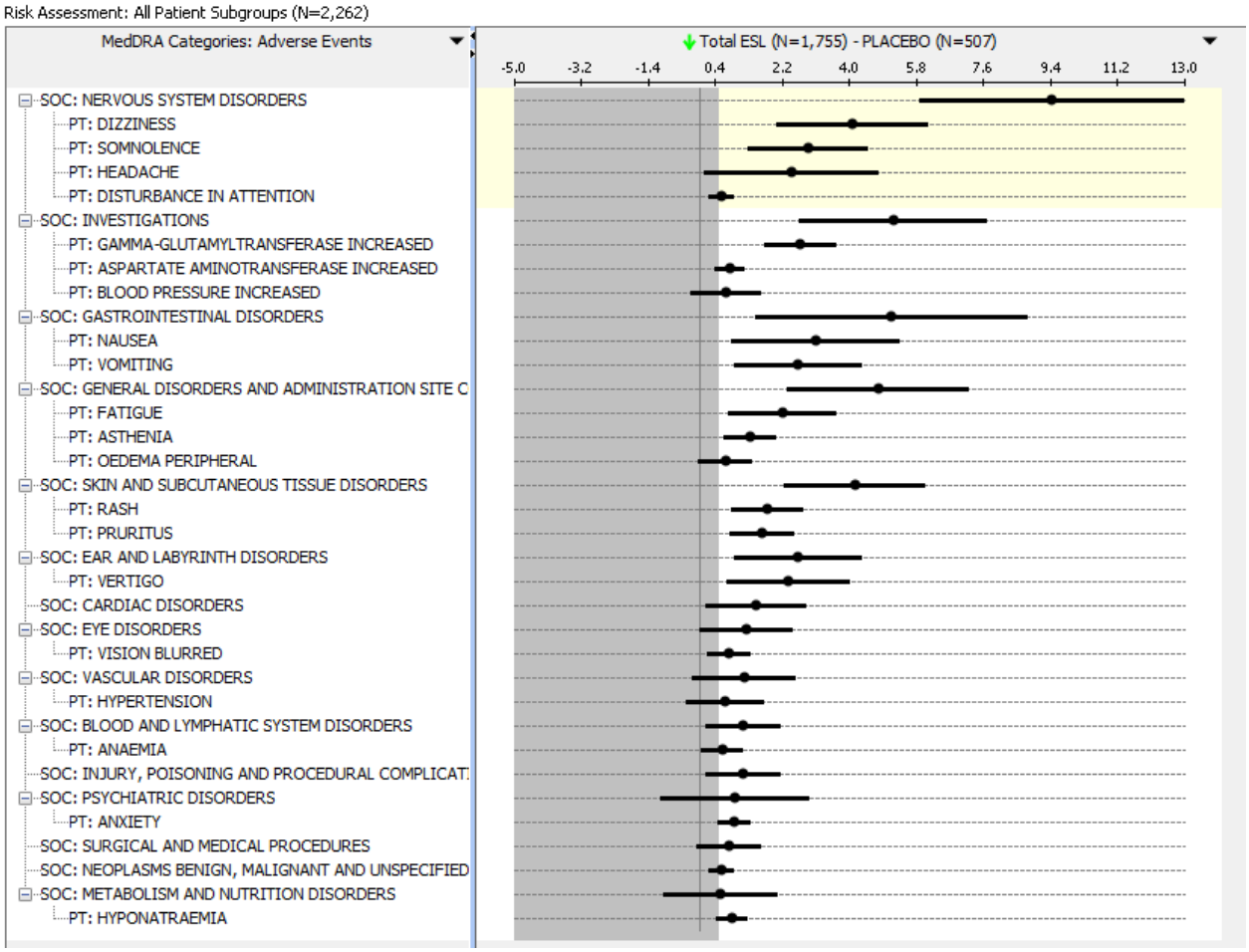
| Pooled Group | Placebo n (%) | ESL n (%), Randomized Dose Groups | | | | |
|---|---|---|---|---|---|---|
| | | <600 mg | 600-<1000 | 1000-<1400 | ≥1400 mg | Total |
| Total # of subjects | | | | | | |
| Bipolar (203+204) | 51 | 0 | 129 | 9 | 10 | 148 |
| Neuropathy (206+207) | 189 | 0 | 369 | 376 | 190 | 936 |
| Migraine/Fibromyalgia | 267 | 130 | 270 | 271 | 0 | 671 |
| Nonepilepsy DB Pool* | 507 | 130 | 768 | 657 | 200 | 1755 |
| Nonepi Controlled Pool^ | 411 | 303 | 571 | 321 | 99 | 1294 |
| | | | | | | |
| Subjects with TEAEs | | | | | | |
| Bipolar (203+204) | 21 (41) | 0 | 67 (52) | 9 (100) | 10 (100) | 86 (58.1) |
| Neuropathy (206+207) | 64 (34) | 0 | 165 (45) | 186 (49) | 101 (53.2) | 452 (48.3) |
| Migraine/Fibromyalgia | 124 (46) | 86 (66) | 160 (59) | 169 (62) | 0 | 415 (61.8) |
| Nonepilepsy DB Pool* | 209 (41) | 86 (66) | 392 (51) | 364 (55) | 111 (55.5) | 953 (54.3) |
| using ADEVENTX | 215 (42) | 87 (67) | 410 (53) | 374 (57) | 116 (58) | 987 (56.2) |
| Nonepi Controlled Pool^ | 176 (43) | 181 (60) | 328 (57) | 177 (55) | 48 (48.5) | 734 (56.7) |
| using ADEVENTX | 178 (43) | 187 (62) | 337 (59) | 184 (57) | 48 (48.5) | 756 (58.4) |

Source: ISS Tables 7.4.1.1, 7.4.1.1.s1 and created by the reviewer using JReview (ADEVENTX and ADSL) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)
*Nonepilepsy DB Pool includes Study 206 Part 1
^Nonepilepsy Controlled Pool excludes Study 206 Part 1 and uses mean dose group

The following forest plot summarizes the TEAEs by SOC (and by PT) with a risk difference of ≥ 0.5% between the total ESL group and placebo. The largest risk difference between ESL and placebo subjects was identified for the SOC Nervous system disorders (PTs dizziness, somnolence, headache, disturbance in attention). The distribution of the TEAEs was different between the epilepsy and nonepilepsy

populations. In the nonepilepsy populations, there was a greater risk difference for the following adverse events: GGT increased, AST increased, BP increased, oedema peripheral, rash, pruritus, hypertension, anaemia, and anxiety.

**Figure 20. TEAEs with ≥0.5% Risk Difference (Total ESL-Placebo), Nonepilepsy Double-blind Pool**




Source: Created by the reviewer using JReview (ADEVENTX: AEDECOD, AEBODSYS and ADSL: TRTP1) for studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2')

Phase 1 Study Pool

In the Phase I Study Pool, there was a greater incidence of TEAEs for the total ESL group (68.6%) compared with placebo (41.7%) (ISS Table 7.5.1.1.s2). The SOCs with the highest incidence of TEAEs included nervous system disorders and gastrointestinal disorders. Events (PTs) with ≥2% greater incidence for the total ESL group compared with placebo included somnolence, headache, dizziness, paraesthesia, paraesthesia oral, nausea, vomiting, fatigue, asthenia, pruritus, upper respiratory tract infection, constipation, dry mouth, abdominal pain, hypoaesthesia oral, back pain, disturbance in attention, oropharyngeal pain, and rash.

In the hepatic impairment Study 111 in mild to moderate hepatic impairment, 77.8% (7/9) of the ESL subjects reported the following TEAEs: abdominal pain lower, abdominal pain upper, diarrhoea, dyspepsia, nausea, vomiting, chills, pyrexia, scratch, wound, blood magnesium decreased, arthralgia, back pain, dizziness, headache, hepatic encephalopathy, epistaxis, haemoptysis, and pruritus (reported in 1 or 2 subjects each). In the renal impairment Study 112, 56.3% (18/32) of the ESL subjects reported the following TEAEs: vomiting, bacterial infection, upper respiratory tract infection, urinary tract infection, gout, dizziness, headache, somnolence, and nasal congestion.

*Comment: Of note, in the All Studies Pool (including 303 using the ADEVENTX dataset), I identified 14 ESL subjects with the PT "unevaluable event." The verbatim terms are listed below (along with information regarding SAEs and TEAEs leading to DC):*

*"intensive physical activity" (210-523-523008, data review event during SAE of increased CPK),*
*"patient did not communicate" (205-548-203063, data review event during SAE/DC of depression),*
*"special projects elaboration" (205-544-203176, data review event during SAE/DC of bipolar d/o),*
*"I even need to spend more time with my wife (as subject stated)" (subject 203-334-203052, data review event during SAE of mania),*
*"slightly elevated CT02(A) 11.6 mmol/L (6.7-10.3 mmol/L)" (302-385-80426, data review event during death due to SAE of drowning),*
*"TAG:1.50" (206-566-566007, data review event during SAE of myocardial infarction),*
*"conmed clonazepam," "conmed lorazepam,"*
*"hypolipemiant," "frequency,"*
*"exclusion soft part process right upper arm,"*
*"micrograms on 31Jan2012," "aware of head/brain,"*
*"con med page. medication 1-seroquel. no information connected with this drug,"*
*"post-surgery: no surgical complication"*

## 7.4.2 Laboratory Findings

In their NDA presentation, the Sponsor separately summarized hematology (including blood coagulation parameters), chemistry (including thyroid function parameters), and urinalysis results. In the ISS, the Sponsor provided measures of central tendency, shift changes, and potentially clinically significant values for hematology and chemistry parameters. The Sponsor also provided categorical summaries for urinalysis parameters. Additional analyses were performed for serum sodium values. This approach was acceptable to the reviewer.

### 7.4.2.1 Hematology

The following table summarizes the potentially clinically significant changes (for subjects with normal values at baseline) in hematology parameters for the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Controlled Pool. In both of the DB pools, the incidences of PCS hematology changes were small and similar between the placebo and total ESL groups.

**Table 106. PCS Hematology Values for Subjects Normal at Baseline**

| | Phase 3 Epilepsy Controlled Pool | | | | Nonepilepsy Controlled Pool^ | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| **Parameter** | n | #PCS (%) | n | #PCS (%) | n | #PCS (%) | n | #PCS (%) |
| RBC ≤3.5 $x10^6/mm^3$ | 418 | 4 (1.0) | 980 | 15 (1.5) | 387 | 0 | 1215 | 10 (0.8) |
| Hematocrit ≤37% (male) or ≤32% (females) | 412 | 5 (1.2) | 975 | 17 (1.7) | 382 | 4 (1.1) | 1214 | 26 (2.2) |
| Hemoglobin ≤11.5 g/dL (M) or ≤9.5 g/dL (female) | 418 | 3 (0.7) | 981 | 4 (0.4) | 385 | 3 (0.8) | 1211 | 9 (0.7) |
| WBC ≤2.8 $x10^3/mm^3$ | 418 | 2 (0.5) | 984 | 12 (1.2) | 390 | 4 (1.0) | 1215 | 10 (0.8) |
| Neutrophils <1.5$x10^3/mm^3$ | 414 | 10 (2.4) | 959 | 22 (2.3) | 348 | 11 (3.2) | 1093 | 26 (2.4) |
| Platelets ≤75 $x10^3/mm^3$ | 420 | 1 (0.2) | 986 | 2 (0.2) | 386 | 0 | 1211 | 2 (0.2) |
| | | | | | | | | |
| INR >1.5 xULN | 197 | 2 (1.0) | 569 | 5 (0.9) | 48 | 0 | 134 | 0 |
| aPTT >1.5 xULN | 189 | 6 (3.2) | 556 | 19 (3.4) | 42 | 0 | 114 | 0 |

Source: ISS Tables 9.1.8, 9.4.7.1 and Safety Information Amendment 5/20/13 Table 9.1.8.r1
^excludes Study 206

*Comment: I noted that for the nonepilepsy controlled pool, the number of subjects who had values reported for WBC differentials (1093 and 348 for the ESL and placebo groups, respectively) was less than the number of subjects who had values for WBC (1215 and 390, respectively). Upon further examination of the case report forms for the subjects in the bipolar studies (studies 203, 204, 205), the WBC differentials that were missing from the analysis datasets were indeed present within the CRFs (but recorded as a percentage rather than absolute values). The WBC differentials that were recorded as absolute values in the CRF were integrated in the analysis datasets. In the Safety Information Amendment dated 8/1/13, the Sponsor explained that they "elected to exclude the WBC differentials for these studies from the integrated dataset" and confirmed that the missing WBC differentials were limited to the 3 bipolar studies. The Sponsor justified their decision to exclude these values from the integrated dataset due to "challenges in accurate interpretation of WBC differential data from these studies" and "analysis of medical risk in context of other data." The Sponsor gave multiple examples of highly variable results between sites, within sites and within multiple reports for an individual subject. Furthermore, the Sponsor stated that the missing WBC differential data constitutes data from approximately 30 subjects, "which is small in comparison to the data available for 1294 ESL treated subjects from nonepilepsy studies and 1021 ESL treated subjects from epilepsy studies."*

*I do not agree with the Sponsor's approach and explanation. Using the Sponsor's ADLAB integrated laboratory dataset, I identified that while all of the ESL subjects had WBC counts measured, approximately only one-fourth of ESL subjects (25.0-30.4%) had WBC differentials reported (in absolute values for basophils, eosinophils, lymphocytes, monocytes, and neutrophils). Therefore, 70-75% of the ESL subjects in the bipolar studies (more than 100 subjects) were missing WBC differentials rather than 30 subjects (as reported by the Sponsor above). These missing values do preclude a comprehensive assessment of hematologic adverse events such as neutropenia,*

*lymphopenia, and eosinophilia. If any of these events (using PCS values) occurred in these ~100 subjects, I would not be able to identify these cases using the integrated datasets provided by the Sponsor. However, the percentage of subjects with missing WBC differentials is low compared to the overall number of ESL-treated subjects (<5%).*

The following table summarizes the consecutive potentially clinically significant values for ≥2 visits (for subjects with normal values at baseline) in hematology parameters for the Phase 3 Epilepsy Controlled Pool. There were very few subjects with consecutive PCS hematology values (all ≤0.5%).

**Table 107. Consecutive PCS Hematology Values for ≥ 2 visits (for subjects with normal values at baseline), Phase 3 Epilepsy Controlled Pool**

| Category | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=426 | n=196 | n=415 | n=410 | n=1021 |
| RBC ≤3.5 x$10^6$/$mm^3$ | 0 | 1 (0.5) | 2 (0.5) | 0 | 3 (0.3) |
| Hematocrit ≤37% (male) or ≤32% (females) | 1 (0.2) | 0 | 0 | 2 (0.5) | 2 (0.2) |
| Hemoglobin ≤11.5 g/dL (M) or ≤9.5 g/dL (female) | 1 (0.2) | 0 | 0 | 0 | 0 |
| WBC ≤2.8 x$10^3$/$mm^3$ | 0 | 2 (1.0) | 0 | 0 | 2 (0.2) |
| Neutrophils <1.5x$10^3$/$mm^3$ | 0 | 1 (0.5) | 0 | 0 | 1 (0.1) |
| Platelets ≤75 x$10^3$/$mm^3$ | 1 (0.2) | 0 | 0 | 0 | 0 |

Source: Safety Information Amendment 5/20/13 Table 9.1.12.8.r1

Additionally, the clinical significance of the lab values, as assessed by the investigator and documented as adverse events, was summarized for hematology parameters in ISS Table 9.1.9. The incidences of these clinically significant post-dose laboratory values were small and slightly higher in ESL subjects (2.3%) than placebo subjects (1.4%). The following values occurred in more than 1 ESL subject and greater than placebo: leukocytes (0.4% vs 0.2%) and neutrophils (0.5% vs 0).

In Study 201, the clinically relevant changes that were documented as AEs included increased INR and anaemia in ESL subjects and leukopenia, leukocytosis, and platelets decreased in placebo subjects (Study 201 CSR Table 63).

In the Phase 1 Study Pool, the following potentially clinically significant values for hematology parameters occurred in ESL subjects greater than placebo: low RBC (0.4% vs 0), low hemoglobin (0.6% vs 0), low leukocytes (0.9% vs 0), low neutrophils (2.3% vs 0.7%) (ISS Table 9.5.1). The incidence of clinically significant (as assessed by the investigator) post-dose laboratory values overall was higher in the total ESL group (4.7%) compared with placebo (1.7%). The following values occurred in more than 1 ESL subject and greater than placebo: leukocytes (0.9% vs 0), neutrophils (0.7% vs 0), and platelets (0.2% vs 0) (ISS Table 9.5.2).

The following table summarizes the mean changes from baseline to the end of treatment for the hematology parameters. The mean values were within normal ranges at baseline and the end of treatment for all treatment groups. The mean changes were similar in the ESL and placebo groups except for slightly lower mean values for RBC, hemoglobin, and hematocrit in the ESL group compared with placebo in both controlled pools. However, the mean changes tended to be small and of unknown clinical significance.

**Table 108. Mean Change from Baseline to End of Treatment for Hematology Labs**

| | **Phase 3 Epilepsy Controlled Pool** | | | | **Nonepilepsy Controlled Pool^** | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| **Parameter** | n | mean Δ | n | mean Δ | n | mean Δ | n | mean Δ |
| RBC ($x10^6/mm^3$) | 421 | -0.012 | 990 | -0.035 | 390 | -0.019 | 1224 | -0.050 |
| Hematocrit (%) | 421 | -0.3 | 990 | -0.4 | 390 | 0.2 | 1224 | -0.8 |
| Hemoglobin (g/L) | 421 | 0.0 | 990 | -0.1 | 390 | -0.1 | 1225 | -0.2 |
| WBC ($x10^3/mm^3$) | 421 | 0.01 | 990 | 0.0 | 390 | -0.09 | 1218 | -0.20 |
| Neutrophils ($x10^3/mm^3$) | 420 | 0.04 | 984 | 0.03 | 350 | -0.13 | 1100 | -0.13 |
| Platelet ($x10^3/mm^3$) | 420 | 2.6 | 986 | 7.1 | 386 | 2.0 | 1213 | 1.9 |
| | | | | | | | | |
| INR | 197 | 0.031 | 572 | 0.022 | 48 | 0.006 | 134 | 0.005 |
| aPTT (s) | 197 | -1.4 | 570 | -0.7 | 42 | 0.6 | 114 | 0.2 |

Source: ISS Tables 9.1.1, 9.4.1, 9.1.3, 9.4.3 and Safety Information Amendment 5/20/13 Table 9.1.1.r1
^excludes Study 206

In Study 201, the mean changes tended to be small and similar between the ESL and placebo groups (Study 201 CSR Table 64).

The following table summarizes the percentages of subjects who shifted from normal or high values at baseline to low values for hematology parameters. In the Phase 3 Epilepsy Controlled Pool, the incidences of shifts to low values were ≥1% higher in the ESL group than placebo for hemoglobin (3.1% vs 1.8%) and RBC (6.5% vs 5.2). There were some additional small differences in shifts that were seen in the Nonepilepsy Controlled Pool that was not seen in the Phase 3 Epilepsy Controlled Pool: shifts to high INR (4.8% vs 2.1%) and low WBC (4.9% vs 2.8%).

**Table 109. Shifts from Normal for Hematology Parameters**

| **Parameter** | **Phase 3 Epilepsy Controlled Pool** | | | | **Nonepilepsy Controlled Pool^** | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| | n | # shift (%) | n | #shift (%) | n | # shift (%) | n | #shift (%) |
| RBC low | 366 | 19 (5.2) | 878 | 57 (6.5) | 365 | 2 (0.5) | 1146 | 22 (1.9) |
| Hematocrit low | 382 | 6 (1.6) | 914 | 22 (2.4)* | 348 | 17 (4.9) | 1085 | 79 (7.3) |
| Hemoglobin low | 389 | 7 (1.8) | 906 | 28 (3.1)* | 328 | 31 (9.5) | 1024 | 86 (8.4) |
| WBC low | 384 | 15 (3.9) | 897 | 31 (3.5) | 353 | 10 (2.8) | 1097 | 54 (4.9) |
| Neutrophils low | 380 | 29 (7.6) | 886 | 38 (4.3) | 326 | 9 (2.8) | 1016 | 17 (1.7) |
| Platelet low | 405 | 10 (2.5) | 940 | 16 (1.7) | 371 | 5 (1.3) | 1149 | 21 (1.8) |
| | | | | | | | | |
| INR high | 179 | 9 (5.0) | 527 | 20 (3.8) | 47 | 1 (2.1) | 124 | 6 (4.8) |
| aPTT high | 161 | 11 (6.8) | 477 | 26 (5.5) | 42 | 3 (7.1) | 104 | 3 (2.9) |

Source: ISS Tables 9.1.6.1.s1, 9.4.5.1.s1, 9.1.6.3.s1, 9.4.5.3.s1 and Safety Information Amendment 5/20/13 Table 9.1.6.1.r1
*Dose-related increase from 400 mg to 800 mg to 1200 mg randomized dose groups
^excludes Study 206

Hematology-related TEAEs
The following table summarizes the TEAEs, SAEs, and DCs in the MedDRA SOC Blood and lymphatic system disorders along with the hematology-related PTs in the SOC Investigations (HLGTs Haematology investigations and Haematological/lymphoid tissue therapeutic procedures). Incidences of TEAEs in this entire SOC were low (<5%) and similar between the ESL and placebo groups in both the Phase 3 Epilepsy and Nonepilepsy Double-blind Pool.

**Table 110. Summary of TEAEs, SAEs, DCs in the Blood and Lymphatic System Disorders SOC**

| SOC Blood and Lymphatic System Disorders | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=426 | n=1021 | n=507 | n=1755 |
| TEAEs | 11 (2.6%) | 32 (3.1%) | 6 (1.2%) | 44 (2.5%) |
| SAEs | 0 | 6 (0.6%) | 0 | 3 (0.2%) |
| Discontinuations (DCs) | 2 (0.5%) | 5 (0.5%) | 0 | 3 (0.2%) |

Source: Created by the reviewer using JReview (ADEVENTX: AESER='Y', DISC=1 and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

Using the integrated adverse event dataset (ADEVENTX), I identified the following subjects with hematology-related SAEs. In the Phase 3 Epilepsy Controlled Pool, hematology-related SAEs occurred in 6 ESL subjects (vs 0 placebo) with 5 subjects developing cytopenias (3 anemia, 3 leukopenia/lymphopenia, 2 thrombocytopenia – narratives summarized below) and 1 subject developing polycythaemia.

301-111-90341: leukopenia, thrombocytopenia in the setting of severe rash (likely DRESS, subject discussed further in Section 7.3.4)
301-172-90408: haematocrit/platelet count decreased (on OLE Day 486)
302-312-80299: anaemia, haemoglobin decreased, lymphopenia (stable from low baseline values)
302-382-80440: haematocrit/haemoglobin/RBC decreased (only minimal decreases below the LLN on Day 66 noted during hospitalization for paranoia, aggression)
304-953-95306: WBC count decreased, lymphocyte count increased (infection with vivax malaria)

In the Nonepilepsy Double-blind Pool, hematology-related SAEs occurred in 3 ESL subjects (vs 0 placebo). Only 1 ESL subject developed a cytopenia (203-301-203215 with leukopenia) while the other 2 ESL subjects reported PTs of leukocytosis and WBC count increased.

In addition to these 9 ESL subjects, hematology-related SAEs occurred in 11 ESL subjects (in OLE studies and Phase 1 and 2 studies) with only 4 subjects (36%) developing cytopenias (2 anemia, 1 leukopenia/neutropenia, 1 thrombocytopenia) and 6 subjects developing non-cytopenias (e.g., leukocytosis/WBC count increased,

haemoglobin increased, lymphadenopathy/lymphadenitis). Notably, there was 1 ESL subject who developed the SAE of pancytopenia in the setting of chemotherapy for follicular lymphoma (subject 302-395-80794 described further in Section 7.6.1 of this review).

*Comment: Of note, the Sponsor reported that for the All Studies Pool, only 5 ESL subjects developed SAEs of cytopenias and selected blood dyscrasias (ISS Table 59).*

*Additionally, I identified only 1 ESL subject with the SAE ecchymosis (subject 301-123-90356 who had autopsy findings that included pleural ecchymoses, described further in Section 7.3.1 on Deaths). There was also 1 ESL subject with the TEAE of pancytopenia: subject 303-701-70290 who developed moderate pancytopenia on Day 140 of ESL. Labs revealed the following values: Hgb 1 g/dL (normal range 11.6-15.4, likely transcription error noted by the Sponsor), Hct 32% (35-45), platelets 67 (145-420), leukocytes 3.1 (4-10.3). ESL was continued and events resolved by the next routine lab draw 5 months later (and remained WNL until the end of the study on Day 500).*

In the ongoing studies, the Sponsor reported that only 1 ESL subject developed an SAE in the SOC Blood and Lymphatic System Disorders (PT anaemia) (subject 304-30706 listed in Table 2 of Safety Information Amendment dated 4/19/13 but narrative of this SAE was not included in the NDA submission).

In the postmarketing database, the Sponsor reported that 7 ESL subjects developed the following SAEs in the SOC Blood and Lymphatic System Disorders (ISS Table 117): thrombocytopenia (3), bicytopenia (2), lymphopenia (1), leukopenia (1), neutropenia (1), and pancytopenia (1, see narrative below provided in Safety Information Amendment 6/10/13).

> BIAL 01129 with a history of iron deficiency anemia (on intravenous treatment) went to the ER with malaise and fever on day 10 of ESL. Labs revealed “mild pancytopenia” and urinary tract infection and the pt was hospitalized. ESL was discontinued and treatment was started with ceftriaxone. Peripheral smear revealed “hyporegenerative anemia, activated lymphocytes with full cytoplasma, mild neutropenia with left deviation, thrombocytopenia. Drug induced myelotoxicity vs viral infection.” Monotest and toxoplasma tests were negative. Urine culture revealed E. coli. Pt was discharged 7 days later “completely recovered.” Baseline labs were not reported. Concomitant medications included phenytoin and clobazam.
> *Comment: It is difficult to attribute the pancytopenia solely to ESL during the episode of infection and with the patient’s underlying history of anemia.*

Importantly, there were no adverse events coded to the PTs agranulocytosis or aplastic anemia in the completed clinical trials (using the Sponsor’s integrated adverse events dataset ADEVENTX) or reported by the Sponsor for the ongoing studies or postmarketing database.

In conclusion, ESL use was associated with slightly higher frequencies of decreases in hemoglobin and hematocrit values compared to placebo. However, the incidences were small (PCS values ≤ 2%) with only rare SAEs and TEAEs leading to

discontinuation. Furthermore, there were no events coded to aplastic anemia (or agranulocytosis) and only 2 cases coded to pancytopenia (that were confounded). Therefore, I recommend postmarketing surveillance to continue to investigate the effects of ESL exposure on hematologic parameters particularly the erythrocytes. Of note, some WBC differential values were missing from the integrated laboratory dataset. However, the percentage of subjects with missing WBC differentials was low compared to the overall number of ESL-treated subjects (<5%).

7.4.2.2 Chemistry

The following table summarizes the potentially clinically significant changes (for subjects with normal values at baseline) in chemistry parameters for the Phase 3 Epilepsy Controlled Pool and Nonepilepsy Controlled Pool. Of note, thyroid function tests are discussed in Section 7.3.4 of this review. In both of the controlled pools, the PCS chemistry change that occurred in at least 2% of ESL subjects and greater than placebo was low sodium and low chloride (discussed in more detail in Section 7.4.2.3). Smaller differences between the ESL and placebo subjects are noted for PCS high phosphate, CPK, and lipid parameters (LDL, cholesterol, triglycerides) (discussed in more detail in Section 7.4.2.3). Notably, the incidences of PCS values for high AST, ALT, alkaline phosphatase, and total bilirubin in both the ESL and placebo groups were very low (<1.0%). Additional analyses of these hepatobiliary parameters are provided in Section 7.3.4.

*Comment: Of note, in the Safety Information Amendment dated 5/20/13, the Sponsor reported that bicarbonate values were only collected in 5 Phase 1 studies (101, 102, 150, 153, and 155) and magnesium values were only collected in 3 Phase 1 studies (150, 153, and 155); these values were not collected in the Phase 3 studies. There were no clinically meaningful differences between ESL and placebo subjects in mean changes, shift results, and PCS changes for the available bicarbonate and magnesium values (Tables 9.5.6.1.r1 and 9.5.6.2.r1).*

**Table 111. PCS Chemistry Values (for Subjects Normal at Baseline)**

| | Phase 3 Epilepsy Controlled Pool | | | | Nonepilepsy Controlled Pool^ | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| **Parameter** | n | #PCS (%) | n | #PCS (%) | n | #PCS (%) | n | #PCS (%) |
| **Electrolytes** | | | | | | | | |
| Sodium ≤130 meq/L | 421 | 3 (0.7) | 981 | 53 (5.4) | 390 | 7 (1.8) | 1222 | 61 (5.0) |
| Sodium ≥150 meq/L | 421 | 3 (0.7) | 981 | 3 (0.3) | 390 | 3 (0.8) | 1222 | 6 (0.5) |
| Potassium ≤3.0 meq/L | 420 | 0 | 985 | 0 | 388 | 1 (0.3) | 1214 | 0 |
| Potassium ≥5.5 meq/L | 420 | 4 (1.0) | 985 | 14 (1.4) | 388 | 6 (1.5) | 1214 | 31 (2.6) |
| Chloride ≤90 meq/L | 420 | 2 (0.5) | 990 | 24 (2.4) | 390 | 1 (0.3) | 1229 | 25 (2.0) |
| Chloride ≥118 meq/L | 420 | 0 | 990 | 1 (0.1) | 390 | 1 (0.3) | 1229 | 5 (0.4) |
| Calcium <7 mg/dL | 420 | 0 | 990 | 1 (0.1) | 48 | 0 | 143 | 1 (0.7) |
| Calcium ≥12 mg/dL | 420 | 1 (0.2) | 990 | 0 | 48 | 0 | 143 | 0 |
| **Renal** | | | | | | | | |
| Creatinine >1.5 xULN | 383 | 0 | 925 | 0 | 377 | 0 | 1137 | 1 (<0.1) |
| BUN ≥30 mg/dL | 421 | 0 | 988 | 2 (0.2) | 301 | 1 (0.3) | 781 | 3 (0.4) |
| **Hepatobiliary** | | | | | | | | |
| AST >3.0xULN | 421 | 1 (0.2) | 992 | 1 (0.1) | 391 | 1 (0.3) | 1229 | 5 (0.4) |
| ALT >3.0xULN | 420 | 1 (0.2) | 992 | 3 (0.3) | 391 | 2 (0.5) | 1229 | 11 (0.9) |
| ALP >400 U/L | 421 | 0 | 992 | 0 | 390 | 0 | 1231 | 1 (<0.1) |
| Bilirubin ≥2 mg/dL | 421 | 1 (0.2) | 991 | 0 | 390 | 0 | 1226 | 3 (0.2) |
| **Other** | | | | | | | | |
| Phosphate <2.0 mg/dL | 416 | 2 (0.5) | 977 | 5 (0.5) | 48 | 0 | 135 | 0 |
| Phosphate >5.0 mg/dL | 416 | 5 (1.2) | 977 | 23 (2.4) | 48 | 3 (6.3) | 135 | 10 (7.4) |
| Glucose ≤50 mg/dL | 421 | 1 (0.2) | 986 | 4 (0.4) | 388 | 0 | 1221 | 3 (0.2) |
| Glucose ≥250 mg/dL | 421 | 0 | 986 | 3 (0.3) | 388 | 1 (0.3) | 1221 | 6 (0.5) |
| CPK >2.5xULN | 416 | 3 (0.7) | 983 | 26 (2.6) | 384 | 9 (2.3) | 1208 | 16 (1.3) |
| Cholesterol >300 mg/dL | 417 | 3 (0.7) | 975 | 17 (1.7) | 380 | 10 (2.6) | 1199 | 30 (2.5) |
| LDL >160 mg/dL | 385 | 25 (6.5) | 857 | 70 (8.2) | 40 | 3 (7.5) | 121 | 12 (9.9) |
| HDL <30 mg/dL | 413 | 4 (1.0) | 981 | 15 (1.5) | 47 | 3 (6.4) | 139 | 7 (5.0) |
| Triglycerides >300 mg/dL | 410 | 6 (1.5) | 957 | 25 (2.6) | 124 | 8 (6.5) | 546 | 34 (6.2) |

Source: ISS Tables 9.1.8, 9.4.7.1, Safety Information Amendment 5/20/13 Tables 9.1.12.1.r1, 9.4.10.1.r1, 9.1.8.r1
^excludes Study 206

*Comment: In the ISS, there were discrepancies between the number of subjects with bilirubin, cholesterol, and glucose values versus other chemistry parameters. In response to the Division's information request to explain these discrepancies, the Sponsor reported that "incomplete integration of the data regarding glucose, bilirubin and cholesterol occurred due to a programming error that did not identify differences in the nomenclature for these tests and therefore omitted a portion of the data in the raw datasets from the integrated dataset (specifically for Study 304)."*

*In response to the Division's request for the identification of "any other laboratory, vital, or ECG values that are missing from the ISS analysis datasets," the Sponsor performed a systematic review of the programming for laboratory parameters and reported additional instances of incomplete integration had occurred for the following: Total protein, absolute counts of WBC differential (basophils, eosinophils, lymphocytes,*

*monocytes, and neutrophils) from study 304, GGT values from study 301 Part 4, and urine microscopy parameters (bacteria, casts, crystals, epithelial cells, RBC, WBC) in studies 101, 102 and 130. In response to the Division's request for "new updated analysis datasets and analyses that include these missing values," revised integrated lab datasets and analyses were provided by the Sponsor in the Safety Information Amendment dated 5/20/13. I included these revised values in the table above.*

*However, I identified additional errors in these revised lab datasets. For example, for subject 2093114-000-0008, laboratory values after the April 11, 2005 visit were not included in the integrated lab dataset. In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 6/22/13 to provide additional information regarding this subject. The Sponsor stated that "[w]hile researching the response for this question which was submitted June 14, 2013 (NDA Sq.0098), it was discovered that an incorrect subject identification variable was used during the ISS data integration process of the raw data for labs, vital signs, medical history, and physical exams for the subjects in study 2093-114. For example, lab data for subject 2093114-000-00008 was misassigned to subject 2093114-000-00005. Thus, all data are present in the integrated datasets, but for the indicated datasets, they are identified with the incorrect subject identifier." The Sponsor corrected this error and provided revised narratives and datasets (ADLAB, ADMH, ADPE, ADVS, ADSI, ADSIEVNT, ADSIEVTX).*

Additionally, the clinical significance of the lab values, as assessed by the investigator and documented as adverse events, was summarized for chemistry parameters in ISS Table 9.1.9. The incidences of these clinically significant post-dose laboratory values were small and slightly higher in ESL subjects (2.3%) than placebo subjects (1.4%). The following chemistry values occurred in more than 1 ESL subject and greater than placebo: sodium (0.6% vs 0), chloride (0.5% vs 0), CPK (0.3% vs 0), and potassium (0.2% vs 0), (ISS Table 9.1.9).

In the Phase 1 studies, the following PCS values occurred in ≥1% of the total ESL group and greater than placebo: low sodium (2.0% vs 0), low chloride (0.9% vs 0), high phosphate (5.1% vs 0.7%), high BUN (7.5% vs 2.2%), ALT ≥3 xULN (1.2% vs 0), high total cholesterol (1.1% vs 0), and high triglycerides (1.6% vs 0). There was a smaller difference for high potassium (1.9% vs 1.4%).

The following table summarizes the mean changes from baseline to the end of treatment for the chemistry parameters. In both controlled pools, the mean changes were small and similar between the treatment groups except for lower mean changes in the ESL group compared to placebo for sodium and chloride and higher mean changes for cholesterol and HDL.

**Table 112. Mean Change from Baseline to End of Treatment for Chemistry Labs**

| Parameter | Phase 3 Epilepsy Controlled Pool | | | | Nonepilepsy Controlled Pool^ | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| | n | mean Δ | n | mean Δ | n | mean Δ | n | mean Δ |
| **Electrolytes** | | | | | | | | |
| Sodium meq/L | 421 | 0.1 | 993 | -0.6 | 411 | -0.1 | 1293 | -1.1 |
| Potassium meq/L | 421 | 0.0 | 991 | 0.01 | 391 | -0.04 | 1232 | -0.05 |
| Chloride meq/L | 421 | 0.1 | 993 | -0.7 | 391 | 0.1 | 1232 | -1.0 |
| Calcium mg/dL | 421 | -0.024 | 991 | -0.003 | 48 | 0.096 | 143 | -0.025 |
| **Renal** | | | | | | | | |
| Cr mg/dL | 421 | 0.0 | 993 | -0.01 | 391 | -0.01 | 1232 | -0.02 |
| BUN mg/dL | 421 | -0.06 | 992 | -0.19 | 303 | -0.29 | 784 | -0.10 |
| **Hepatobiliary** | | | | | | | | |
| AST IU/L | 421 | 1.0 | 993 | 0.3 | 391 | 0.1 | 1230 | 0.4 |
| ALT IU/L | 421 | 1.0 | 993 | 0.3 | 391 | -0.1 | 1231 | 1.4 |
| ALP IU/L | 421 | -1.7 | 992 | -0.2 | 391 | -1.2 | 1232 | 3.7 |
| Bilirubin mg/dL | 421 | -0.01 | 991 | -0.02 | 391 | -0.01 | 1228 | -0.03 |
| **Other** | | | | | | | | |
| Phosphate mg/dL | 421 | 0.029 | 993 | 0.091 | 48 | 0.042 | 142 | 0.085 |
| Glucose mg/dL | 421 | -0.64 | 992 | 0.32 | 390 | 0.65 | 1226 | 0.29 |
| CPK IU/L | 421 | 1.0 | 992 | -0.2 | 388 | 3.2 | 1222 | -2.6 |
| Cholesterol mg/dL | 421 | 0.66 | 993 | 1.97 | 391 | -1.62 | 1232 | 3.30 |
| LDL chol mg/dL | 420 | 0.75 | 986 | 0.43 | 47 | -7.03 | 140 | 4.85 |
| HDL chol mg/dL | 421 | 0.15 | 992 | 1.46 | 49 | 0.55 | 142 | 1.59 |
| Triglycerides mg/dL | 421 | -2.09 | 993 | -0.65 | 135 | 7.16 | 586 | 3.57 |

Source: ISS Tables 9.1.4.1.s1, 9.4.4.s1, 9.1.2, 9.4.2 and Safety Information Amendment 5/20/13 Table 9.1.2.r1
^excludes Study 206

The following table summarizes the shift results from normal at baseline to low or high, depending on the chemistry parameter. In both controlled pools, the incidences of shifts were greater in the ESL group than placebo for low sodium and chloride and high lipid parameters (cholesterol, triglycerides). Incidences of shifts to high CPK and calcium were greater in the ESL group than placebo for the Phase 3 Epilepsy Controlled Pool but not for the Nonepilepsy Controlled Pool. A small difference in the incidence of shifts to high AST (7.0% vs 6.0%) and high alkaline phosphatase (3.2% vs 1.4%) was seen between the ESL and placebo groups for the Nonepilepsy Controlled Pool.

**Table 113. Shift Results (from normal) for Chemistry Parameters**

| Parameter | Phase 3 Epilepsy Controlled Pool | | | | Nonepilepsy Controlled Pool^ | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo | | ESL | | Placebo | | ESL | |
| | n | # shift (%) | n | # shift (%) | n | # shift (%) | n | # shift (%) |
| **Electrolytes** | | | | | | | | |
| Sodium Low | 406 | 4 (1.0) | 937 | 46 (4.9)* | 377 | 3 (0.8) | 1195 | 71 (5.9) |
| Sodium High | 406 | 14 (3.4) | 937 | 25 (2.7) | 377 | 3 (0.8) | 1195 | 5 (0.4) |
| Potassium Low | 411 | 1 (0.2) | 950 | 1 (0.1) | 383 | 2 (0.5) | 1194 | 3 (0.3) |
| Potassium High | 411 | 11 (2.7) | 950 | 25 (2.6) | 383 | 7 (1.8) | 1194 | 27 (2.3) |
| Chloride Low | 386 | 6 (1.6) | 908 | 51 (5.6) | 382 | 5 (1.3) | 1198 | 46 (3.8) |
| Chloride High | 386 | 18 (4.7) | 908 | 34 (3.7) | 382 | 6 (1.6) | 1198 | 10 (0.8) |
| Calcium Low | 384 | 2 (0.5) | 899 | 2 (0.2) | 43 | 1 (2.3) | 131 | 6 (4.6) |
| Calcium High | 384 | 8 (2.1) | 899 | 52 (5.8) | 43 | 1 (2.3) | 131 | 1 (0.8) |
| **Renal** | | | | | | | | |
| Cr High | 383 | 7 (1.8) | 925 | 13 (1.4) | 377 | 9 (2.4) | 1137 | 18 (1.6) |
| BUN High | 397 | 5 (1.3) | 934 | 19 (2.0) | 296 | 2 (0.7) | 768 | 10 (1.3) |
| **Hepatobiliary** | | | | | | | | |
| AST High | 406 | 11 (2.7) | 957 | 25 (2.6) | 366 | 22 (6.0) | 1121 | 79 (7.0) |
| ALT High | 390 | 16 (4.1) | 930 | 34 (3.7) | 346 | 25 (7.2) | 1100 | 80 (7.3) |
| ALP High | 384 | 9 (2.3) | 903 | 25 (2.8) | 359 | 5 (1.4) | 1135 | 36 (3.2) |
| Bilirubin High | 394 | 3 (0.8) | 903 | 1 (0.1) | 380 | 6 (1.6) | 1196 | 12 (1.0) |
| **Other** | | | | | | | | |
| Phosphate Low | 392 | 10 (2.6) | 908 | 14 (1.5) | 42 | 2 (4.8) | 131 | 4 (3.1) |
| Phosphate High | 392 | 22 (5.6) | 908 | 45 (5.0) | 42 | 1 (2.4) | 131 | 4 (3.1) |
| Glucose Low | 400 | 16 (4.0) | 923 | 23 (2.5) | 358 | 3 (0.8) | 1082 | 14 (1.3) |
| Glucose High | 400 | 8 (2.0) | 923 | 25 (2.7) | 358 | 23 (6.4) | 1082 | 60 (5.5) |
| CPK High | 382 | 18 (4.7) | 906 | 53 (5.8) | 353 | 22 (6.2) | 1113 | 60 (5.4) |
| Cholesterol High | 261 | 38 (14.6) | 562 | 108 (19.2) | 292 | 16 (5.5) | 933 | 93 (10.0) |
| LDH High | 298 | 44 (14.8) | 619 | 84 (13.6) | 21 | 3 (14.3) | 76 | 13 (17.1) |
| HDL Low | 282 | 8 (2.8) | 699 | 21 (3.0) | 34 | 4 (11.8) | 99 | 5 (5.1) |
| Triglycerides High | 344 | 17 (4.9) | 793 | 59 (7.4) | 87 | 11 (12.6) | 369 | 59 (16.0) |

Source: ISS Tables 9.1.6.2.s1, 9.1.6.4.s1, 9.4.5.4.s1 and Safety Information Amendment 5/20/13 Table 9.1.6.2.r1
*Dose-related increase from 400 mg to 800 mg to 1200 mg randomized dose groups
^excludes Study 206

7.4.2.3 Additional Analyses for Chemistry Parameters

In this section, I will present additional analyses for hyponatremia, hypochloremia, hyperlipidemia, and increased CPK.

In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 5/20/13 to further evaluate the incidence of consecutive PCS values. The following table summarizes the number of consecutive PCS values for at least 2 visits for subjects with normal values at baseline for the following laboratory parameters: high potassium, phosphate, CPK, cholesterol, LDL, triglycerides and low chloride and HDL (low sodium is described below in the next section). The incidence of consecutive PCS values was small (<0.5%) and/or similar between ESL

and placebo subjects except for low chloride (0.5% vs 0). Hypochloremia will be discussed further later in this section.

**Table 114. Consecutive PCS Chemistry Values for ≥2 visits (for subjects with normal values at baseline), Phase 3 Epilepsy Controlled Pool**

| Category | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=426 | n=196 | n=415 | n=410 | n=1021 |
| Potassium ≥5.5 meq/L | 0 | 0 | 0 | 1 (0.2) | 1 (0.1) |
| Chloride ≤90 meq/L | 0 | 0 | 2 (0.5) | 3 (0.7) | 5 (0.5) |
| Phosphate >5.0 mg/dL | 0 | 0 | 0 | 0 | 0 |
| CPK >2.5xULN | 0 | 2 (1.0) | 0 | 0 | 2 (0.2) |
| Cholesterol >300 mg/dL | 0 | 0 | 2 (0.5) | 1 (0.2) | 3 (0.3) |
| LDL >160 mg/dL | 8 (1.9) | 2 (1.0) | 6 (1.4) | 7 (1.7) | 15 (1.5) |
| HDL <30 mg/dL | 1 (0.2) | 1 (0.5) | 2 (0.5) | 0 | 3 (0.3) |
| Triglycerides >300 mg/dL | 2 (0.5) | 1 (0.5) | 2 (0.5) | 2 (0.5) | 5 (0.5) |

Source: Safety Information Amendment 5/20/13 Table 9.1.12.8.r1

Hyponatremia

The following table summarizes the incidences of potentially clinically significant sodium values and consecutively low sodium values for the Phase 3 Epilepsy Controlled Pool. A higher percentage of ESL subjects than placebo developed hyponatremia (19% vs 6% for sodium values ≤135 meq/L). Severe hyponatremia (sodium values ≤125 meq/L) occurred in only ESL subjects (1.1%) vs 0 placebo subjects. A higher percentage of ESL subjects than placebo subjects experienced decreases in sodium values >10 meq/L (5.1% vs 0.7%) and consecutive low sodium values for at least 2 visits (1.4% vs 0). A dose response relationship was observed.

**Table 115. Minimum Post-Dose Sodium Levels, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=421 | n=194 | n=401 | n=398 | n=993 |
| Sodium >135 meq/L | 396 (94) | 164 (85) | 328 (82) | 311 (78) | 803 (81) |
| Sodium >130-≤135 meq/L | 22 (5.2) | 24 (12.4) | 48 (12.0) | 57 (14.3) | 129 (13.0) |
| Sodium >125-≤130 meq/L | 3 (0.7) | 5 (2.6) | 21 (5.2) | 24 (6.0) | 50 (5.0) |
| Sodium ≤125 meq/L | 0 | 1 (0.5) | 4 (1.0) | 6 (1.5) | 11 (1.1) |
| Decrease >10 meq/L | 3 (0.7) | 6 (3.1) | 19 (4.7) | 26 (6.5) | 51 (5.1) |
| Consecutive Low ≥2 Visits* | 0 | 1 (0.5) | 4 (1.0) | 9 (2.2) | 14 (1.4) |

Source: ISS Table 9.1.7.1 and Safety Information Amendment 5/20/13 Table 9.1.12.8.r1
*for subjects with normal values at baseline

The following table summarizes the incidences of potentially clinically significant sodium values and consecutively low sodium values for the Nonepilepsy Controlled Pool. Again, a higher percentage of ESL subjects than placebo developed hyponatremia (12% vs 4% for sodium values ≤135 meq/L). Severe hyponatremia (sodium values ≤125 meq/L) occurred in ESL subjects (1.9%) more frequently than placebo subjects (0.3%). A higher percentage of ESL subjects than placebo subjects experienced

decreases in sodium values >10 meq/L (6.0% vs 1.0%). A dose response relationship was observed.

**Table 116. Minimum Post-Dose Sodium Levels, Nonepilepsy Controlled Pool (excludes Study 206)**

| Category | Placebo n (%) | ESL n (%) | | | | |
|---|---|---|---|---|---|---|
| | | <600 mg | 600-<1000 | 1000-<1400 | ≥1400 mg | Total |
| | n=391 | n=279 | n=547 | n=312 | n=95 | n=1233 |
| Sodium >135 meq/L | 375 (96) | 257 (92) | 485 (89) | 271 (87) | 66 (70) | 1079 (88) |
| Sodium >130-≤135 meq/L | 9 (2.3) | 16 (5.7) | 35 (6.4) | 23 (7.4) | 13 (14) | 87 (7.1) |
| Sodium >125-≤130 meq/L | 6 (1.5) | 5 (1.8) | 19 (3.5) | 10 (3.2) | 10 (10) | 44 (3.6) |
| Sodium ≤125 meq/L | 1 (0.3) | 1 (0.4) | 8 (1.5) | 8 (2.6) | 6 (6.3) | 23 (1.9) |
| Decrease >10 meq/L | 4 (1.0) | 11 (3.9) | 34 (6.2) | 19 (6.1) | 10 (10) | 74 (6.0) |

Source: ISS Table 9.1.7.1

Furthermore, hyponatremia SAEs and DCs occurred only in ESL subjects (vs 0 placebo subjects) in both controlled pools.

**Table 117. Hyponatremia SAEs and DCs**

| | Placebo | ESL |
|---|---|---|
| **Phase 3 Epilepsy Controlled Pool** | n = 426 | n = 1021 |
| SAEs | 0 | 2 (0.2) |
| TEAEs leading to DC | 0 | 5 (0.5) |
| **Nonepilepsy Double-blind Pool** | n=507 | n=1755 |
| SAEs | 0 | 3 (0.2) |
| TEAEs leading to DC | 0 | 3 (0.2) |

Source: ISS Table 7.1.11.1.s2 and created by the reviewer using JReview (ADEVENTX: AESER='Y', DISC=1 and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

In the All Studies Pool (including 303), I identified a total of 10 ESL subjects with SAEs of hyponatremia (n=8) or blood sodium decreased (n=2) using the ADEVENTX dataset. I reviewed the narratives and datasets for these ESL subjects:

Subject 302-306-80614 with Na=123 on Study Day 8 identified during hospitalization for severe ataxia, diplopia, nausea, and vomiting (that started on Day 5). Events resolved 8 days after ESL discontinuation. (Medical treatment received during hospitalization was not included in the narrative.)
Subject 304-307-30720 with Na=125 on Day 7 (symptomatic with dizziness, gait imbalance, nausea/vomiting, nystagmus that started on Day 3) after taking ESL incorrectly in double doses. Subject went to the ER but was not hospitalized. ESL was interrupted but reintroduced at the lower, correct dose (400 mg). Sodium levels improved (127-139) and the subject completed the study.
Subject 301-171-90403 with Na=126 on Day 132 identified during hospitalization for vertigo, diplopia, nystagmus, and vomiting (could not take any food or fluids). ESL dose was reduced to 400 mg (from 800 mg). Events resolved and the subject completed the DB study (and the OLE study 1 year later).
Subject 207-285-285001 with Na=112 on Day 3 identified during hospitalization for disorientation, confusion, psychosis, nausea, and vomiting (and dehydration). ESL was discontinued along with "corrective pathophysiological treatment." Events resolved and the subject was discharged from the hospital 11 days later with Na=137. Concomitant medications included a thiazide diuretic.
Subject 207-284-284004 with Na=124 on Day 31 identified during hospitalization for an episode of "fainting without loss of consciousness." ESL was discontinued and subject was treated with

hypertonic saline (10% NaCl) intravenous fluids. Events resolved and subject was discharged from the hospital 7 days later.
Subject 210-806-806001 with Na=131 on Day 35 and ESL was discontinued. Labs ~5 weeks later revealed resolution of hyponatremia (Na=140).
Subject 203-301-203215 with Na=128 on Day 12 and ESL was discontinued. Hyponatremia resolved 1 day later.

Some subjects (n=3) were also taking carbamazepine (301-171-90403, 302-306-80614, 303-601-70156). One subject (303-601-70156) had low values at baseline that persisted (or worsened) during the study with continued ESL use. One subject (301-141-90181) developed decreases to 129 meq/L without worsening while ESL was continued into the OLE study. One subject (302-385-80426) experienced the SAE of blood sodium decreased as a data review event (Na=134) on Day 580 (day of death due to drowning).

Associated adverse events included somnolence, nausea, vomiting, disorientation, confusion, fall, vertigo, ataxia, diplopia, coordination abnormal, gait disturbance, dizziness, and balance disorder. Concurrent hypochloremia was present in the subjects.

*Comment: Of note, the Sponsor reported in the ISS that there were only 7 SAEs (instead of the 10 subjects identified above) of hyponatraemia or blood sodium decreased in the entire eslicarbazepine acetate drug development program, including Study 2093-303 (ISS Table 43). The Sponsor reported that there were also 2 SAEs of brain oedema, which is listed in the MedDRA SMQ for hyponatremia as a possible indicator event. However, in both cases the sodium was not decreased (301-123-90356 and 301-124-90486).*

*Furthermore, I identified that the sodium values reported in the narratives that were collected during hospitalizations (some ≤125 meq/L) were not included in the integrated lab dataset. Therefore, the Sponsor's tables (for hyponatremia based on actual sodium values) that use the integrated lab dataset may underestimate the incidence of hyponatremia events (including cases of severe hyponatremia).*

*I also reviewed the narratives and datasets for the 11 ESL subjects in Table 115 above, with sodium values ≤125 meq/L. Discontinuations due to hyponatremia occurred in 3 of these subjects: subject 304-005-00525 with Na=123 on Study Day 57 which resolved 7 days after ESL discontinuation, subject 304-051-05101 with Na=123 on Day 57 which resolved 3 days after ESL discontinuation, subject 304-953-95314 with Na=118 on Day 59 (lost to follow up after subject was discontinued from the study).*

*Other subjects (n=5) had low values at baseline that persisted (or worsened) during the study with continued ESL use (302-334-80105, 304-019-01902, 304-350-35005, 304-426-42603, 304-078-07801). Most of the subjects (n=7) were also taking carbamazepine (301-193-90158, 302-334-80105, 304-005-00525, 304-019-01902, 304-*

*350-35005, 304-426-42603, 304-078-07801). One subject developed isolated decreases to ≤125 meq/L in the background of milder hyponatremia (130-135 meq/L) while continued on ESL into the OLE study (301-193-90158).*

*Associated adverse events included partial seizures, somnolence, headache, nausea, vomiting, memory impairment, skeletal injury (R costal trauma), balance disorder, and dizziness. Concurrent hypochloremia was present in all of the subjects.*

*Of note, for subject 304-051-05101, the labs drawn during the discontinuation visit and post-study visit (reported in the narrative) were not included in either the integrated laboratory dataset or the tabulations laboratory dataset for Study 304. In response to the Division's information request, the Sponsor explained that these labs were drawn during Part 2 of the study (OLE portion) which is currently an ongoing study and, therefore, not integrated into the ISS dataset (Safety Information Amendment 8/16/13).*

In the ongoing studies, the Sponsor reported 1 ESL subject with the SAE blood sodium decreased and 9 ESL subjects with hyponatremia (Safety Information Amendment 4/19/13 Table 2).

In the postmarketing database, the Sponsor reported 121 patients with hyponatremia or blood sodium decreased of which the majority (81%, n=98) were reported as SAEs (ISS Table 108). In 8 cases, a concomitant seizure event was reported. The Sponsor calculated the reporting rate for hyponatremia events as 102 events per 10,000 patient-years.

In response to the Division's information request, the Sponsor performed analyses of time to and duration of hyponatremia determined by sodium values <130 meq/L (Safety Information Amendment, 5/20/13 Tables 9.1.7.8.r1 and 9.4.6.3.r1). In the Phase 3 Epilepsy Controlled Pool, the duration of hyponatremia for ESL subjects (n=22) was 33.0 days (no placebo subjects). The onset of these events was more rapid for ESL subjects (n=46) at 69.0 days than for placebo subjects at 127.0 days (n=1). In the Nonepilepsy Controlled Pool, the duration of hyponatremia was 21.5 days for ESL subjects (n=25) and 16.7 days for placebo subjects (n=3). The onset of these events was more rapid for ESL subjects (n=55) at 28.6 days than for placebo subjects at 37.8 days (n=5).

*Comment: The following table summarizes my own analyses for the timing of the onset of PCS sodium values (≤130 meq/L) in the Phase 3 Epilepsy Controlled Pool. These events occurred earlier in the ESL group (mean study day of 76) than in the placebo group (mean day=117). However, after stratifying by visit number, I found that the study day of onset was driven by the visit number (due to the fact that the first scheduled laboratory draw was on Visit 4 or Day 56 according to the study protocols). Laboratory values drawn outside of those study visits (e.g., during hospitalizations) were not included in the integrated analysis lab datasets by the Sponsor. Furthermore, earlier*

*onset days (3 to 35 days) were reported in the SAE narratives that included sodium values measured during hospitalizations, etc. Therefore, the calculated mean onset day of these hyponatremia events using the lab datasets overestimates the length of the true latency period.*

**Table 118. PCS Sodium Values by Visit Number and Outcome, Phase 3 Epilepsy Controlled Pool**

| PCS Sodium Values (≤130 mEq/L) | Placebo | ESL |
|---|---|---|
| | n=3 | n=61 |
| Baseline sodium ≤130 mEq/L | 0 | 8 (13.1) |
| Study day of specimen collection (mean) | 117 | 76 |
| Visit name of specimen collection | | |
| Visit 4 (week 8 or day 56)* | 0 | 26 (42.6) |
| Visit 5 (week 14 or day 98) | 1 (33.3) | 26 (42.6) |
| Visit 6 | 2 (66.7) | 0 |
| Early discontinuation visit | 0 | 8 (13.1) |
| Unscheduled | 0 | 1 (1.6) |
| Outcome | | |
| Completed Part 1 (DB) | 3 (100) | 49 (80.3) |
| Did not complete Part 1 | 0 | 12 (19.7) |
| Completed Part 1 & continued in Part 2 | 3 (100) | 47 (77.0) |
| Completed Part 1 and Part 2 (OLE) | 2 (66.7) | 17 (27.9) |

Source: Created by the reviewer using JReview (ADLAB: LBNACAT, VISIT, LBDY and ADSL: P1COMP) for studies 301, 302, 304 (PART='Part 1', DOSCATC)
*first scheduled laboratory draw according to the study protocols' schedule of safety assessments

To analyze for the associated adverse events, I performed analyses of the incidence of TEAEs by minimum sodium value for the total ESL group. The following table shows that ESL subjects with greater degrees of hyponatremia had a higher incidence of TEAEs, especially in specific HLGTs of the SOC Nervous System Disorders, Gastrointestinal Disorders, and Eye Disorders. Typical symptoms of hyponatremia (depending on the severity) can include nausea/vomiting, headache, confusion, loss of energy, fatigue, restlessness/irritability, muscle weakness/spasms, seizures, and coma.

**Table 119. TEAEs by Minimum Sodium Value, Phase 3 Epilepsy Controlled Pool**

| | Total ESL Group (%) | | | |
|---|---|---|---|---|
| | Na >135 | Na ≤135 | Na ≤130 | Na ≤125 |
| # of subjects | n=803 | n=190 | n=61 | n=11 |
| Any TEAE | 538 (67.0) | 147 (77.4) | 55 (90.2) | 11 (100) |
| SOC Nervous system disorders | 338 (42.1) | 102 (53.7) | 39 (63.9) | 6 (54.5) |
| HLGT Neurological disorders NEC^ | 268 (33.4) | 83 (43.7) | 33 (54.1) | 5 (45.5) |
| HLGT Headaches | 86 (10.7) | 31 (16.3) | 10 (16.4) | 2 (18.2) |
| HLGT Seizures (incl subtypes) | 19 (2.4) | 7 (3.7) | 2 (3.3) | 1 (9.1) |
| SOC Eye disorders | 94 (11.7) | 48 (25.3) | 22 (36.1) | 3 (27.3) |
| Gastrointestinal: PTs nausea/vomiting | 93 (11.6) | 30 (15.8) | 12 (19.7) | 5 (45.5) |

Source: Created by the reviewer using JReview (ADLAB: LBNACAT and ADAE: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')
^driven by PTs dizziness, somnolence, ataxia, balance disorder

In terms of relative risk, subjects with hyponatremia had a greater relative risk (incidence in ESL group divided by incidence in placebo group) of TEAEs (particularly in the SOCs Nervous System Disorders and Eye Disorders) compared with subjects without hyponatremia. The risk appeared to increase with severity of hyponatremia. However, the small numbers (many zero values) in the placebo group limited these analyses.

**Table 120. Relative Risk of TEAEs by Minimum Sodium Values, Phase 3 Epilepsy Controlled Pool**

| | Relative Risk (Total ESL vs Placebo) | | | |
|---|---|---|---|---|
| | **Na >135** | **Na ≤135** | **Na ≤130** | **Na ≤125** |
| Any TEAE | 1.26* | 1.38 | 2.70 | NA |
| SOC Nervous system disorders | 1.75* | 2.68* | NA | NA |
| HLGT Neurological disorders NEC^ | 2.13* | 2.73* | NA | NA |
| HLGT Headaches | 1.33 | 4.08 | NA | NA |
| HLGT Seizures (incl subtypes) | 0.62 | 0.92 | NA | NA |
| SOC Eye disorders | 2.58* | 6.32 | NA | NA |
| Gastrointestinal: PTs nausea/vomiting | 2.55* | 1.97 | NA | NA |

Source: Created by the reviewer using JReview (ADLAB: LBNACAT and ADAE: AEDECOD and ADSL: DOSCATC) for studies 301, 302, 304 (PART='Part 1')
*p<0.05
NA due to zero values in placebo group
^driven by PTs dizziness, somnolence, ataxia, balance disorder

Due to small numbers of patients with hyponatremia, it was not possible to characterize the risk factors for hyponatremia in the epilepsy and nonepilepsy double-blind pools.

In conclusion, there is reasonable evidence of a causal relationship between ESL use and hyponatremia. Serious, life threatening complications were reported with ESL-associated hyponatremia (as low as 112 meq/L) including seizures, severe nausea/vomiting leading to dehydration, severe gait instability, and skeletal injury. Some subjects required hospitalization and prolonged medical treatment. However, typically, normalization of serum sodium occurred within a few days after ESL dose reduction or discontinuation. In a few subjects, ESL was continued and the hyponatremia did not worsen. Conversely, in some subjects with preexisting hyponatremia, ESL use further decreased the sodium levels. ESL-associated hyponatremia developed as early as Study Day 3.
Concurrent hypochloremia was present in most of these cases. Many subjects were also on concomitant carbamazepine that is also associated with hyponatremia, but the time course was associated with addition of eslicarbazepine. The numbers of patients with hyponatremia were too small to characterize risk factors.

There were many cases of symptomatic hyponatremia, and ESL subjects with greater degrees of hyponatremia had a higher incidence of TEAEs typical for hyponatremia.

Consequently, these signs and symptoms may identify the ESL patients who should have sodium values measured sooner. Therefore, because of the serious nature of ESL-associated hyponatremia along with possible ways to mitigate the risk of complications (laboratory measurements of sodium), I recommend that hyponatremia be included in the Warnings and Precautions section of ESL labeling.

Hypochloremia
In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 5/20/13 to analyze the correlation between the events of hypochloremia and hyponatremia. The following table summarizes the incidences of concurrent low chloride and low sodium values in the Phase 3 Epilepsy Controlled Pool. For placebo subjects, there was no correlation between low chloride levels and low sodium levels with only 18% of the subjects with chloride levels ≤LLN also had sodium levels ≤130 meq/L. Conversely, for ESL subjects about half of the subjects (46%) with chloride levels ≤LLN also had sodium levels ≤130 meq/L. Furthermore for ESL subjects, there was even greater correlation using PCS chloride levels (≤90 meq/L) with almost all of these subjects (96%) with concurrent sodium levels ≤130 meq/L (compared with 50% of placebo subjects).

**Table 121. Concurrent Low Chloride and Sodium Values, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=426 | n=196 | n=415 | n=410 | n=1021 |
| Chloride ≤90 meq/L and | n=2 | n=1 | n=11 | n=14 | n=26 |
| sodium >135 meq/L | 0 | 0 | 0 | 0 | 0 |
| sodium >130-≤135 | 1 (50) | 0 | 0 | 1 (7.1) | 1 (3.8) |
| sodium >125-≤130 | 1 (50) | 0 | 7 (64) | 7 (50) | 14 (54) |
| sodium ≤125 meq/L | 0 | 1 (100) | 4 (36) | 6 (43) | 11 (42) |
| | | | | | |
| Chloride ≤ LLN and | n=17 | n=22 | n=47 | n=58 | n=127 |
| sodium >135 meq/L | 4 (24) | 5 (23) | 8 (17) | 3 (5) | 16 (13) |
| sodium >130-≤135 | 10 (59) | 11 (50) | 15 (32) | 26 (45) | 52 (41) |
| sodium >125-≤130 | 3 (18) | 5 (23) | 20 (43) | 23 (40) | 48 (38) |
| sodium ≤125 meq/L | 0 | 1 (5) | 4(9) | 6 (10) | 11 (9) |

Source: Safety Information Amendment 5/20/13 Table 9.1.12.2.r1
*concurrent values at the same lab visit
LLN= lower limit of normal

In the Phase 3 Epilepsy Controlled and Uncontrolled Pool, the majority of the ESL subjects (93%) who had chloride values ≤90 meq/L also had sodium values ≤130 meq/L (Safety Information Amendment 5/20/13 Table 9.3.4.2.r1).

In the Nonepilepsy Controlled Pool, there were similar results. For placebo subjects, there was no correlation between low chloride levels and low sodium levels with none of the subjects with chloride levels ≤LLN also had sodium levels ≤130 meq/L. Conversely, for ESL subjects, 88% of the subjects with PCS chloride levels ≤90 meq/L also had

sodium levels ≤130 meq/L (compared with 0 placebo subjects) (Safety Information Amendment 5/20/13 Table 9.4.10.3.r1).

In conclusion, there is a higher incidence of PCS low chloride values, lower mean changes, and shifts to low chloride in ESL subjects than placebo subjects (as detailed in Section 7.4.2.2 of this review). Therefore, there is reasonable evidence of a causal relationship between ESL use and hypochloremia. However, ESL subjects developed hypochloremia and hyponatremia concurrently (while placebo subjects did not). Thus, the mechanism of ESL-associated hyponatremia and hypochloremia are likely linked. Of note, metabolic alkalosis can be associated with these electrolyte abnormalities. However, the Sponsor reported that bicarbonate values were not collected in any of the Phase 2 or 3 studies (only in five Phase 1 studies). Therefore, there is not enough information in this NDA to provide any conclusions regarding the association between ESL use and acid-base abnormalities, and a postmarketing requirement should be implemented to further study this possible association.

Hyperlipidemia
In the Phase 3 Epilepsy Controlled Pool, measurements of total cholesterol, triglycerides, LDL, and HDL were performed after an 8 hour fast. The following table summarizes the incidence of clinically significant increases or shifts in total cholesterol and triglyceride levels. There was only one category in which the ESL group had a >2% higher frequency than placebo: shift from normal to borderline total cholesterol (17% vs 14%). No dose response relationship was seen.

**Table 122. Increases and Shifts in Lipids, Phase 3 Epilepsy Controlled Pool**

| Laboratory Evaluation | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| **Total cholesterol** | n=421 | n=194 | n=401 | n=398 | n=993 |
| Increase ≥50 mg/dL* | 16 (3.8%) | 10 (5.2%) | 15 (3.7%) | 18 (4.5%) | 43 (4.3%) |
| Increase ≥100 mg/dL* | 1 (0.2%) | 1 (0.5%) | 0 | 3 (0.8%) | 4 (0.4%) |
| Shift from Normal to borderline (<200 to ≥200 and <240) | 57 (14%) | 33 (17%) | 63 (16%) | 69 (17%) | 165 (17%) |
| Shift from Normal to High (<200 to ≥240 ) | 5 (1.2%) | 4 (2.1%) | 5 (1.2%) | 3 (0.8%) | 12 (1.2%) |
| Shift from Borderline to High (≥200 and <240 to ≥240) | 27 (6.4%) | 14 (7.2%) | 26 (6.5%) | 38 (9.5%) | 78 (7.9%) |
| **Triglycerides** | n=421 | n=194 | n=401 | n=398 | n=993 |
| Increase ≥50 mg/dL* | 62 (14.7%) | 29 (14.9%) | 62 (15.5%) | 62 (15.6%) | 153 (15.4%) |
| Increase ≥100 mg/dL* | 20 (4.8%) | 11 (5.7%) | 26 (6.5%) | 18 (4.5%) | 55 (5.5%) |
| Shift from Normal to borderline (<150 to ≥150 and <200) | 34 (8.1%) | 10 (5.2%) | 42 (10.5%) | 39 (9.8%) | 91 (9.2%) |
| Shift from Normal to High (<150 to ≥200) | 11 (2.6%) | 3 (1.5%) | 16 (4.0%) | 9 (2.3%) | 28 (2.8%) |
| Shift from Borderline to High (≥150 and <200 to ≥200) | 14 (3.3%) | 6 (3.1%) | 16 (4.0%) | 16 (4.0%) | 38 (3.8%) |
| Shift from Normal to Very High (<150 to ≥500) | 0 | 0 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| Shift from Borderline to Very High (≥150 and <200 to ≥500) | 0 | 0 | 0 | 1 (0.3%) | 1 (0.1%) |

Source: Safety Information Amendment 5/20/13 Table 9.1.12.3.r1
*Number (%) of Subjects with at least one post-baseline measurement that crossed the specified thresholds of abnormalities

In the Nonepilepsy Controlled Pool, there were only two categories in which the ESL group had a >2% higher frequency than placebo: shift from normal to borderline total cholesterol (14.9% vs 12.3%) and shift from normal to high triglycerides (8.5% vs 4.4%) (Safety Information Amendment 5/20/13 Table 9.4.10.5.r1). No dose response relationship was seen.

Creatine Phosphokinase (CPK)
The following table summarizes the CPK test outlier results for the Phase 3 Epilepsy Controlled Pool. A slightly higher percentage of ESL subjects than placebo developed extremely high CPK values (3 to 5 times ULN and >5x ULN). A dose response relationship was not observed for the 3 to 5 times ULN. Only a small percentage of subjects (0.6% vs 0.2%) experienced CPK values >5xULN. Most of the 6 ESL subjects with CPK values >5xULN only had single elevated CPK values that resolved on continued ESL treatment (subjects 301-151-90495, 304-851-85108, 302-312-80273, 304-852-85201). The remaining 2 ESL subjects (304-752-75202 and 301-192-90258) had single elevated CPK values (2367 U/L on Visit 5 and 2548 U/L on Visit 4, respectively) and subsequent discontinuation of ESL.

**Table 123. Creatine Phosphokinase Outliers, Phase 3 Epilepsy Controlled Pool**

| Test/Cutoff threshold | Placebo n (%) | ESL n (%) | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=421 | n=194 | n=401 | n=397 | n=992 |
| CPK ≤3x ULN | 419 (99.5) | 186 (95.9) | 397 (99.0) | 389 (98.0) | 972 (98.0) |
| CPK >3x and ≤5x ULN | 1 (0.2) | 8 (4.1) | 1 (0.2) | 5 (1.3) | 14 (1.4) |
| CPK >5x ULN | 1 (0.2) | 0 | 3 (0.7) | 3 (0.8) | 6 (0.6) |

Source: Safety Information Amendment 5/20/13 Table 9.1.12.4.r1
ULN= upper limit of normal

The following table summarizes the SMQ results for the epilepsy and nonepilepsy DB pools. In both pools, a slightly lower percentage of ESL subjects than placebo subjects experienced TEAEs in the SMQ Rhabdomyolysis and Myopathy (using broad PTs). There was 1 ESL subject in the Nonepilepsy Double-blind Pool who reported an adverse event in the narrow SMQ (subject 206-566-566007, 75 year-old male with PT myoglobin blood increased during events of myocardial infarction, pulmonary hypertension, and dyspnoea with CPK values within the normal range).

**Table 124. SMQ Rhabdomyolysis and Myopathy**

| | Phase 3 Epilepsy DB Pool | | Nonepilepsy DB Pool | |
|---|---|---|---|---|
| **SMQ Rhabdomyolysis** | **Placebo** | **ESL** | **Placebo** | **ESL** |
| | n=426 | n=1021 | n=507 | n=1755 |
| Broad PTs | 15 (3.5%) | 33 (3.2%) | 15 (3.0%) | 40 (2.3%) |
| Narrow PTs | 0 | 0 | 0 | 1 (0.1%) |

Source: Created by the reviewer using MAED tool (ADEVENTX and ADSL) for studies 301, 302, 304 (PART='Part 1', DOSCATC) and studies 203, 204, 206, 207, 209, 210 (PART ≠'Part 2', TRTP1)

In the All Studies Pool (including 303), there was 1 ESL subject with an SAE of blood creatine phosphokinase increased. Although the increase in CPK was temporally related to ESL initiation, this case is confounded by statin use and physical exertion as the CPK elevation persisted (>7 weeks) after ESL discontinuation.

Subject 210-523-523008, a 62 year-old female who developed a significant elevation in CPK to 704 U/L (ULN 167 U/L) on Day 91 of ESL 400 mg (last day of the trial). Baseline values for CPK were WNL (83 U/L). On Study Day 35, CPK increased to 228 U/L. The investigator stated that the subject had reported intensive physical activity and muscle stiffness. AST and ALT values were slightly elevated (<2x ULN). Creatinine values were WNL. ESL was discontinued on Study Day 91 when the subject finished the study. Two weeks later, CPK was slightly lower at 631 U/L. Another 5 weeks later, CPK was lower at 457 U/L but still >2x ULN. Past medical history included hypertension, dyslipidemia, hepatic steatosis, and nephrolithiasis. Concomitant medications included simvastatin (~2 years) and enalapril.

Importantly, there were no adverse events coded to the PT rhabdomyolysis in the completed clinical trials (using the Sponsor's integrated adverse events dataset ADEVENTX) or reported by the Sponsor for the ongoing studies or postmarketing database.

7.4.2.4 Urinalysis

In response to the Division's information request, on 5/20/13 the Sponsor submitted analyses for the urine parameters including mean changes from baseline for pH and specific gravity (for Phase 1 studies) and shift results to abnormal (for Phase 3 epilepsy studies, Study 201, and Phase 1 studies) for RBC, WBC, bacteria, casts, crystals, epithelial cells, and yeast/fungi. The Sponsor reports that specific gravity and pH values were only collected for Phase 1 studies, specifically Studies 101, 102, 103, 104, 105, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124 (pH only), 125, 126, 128, 129 (pH only), 130 (pH only), 150, 153, 155 (i.e., not in studies 106 and 127). The Sponsor also reports that in study 106, specific gravity and pH data were to be collected only in the case that values were outside the normal reference ranges, which did not occur.

In the Phase 3 Epilepsy Controlled Pool, shifts from normal at baseline to abnormal for the urine parameters were infrequent and occurred in similar frequencies between the ESL and placebo groups (Safety Information Amendment 5/20/13 Table 9.1.6.5.r1). In the Phase 1 Study Pool, the shift from normal to abnormal for urine WBC was higher for

ESL subjects (9.1%) than placebo (5.3%). However, there was no dose response observed (Safety Information Amendment 5/20/13 Table 9.5.5.1.r1). The mean changes from baseline to final for pH and specific gravity were similar for ESL and placebo subjects (Safety Information Amendment 5/20/13 Table 9.5.4.4.r1).

*Comment: Of note, the Sponsor reported an incorrect number in the Safety Information Amendment: that in the Phase 1 Study Pool, white blood cells in the urine shifted from normal to abnormal in 5.3% of placebo versus 56.3% of ESL treated subjects. However, 56.3% of ESL treated subjects remained abnormal (shifted from abnormal to abnormal while 9.1% of ESL subjects shifted from normal to abnormal for urine WBC) (Safety Information Amendment 5/20/13 Table 9.5.4.4.r1).*

### 7.4.3 Vital Signs

The following table summarizes the potentially clinically significant values in vital sign parameters for the controlled pools. Using the Sponsor's cut-off values, PCS values for BP and HR occurred in a small percentage of the subjects (<1%) with similar percentages between the treatment groups. PCS values for weight occurred in more subjects with conflicting results: higher percentage of ESL subjects than placebo subjects both gained and lost weight in the Phase 3 Epilepsy Controlled Pool.

**Table 125. PCS Vital Signs (from normal baseline values)**

| Category | Phase 3 Epilepsy Controlled | | Nonepilepsy Controlled | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=422 | n=1002 | n=407 | n=1294 |
| SBP <90 mmHg and decrease ≥20 | 1 (0.2) | 5 (0.5) | 2 (0.5) | 3 (0.2) |
| SBP >180 mmHg and increase ≥20 | 0 | 5 (0.5) | 1 (0.2) | 6 (0.5) |
| | n=421 | n=1002 | n=406 | n=1271 |
| DBP <50 mmHg and decrease ≥15 | 0 | 1 (<0.1) | 1 (0.2) | 1 (<0.1) |
| DBP >105 mmHg and increase ≥15 | 2 (0.5) | 5 (0.5) | 1 (0.2) | 11 (0.9) |
| | n=421 | n=999 | n=408 | n=1278 |
| HR <50 bpm and decrease ≥15 | 0 | 1 (0.1) | 0 | 3 (0.2) |
| HR >120 bpm and increase ≥25 | 0 | 1 (0.1) | 0 | 0 |
| | n=422 | n=1003 | n=262 | n=971 |
| Weight ≤7% | 4 (0.9) | 37 (3.7) | 3 (1.1) | 15 (1.5) |
| Weight ≥7% | 26 (6.2) | 97 (9.7) | 6 (2.3) | 17 (1.8) |

Source: ISS Tables 11.1.2, 11.4.2.1

The following tables summarize the mean change from baseline to the end of treatment for the vital sign parameters (for both the epilepsy and nonepilepsy controlled pools). The mean values for systolic blood pressure, diastolic blood pressure, and pulse rate were within the normal range at the end of treatment in all groups. The mean changes were small and clinically insignificant (and without dose-response relationship).

**Table 126. Mean Change from Baseline to End of Treatment for Vital Signs, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo | ESL | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=423 | n=194 | n=408 | n=403 | n=1005 |
| SBP (mmHg) | -0.6 | 1.1 | -0.1 | 0.2 | 0.3 |
| DBP (mmHg) | 0.0 | -0.0 | -0.5 | 0.6 | 0.1 |
| HR (bpm) | 0.6 | -0.5 | -0.1 | 0.5 | 0.1 |
| Weight (kg) | 0.3 | 0.6 | 0.3 | 0.3 | 0.4 |
| BMI ($kg/m^2$) | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 |

Source: ISS Table 11.1.1

**Table 127. Mean Change from Baseline to End of Treatment for Vital Signs, Nonepilepsy Controlled Pool (excludes Study 206)**

| Category | Placebo | ESL | | | | |
|---|---|---|---|---|---|---|
| | | <600 mg | 600-<1000 mg | 1000-<1400 mg | ≥1400 mg | Total |
| | n=406 | n=298 | n=565 | n=316 | n=93 | n=1272 |
| SBP (mmHg) | -1.6 | -2.4 | -0.4 | -1.0 | -2.5 | -1.2 |
| DBP (mmHg) | -0.4 | -0.8 | -0.2 | -0.0 | -1.0 | -0.3 |
| HR (bpm) | -1.0 | 0.1 | -0.0 | 0.7 | -1.1 | 0.1 |
| | n=262 | n=267 | n=386 | n=224 | n=94 | n=971 |
| Weight (kg) | 0.0 | 0.0 | 0.1 | 0.1 | 0.3 | 0.1 |
| BMI ($kg/m^2$) | 0.0 | 0.0 | 0.1 | 0.0 | 0.1 | 0.0 |

Source: ISS Table 11.4.1

*Comment: In the ADVS dataset, I noted the following vital sign values that were clearly incorrect: 3 subjects with a respiratory rate of -96 and 2 subjects with an oxygen saturation of -96% (instead of +96%).*

More granular analyses of blood pressure and weight were requested by the Division and submitted by the Sponsor in the Safety Information Amendment dated 5/7/13. The following table summarizes the number (%) of subjects with an increase from baseline in SBP and DBP by different categories of mmHg change and study periods. Although there were small differences (≤ 2%) between ESL subjects and placebo at different periods and blood pressure categories, there were no substantial trends in increases in SBP or DBP. Blood pressure data was also analyzed for the opposite effects of decreases in SBP/DBP from baseline which did not reveal any consistent differences between ESL and placebo subjects (although there were isolated differences of ≤ 2% between ESL and placebo subjects in a couple of the categories) (Safety Information Amendment 5/7/13 Table 9).

**Table 128. Increase from Baseline in SBP and DBP by Study Period, Phase 3 Epilepsy Controlled Pool**

| | Systolic BP | | Diastolic BP | |
|---|---|---|---|---|
| | **Placebo** | **ESL** | **Placebo** | **ESL** |
| **End of Titration Period** | n=423 | n=1005 | n=423 | n=1005 |
| Increase 5 - 10 mm Hg | 87 (20.6%) | 220 (21.9%) | 76 (18.0%) | 241 (24.0%) |
| Increase 11 - 15 mm Hg | 15 (3.5%) | 46 (4.6%) | 14 (3.3%) | 37 (3.7%) |
| Increase 16 - 20 mm Hg | 16 (3.8%) | 42 (4.2%) | 14 (3.3%) | 27 (2.7%) |
| Increase > 20 mm Hg | 16 (3.8%) | 39 (3.9%) | 3 (0.7%) | 8 (0.8%) |
| | | | | |
| **Maintenance Period** | n=410 | n=932 | n=410 | n=932 |
| Increase 5 - 10 mm Hg | 111 (27.1%) | 233 (25.0%) | 118 (28.8%) | 281 (30.2%) |
| Increase 11 - 15 mm Hg | 19 (4.6%) | 65 (7.0%) | 28 (6.8%) | 47 (5.0%) |
| Increase 16 - 20 mm Hg | 27 (6.6%) | 86 (9.2%) | 18 (4.4%) | 47 (5.0%) |
| Increase > 20 mm Hg | 21 (5.1%) | 56 (6.0%) | 5 (1.2%) | 19 (2.0%) |
| | | | | |
| **End of Treatment** | n=423 | n=1005 | n=423 | n=1005 |
| Increase 5 - 10 mm Hg | 93 (22.0%) | 217 (21.6%) | 91 (21.5%) | 219 (21.8%) |
| Increase 11 - 15 mm Hg | 19 (4.5%) | 47 (4.7%) | 19 (4.5%) | 36 (3.6%) |
| Increase 16 - 20 mm Hg | 23 (5.4%) | 55 (5.5%) | 8 (1.9%) | 32 (3.2%) |
| Increase > 20 mm Hg | 8 (1.9%) | 38 (3.8%) | 5 (1.2%) | 16 (1.6%) |

Source: Safety Amendment 5/7/13 Table 8

To further assess for outliers in changes in weight, subjects were categorized into different intervals of the amount of weight changes. The following tables summarize the percentages of subjects in each weight change category by randomized dose group for the Phase 3 Epilepsy Controlled Pool. There was a slightly higher frequency of weight loss in ESL subjects than placebo subjects (with a dose-response relationship). However, with only small risk differences (≤1.0%), no definitive conclusions regarding weight changes and ESL use can be made.

**Table 129. Weight Change Categories, Phase 3 Epilepsy Controlled Pool**

| **Amount Change (kg) from baseline** | **Placebo n (%)** | **ESL n (%)** | | | |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | Total |
| | n=423 | n=194 | n=408 | n=401 | n=1003 |
| ≤ -10 | 0 | 0 | 2 (0.5%) | 4 (1.0%) | 6 (0.6%) |
| -10 to ≤-5 | 5 (1.2%) | 2 (1.0%) | 7 (1.7%) | 10 (2.5%) | 19 (1.9%) |
| -5 to ≤0 | 234 (55%) | 98 (51%) | 224 (55%) | 212 (53%) | 534 (53%) |
| 0 to ≤5 | 174 (41.1%) | 88 (45%) | 163 (40%) | 158 (39%) | 409 (41%) |
| >5 to ≤10 | 10 (2.4%) | 6 (3.1%) | 10 (2.5%) | 13 (3.2%) | 29 (2.9%) |
| >10 to ≤15 | 0 | 0 | 2 (0.5%) | 3 (0.7%) | 5 (0.5%) |
| >15 to ≤20 | 0 | 0 | 0 | 0 | 0 |
| > 20 | 0 | 0 | 0 | 1 (0.2%) | 1 (<0.1%) |

Source: Safety Amendment 5/7/13 Table 10

Phase 1 Studies

The following table summarizes the potentially clinically significant values in vital sign parameters for the Phase 1 Studies. Using the Sponsor's cut-off values, PCS values for BP and HR occurred in a small percentage of the subjects in most of the categories with similar percentages between the treatment groups. PCS values for SBP decreases occurred at a slightly higher incidence in ESL subjects than placebo subjects.

**Table 130. PCS Vital Signs (from normal baseline values), Phase 1 Study Pool**

| Vital Sign Parameter | Placebo | ESL |
|---|---|---|
| | n=185 | n=511 |
| SBP <90 mmHg and decrease ≥20 | 1 (0.5) | 17 (3.3) |
| SBP >180 mmHg and increase ≥20 | 0 | 4 (0.8) |
| | n=186 | n=514 |
| DBP <50 mmHg and decrease ≥15 | 2 (1.1) | 8 (1.6) |
| DBP >105 mmHg and increase ≥15 | 0 | 6 (1.2) |
| | n=185 | n=514 |
| HR <50 bpm and decrease ≥15 | 3 (1.6) | 7 (1.4) |
| HR >120 bpm and increase ≥25 | 0 | 5 (1.0) |
| | n=17 | n=160 |
| Weight ≤7% | 0 | 2 (1.3) |
| Weight ≥7% | 1 (5.9) | 4 (4.4) |

Source: ISS Table 11.5.1

Orthostatic Changes

In response to the Division's information request, the Sponsor submitted a Safety Amendment dated May 7, 2013 to list all of the studies that measure orthostatic changes in vital signs. The Sponsor reported that orthostatic changes in vital signs were captured in the following studies: 101, 102, 124, and 129. However, the Sponsor did not include the data from the DDI studies 124 and 129 in the following summary table because there was no placebo control group. Furthermore, for 5 other studies (103, 104, 107, 108, and 110), the Sponsor reported that vital sign measurements in supine and standing positions were collected on different visit dates (so assessment of orthostatic changes could not be made). The small number of subjects with orthostatic measurements precludes the ability to make any definitive conclusions regarding ESL and orthostatic changes in vital signs.

**Table 131. Concurrent Orthostatic Changes (SBP decrease and HR increase)**

| | **Study 101** | | **Study 102** | |
|---|---|---|---|---|
| | Placebo | ESL | Placebo | ESL |
| | n=16 | n=48 | n=8 | n=24 |
| **SBP decrease ≥20 mmHg and HR increase** | | | | |
| HR increase ≥15 | 3 (18.8) | 3 (6.3) | 0 | 4 (16.7) |
| HR increase ≥30 | 1 (6.3) | 0 | 0 | 1 (4.2) |

Source: Safety Amendment 5/7/13 Table 7

Vital sign-related TEAEs leading to discontinuation and SAEs are discussed in the Cardiac disorders section in Section 7.3.5.

### 7.4.4 Electrocardiograms (ECGs)

The ECG data for ESL come from the thorough QT trial, Study 116, and from ECGs that were performed during the epilepsy, nonepilepsy, and Phase 1 trials. Based on review of the thorough QT study and on data from the clinical studies as discussed below, there is no evidence of QT prolongation with ESL.

The Sponsor's NDA submission included results from a formal QT study that examined the effect of ESL on cardiac repolarization. The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed Study 116 in a review dated October 30, 2009. The IRT reported the following:

- No significant QTc prolongation effect of ESL (1200 mg and 2400 mg) was detected in this TQT study.
- The largest upper bounds of the 2-sided 90% CI for the mean difference between eslicarbazepine acetate (1200 mg and 2400 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.
- The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms indicating that assay sensitivity was established.
- Dose selection was acceptable; the 2400-mg dose is the maximum tolerated dose. The supratherapeutic dose (2400 mg) produces concentrations of 2-fold higher than those with the therapeutic dose (1200 mg).
- There were no clinically relevant effects on the PR and QRS intervals (5 subjects had a post-dose PR interval >200 ms but none experienced a change >25% from baseline).
- None of the events identified to be of clinical importance per the ICH E14 guidelines (e.g., syncope, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

The IRT recommended the following labeling to summarize the results of the formal QT study:

> Cardiac Electrophysiology
> The effect of eslicarbazepine acetate on cardiac repolarization was evaluated in a randomized, double-blind, placebo- and active-controlled 4-period crossover trial in healthy adult men and women. Subjects received eslicarbazepine acetate 1200 mg once daily × 5 days, eslicarbazepine acetate 2400 mg once daily × 5 days, an active-control, moxifloxacin 400 mg × 1 dose on Day 5, and placebo once daily × 5 days. At both doses of eslicarbazepine, no significant effect on the QTc interval was detected.

The following table summarizes the PCS ECG values in the controlled pools. In the Phase 3 Epilepsy Controlled Pool, no ESL subjects had a maximum QT, QTcB, or QTcF interval ≥ 500 msec. Furthermore, the percentages of subjects with increased QTcF values were similar (or less) with ESL compared to placebo. There were small differences (<1.0%) between ESL and placebo subjects in the incidences of prolonged PT interval and QRS interval (described below).

In the Nonepilepsy Controlled Pool, 2 ESL subjects had a maximum QTcB interval ≥500 msec (described in more detail below). It is difficult to make any conclusions regarding ECG use and ECG values for the Nonepilepsy Controlled Pool due to small numbers of subjects with PCS ECG values collected.

**Table 132. PCS ECG Parameters**

| PCS criteria | Phase 3 Epilepsy | | Nonepilepsy^ | |
|---|---|---|---|---|
| | Placebo n=426 | ESL n=1021 | Placebo n=411 | ESL n=1294 |
| **Heart Rate** | n=334 | n=778 | n=17 | n=59 |
| <50 bpm and >20% decrease from baseline | 2 (0.6) | 2 (0.3) | 0 | 0 |
| >120 bpm and >20% increase from baseline | 0 | 0 | 0 | 0 |
| **PR Interval** | n=334 | n=776 | n=17 | n=59 |
| >200 ms and >20% increase from baseline | 0 | 2 (0.3) | 0 | 2 (3.4) |
| >200 ms not present at baseline | 2 (0.6) | 11 (1.4) | 0 | 2 (3.4) |
| >220 ms not present at baseline | 0 | 5 (0.6) | 0 | 2 (3.4) |
| >250 ms not present at baseline | 0 | 2 (0.3) | 0 | 0 |
| **QRS Interval** | n=334 | n=776 | n=17 | n=59 |
| >120 ms and >20% increase from baseline | 0 | 3 (0.4) | 0 | 0 |
| **QT Interval** | n=334 | n=771 | n=17 | n=59 |
| ≥500 ms not present at baseline | 0 | 0 | 0 | 1 (1.7) |
| **QTcB Interval** | n=334 | n=771 | n=17 | n=59 |
| ≥500 ms not present at baseline | 0 | 0 | 0 | 2 (3.4) |
| ≥450 ms not present at baseline | 10 (3.0) | 18 (2.3) | 6 (35) | 9 (15) |
| ≥450 ms not present at baseline in males or ≥470 ms not present at baseline, females | 5 (1.5) | 3 (0.4) | 4 (24) | 7 (12) |
| <340 ms not present at baseline | 1 (0.3) | 4 (0.5) | 0 | 1 (1.7) |
| max change from baseline <30 ms | 290 (87) | 657 (85) | 9 (53) | 44 (75) |
| max change from baseline ≥30-<60 ms | 34 (10.2) | 64 (8.3) | 3 (18) | 5 (8.5) |
| max change from baseline ≥60 ms | 0 | 8 (1.0) | 1 (5.9) | 1 (1.7) |
| max ≥500 ms and Δ from baseline ≥60 ms | 0 | 0 | 0 | 1 (1.7) |
| **QTcF Interval** | n=334 | n=771 | n=17 | n=59 |
| ≥500 ms not present at baseline | 0 | 0 | 0 | 1 (1.7) |
| ≥450 ms not present at baseline | 3 (0.9) | 2 (0.3) | 0 | 3 (5.1) |
| ≥450 ms not present at baseline in males or ≥470 ms not present at baseline, females | 1 (0.3) | 0 | 0 | 2 (3.4) |
| <340 ms not present at baseline | 1 (0.3) | 4 (0.5) | 0 | 0 |
| max change from baseline <30 ms | 302 (90) | 689 (89) | 11 (65) | 45 (76) |
| max change from baseline ≥30-<60 ms | 22 (6.6) | 39 (5.1) | 2 (12) | 4 (6.8) |
| max change from baseline ≥60 ms | 0 | 1 (0.1) | 0 | 1 (1.7) |
| max ≥500 ms and Δ from baseline ≥60 ms | 0 | 0 | 0 | 0 |

Source: ISS Tables 10.1.2, 10.4.2.1, Safety Information Amendment 5/7/13 Table 10.1.2.r1
*Dose-related increase noted for randomized dose groups 400 mg, 800 mg, 1200 mg
^excludes Study 206

*Comment: In response to the Division's information request, the Sponsor submitted a Safety Amendment on May 7, 2013 to explain why only about three-fourths of the ESL subjects had at least one post-dose ECG assessment in the Phase 3 Epilepsy Controlled Pool. The Sponsor stated that while all studies had electrocardiogram (ECG)*

*measurements, some were not included in the analysis because they were deemed uninterpretable. The Sponsor reported that approximately 10-20% of the ECG tracings (Study 301: 20%, Study 302: 17%, Study 304: 11%) were considered uninterpretable or missing (Safety Information Amendment 5/7/13 Table 1). The Sponsor reported that the ECG parameters were obtained by the central ECG overread (performed by (b) (4)) and not the machine-generated parameters reported on the actual ECG tracings. These overreads were retrospectively performed, sometimes 4 years after study completion. The Sponsor reported that this time lapse contributed to the high number of uninterpretable ECGs due to faded tracings, poor quality of photocopies, leads not labeled, missing grids, paper speed or voltage. The Sponsor reported that for Study 304, ECGs were "uninterpretable" largely due to the fact that some sites were only able to provide pdf files of ECG tracings, which were slightly reduced in size and, therefore, "could not be fully analyzed."*

*The unique subject IDs for these subjects with "uninterpretable" ECGs were requested by the Division. In the Sponsor's listing of all uninterpretable ECGs (for Studies 301, 302, 304), subject 301-101-90186 was listed as have ECGs "unable to evaluate." However, I evaluated the CRF for this subject and identified 6 ECGs (dated 2/23/05 to 10/25/06) which were adequate enough to evaluate the ECG parameters. The Sponsor had (b) (4) rereview these ECGs for this subject and stated that these ECGs were "photocopies with reduced grid size" which made them "uninterpretable." The Sponsor reported that the clinical sites only collected and filed the copies of ECGs (and not the actual ECG tracings) for all subjects in Study 304. The Sponsor stated that the ECG overread process utilized by (b) (4) is "consistent with industry standard when analyzing a photocopy ECG." Therefore, the Sponsor deemed it "not feasible to reevaluate ECGs deemed uninterpretable by (b) (4) the central cardiac safety vendor, or to otherwise obtain machine-generated ECG parameters for reanalysis." The Sponsor concluded that "[o]verall, the number of uninterpretable ECGs is minimal. We would not expect this small proportion of data to alter the overall assessment that no clinically relevant ECG abnormalities were observed in the Phase 3 studies."*

*Additionally in the same Safety Information Amendment (upon our request), the Sponsor explained the discrepancy between the number of subjects in the Nonepilepsy Controlled Pool with ECGs listed in ISS Tables 10.4.1/10.4.2.1 (59 ESL subjects and 17 placebo subjects) and ISS Table 10.4.4.1 (1124 ESL subjects and 354 placebo subjects). The Sponsor reported that all of the studies in the Nonepilepsy Controlled Pool had interpretations of ECGs collected, but only the Bipolar studies 2093-203 and 2093-204 had ECG parameters collected (for the PCS values).*

*Lastly in the same Safety Information Amendment (upon our request), the Sponsor provided an explanation for why the sum of the subjects (in ISS Table 10.1.2) with a maximum change from baseline for QTcB/QTcF intervals for the 3 categories (<30 ms, >=30-<60 ms, >=60 ms) was different from the total number of subjects with measured ECG parameters (334 placebo subjects and 771 ESL subjects). In addition to the lack*

*of baseline measurements in some subjects, the Sponsor revealed that "due to a programming error, subjects in the Phase 3 studies who were classified in one PCS category (eg, ≥ 450 ms not present at baseline) were not classified in any other PCS category." In the table above, I incorporated the information in the Sponsor's corrected tables in Appendix of the Safety Information Amendment.*

For Study 201, in response to the Division's request, the Sponsor provided PCS ECG values for the 96 ESL subjects and 47 placebo subjects in the Safety Information Amendment dated 5/20/13 (Table 10.4.2.3.r1). The parameters that had different incidences between ESL and placebo subjects were heart rate <50 bpm and >20% decrease from baseline (2.1% vs 0), PR interval >220 ms not present at baseline (2.1% vs 0), and PR interval >250 ms not present at baseline (1.1% vs 0).

The following table summarizes the PCS ECG values for the PR interval for the Phase 1 studies. ESL subjects had a slightly higher frequency of prolonged PR interval (for all of the categories) than placebo subjects.

**Table 133. PCS ECG Values for the PR Interval, Phase 1 Study Pool**

| PCS criteria | Placebo n=223 | ESL n=847 |
|---|---|---|
| **PR Interval** | n=170 | n=399 |
| >200 ms and >20% increase from baseline | 0 | 2 (0.5) |
| >200 ms not present at baseline | 6 (3.5) | 18 (4.5) |
| >220 ms not present at baseline | 1 (0.6) | 5 (1.3) |
| >250 ms not present at baseline | 0 | 2 (0.5) |

Source: ISS Table 10.5.1

The following table summarizes the mean change from baseline results for the ECG data from the main controlled pools. ESL subjects had larger mean changes for the PR interval than placebo subjects in both controlled pools (2.0 vs 0.6 ms and 7.2 vs 0.5 ms). Otherwise, the mean changes tended to be small and of unknown clinical significance.

**Table 134. Mean Change from Baseline (to End of Study/Early Termination Visit) for ECG Parameters**

| ECG Parameter | Phase 3 Epilepsy Controlled | | | | Nonepilepsy Controlled Pool^ | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo n=426 | | ESL n=1021 | | Placebo n=411 | | ESL n=1294 | |
| | n | mean Δ | n | mean Δ | n | mean Δ | n | mean Δ |
| QT interval (ms) | 324 | 4.0 | 729 | 0.7 | 13 | -5.8 | 50 | -2.9 |
| QTcB (ms) | 324 | 3.0 | 729 | 1.5* | 13 | -2.0 | 50 | -4.5 |
| QTcF (ms) | 324 | 3.4 | 729 | 1.2* | 13 | -3.3 | 50 | -3.7 |
| Heart rate (bpm) | 325 | -0.6 | 739 | 0.1 | 13 | 1.4 | 50 | -1.1 |
| PR interval (ms) | 324 | 0.6 | 735 | 2.0 | 13 | 0.5 | 50 | 7.2 |
| QRS interval (ms) | 325 | 0.5 | 737 | 0.5 | 13 | 0.6 | 50 | 0.2 |

Source: ISS Tables 10.1.1, 10.4.1
*Dose-related increase noted for randomized dose groups 400 mg, 800 mg, 1200 mg
^excludes Study 206

In Study 201, the mean change for the ECG values by visit for HR, PR interval, QRS duration, QT interval, and QTc interval were similar between the ODG, TDG and placebo groups (CSR Table 68).

The following table summarizes the percentages of subjects who developed treatment-emergent ECG abnormalities in the Phase 3 Epilepsy Controlled Pool. There was a slightly higher frequency of conduction and rhythm abnormalities in ESL subjects than placebo subjects in both controlled pools.

**Table 135. Treatment-Emergent ECG Abnormalities**

| | Phase 3 Epilepsy | | Nonepilepsy^ | |
|---|---|---|---|---|
| **ECG Abnormality** | Placebo n=426 | ESL n=1021 | Placebo n=411 | ESL n=1294 |
| # Subjects with ≥ 1 post-dose ECG value | n=334 | n=778 | n=354 | n=1124 |
| Any ECG Abnormality | 136 (41) | 301 (39) | 11 (3.1) | 59 (5.2) |
| Rhythm abnormalities | 80 (24) | 191 (25) | 3 (0.8) | 23 (2.0) |
| Conduction abnormalities | 37 (11) | 100 (13)* | 4 (1.1) | 17 (1.5) |
| Morphology abnormalities | 14 (4.2) | 18 (2.3) | 1 (0.3) | 19 (1.7) |
| Myocardial infarction | 0 | 1 (0.1) | 2 (0.6) | 6 (0.5) |
| Presence of ST segment abnormalities | 0 | 0 | 2 (0.6) | 7 (0.6) |
| Presence of T wave abnormalities | 18 (5.4) | 40 (5.1) | 1 (0.3) | 2 (0.2) |
| Presence of U wave abnormalities | 0 | 0 | 0 | 0 |

Source: ISS Tables 10.1.4, 10.4.4.1
*Dose-related increase noted for randomized dose groups 400 mg, 800 mg, 1200 mg
^excludes Study 206 Part 1

Using the integrated ECG datasets, I further analyzed the ECG parameters for the ESL subjects who developed PCS changes in the QT (>500 ms) and PR (>250 ms or >200 ms and >20% increase from baseline) intervals. None of the following subjects had adverse events in the HLT Cardiac conduction disorders. Of note, ECGs were performed at Visit 3 (week 2) and Visit 5 (week 14) during the Phase 3 epilepsy studies according to the study protocols.

Subject 304-056-05601 developed an increase in the PR interval from 230 ms at baseline to 260 ms at Visit 5. The subject completed the study (no other ECGs were performed). Carbamazepine was started during the study. *Of note, the carbamazepine PI includes information regarding AV block.*

Subject 302-332-80191 developed an isolated increase in the PR interval to >250 ms in the background of milder PR prolongation (202-232 ms) while continued on ESL into the OLE study.

Subject 302-315-80254 developed an increase in the PR interval from 172 ms at baseline to 213 ms on the early discontinuation visit (5 days after stopping ESL for adverse events of visual impairment and ataxia).

Subject 203-309-203004 developed an increase in the PR interval from 176 ms at baseline to 224 ms on Day 21 of ESL 600 mg.

Subject 203-331-203066 developed an increase in the PR interval from 190 ms at baseline to 232 ms in addition to an increase in QTcF from 480 ms at baseline to 533 ms on Day 7 of ESL 600 mg.

Subject 203-352-203012 developed an increase in QTcF from 431 ms at baseline to 496 ms on Day 21 of ESL 800 mg.

In conclusion, although QT prolongation was not associated with ESL use, an association between ESL use and an increase in the PR interval was identified in the PCS and mean change analyses. Additionally, information regarding AV block is included in the carbamazepine prescribing information. Therefore, information regarding PR prolongation should be included in the prescribing information for ESL.

### 7.4.5 Special Safety Studies/Clinical Trials

Two Phase 1 studies 123 and 153 were conducted to specifically examine the effects of ESL on cognitive dysfunction in normal volunteers and recreational CNS depressant users, respectively. These studies are discussed in Section 7.3.4 on nervous system disorders of this review.

### 7.4.6 Immunogenicity

Not applicable.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Generally, there was a dose response observed for safety issues, with increasing dose associated with an increase in adverse events. These are noted in appropriate sections within Section 7. Dose response can be difficult to interpret in the controlled trials given that subjects were titrated to the target dose during the titration periods (of varying lengths) and any AE occurring during titration may have occurred at a dose lower than the subjects' final target dose. Furthermore, within pooled groups, differences in the safety profile among the dose groups may reflect differences in the demographics of the studies that the dose groups represent (discussed further in Section 7.2.1).

The reader is referred to the Pharmacometric review, pending at the time of completion of this review, for further details regarding the population PK/PD analysis based on pooled data from the double-blind, Phase 3 epilepsy studies that examined the relationship between plasma concentrations of ESL and the occurrence of TEAEs.

### 7.5.2 Time Dependency for Adverse Events

The following table summarizes my analyses of the relative risk of TEAEs, SAEs, and DCs by onset in the Phase 3 Epilepsy Controlled Pool. Additional analyses for the adverse events of special interest by timing of onset are further described in the appropriate sections within Section 7. The highest relative risk of TEAEs, TEAEs leading to discontinuation, and SAEs occurred during the titration period.

However, statistically significantly higher rates of adverse events (TEAEs and TEAEs leading to discontinuation) continued to occur during the maintenance period.

**Table 136. Relative Risk by Period/Week of Study, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo | | ESL | | Relative Risk | 95% CI | |
|---|---|---|---|---|---|---|---|
| | n (%) | total | n (%) | total | | LL | UL |
| **TEAEs:** | | | | | | | |
| Anytime during the study | 244 | 426 | 744 | 1021 | 1.27 | 1.16 | 1.39 |
| First week | 135 | 426 | 470 | 1021 | 1.45 | 1.24 | 1.70 |
| Titration period | 156 | 426 | 523 | 1021 | 1.40 | 1.22 | 1.61 |
| Maintenance period | 198 | 410 | 532 | 939 | 1.17 | 1.05 | 1.32 |
| Tapering-off | 13 | 377 | 50 | 811 | 1.79 | 0.98 | 3.25 |
| **TEAEs leading to DC:** | | | | | | | |
| Anytime during the study | 28 | 426 | 179 | 1021 | 2.67 | 1.82 | 3.91 |
| First week | 9 | 426 | 83 | 1021 | 3.85 | 1.95 | 7.58 |
| Titration period | 10 | 426 | 104 | 1021 | 4.34 | 2.29 | 8.22 |
| Maintenance period | 19 | 410 | 92 | 939 | 2.11 | 1.31 | 3.42 |
| Tapering-off | 1 | 377 | 3 | 811 | 1.39 | 0.15 | 13.4 |
| **SAEs:** | | | | | | | |
| Anytime during the study | 12 | 426 | 54 | 1021 | 1.88 | 1.01 | 3.47 |
| First week | 2 | 426 | 20 | 1021 | 4.17 | 0.98 | 17.8 |
| Titration period | 4 | 426 | 26 | 1021 | 2.71 | 0.95 | 7.72 |
| Maintenance period | 9 | 410 | 31 | 939 | 1.50 | 0.72 | 3.13 |
| Tapering-off | 2 | 377 | 5 | 811 | 1.16 | 0.23 | 5.96 |

Source: Created by the reviewer using JReview (ADEVENTX: AESER='Y', DISC=1 and ADSL: AEPERIOD, DOSCATC) for studies 301, 302, 304 (PART='Part 1')

The Sponsor performed an analysis of the TEAEs reported during the titration period stratified by the titration scheme. In the Phase 3 Epilepsy Controlled Pool, all of the subjects in the ESL group (n=1021) either initiated dosing with ESL at 400 mg (n=612) or 800 mg (n=409). After 1 week, some of the subjects started on 400 mg were escalated to 800 mg (n=200). Dose initiation at ESL 800 mg was associated with a much higher incidence of TEAEs compared with dose initiation at ESL 400 mg (especially the 400 mg/800 mg group). The following table summarizes the TEAEs reported in ≥2% of subjects during titration. Therefore, ESL should be initiated at the 400 mg dose and then subsequently titrated to the indicated dose group to minimize the incidence of TEAEs.

**Table 137. TEAEs during the Titration Period by Titration Scheme with an incidence ≥2% in any ESL group, Phase 3 Epilepsy Controlled Pool**

| System Organ Class<br>Preferred Term | Stat. | Placebo/ Placebo (N=426) | ESL 400 mg/ 400 mg (N=412) | ESL 400 mg/ 800 mg (N=200) | ESL 800 mg/ 800 mg (N=409) |
|---|---|---|---|---|---|
| Any Treatment Emergent Adverse Events | n (%) | 123 (28.9%) | 151 (36.7%) | 53 (26.5%) | 246 (60.1%) |
| NERVOUS SYSTEM DISORDERS | n (%) | 55 (12.9%) | 81 (19.7%) | 33 (16.5%) | 185 (45.2%) |
| DIZZINESS | n (%) | 15 ( 3.5%) | 34 ( 8.3%) | 14 ( 7.0%) | 96 (23.5%) |
| SOMNOLENCE | n (%) | 17 ( 4.0%) | 25 ( 6.1%) | 10 ( 5.0%) | 61 (14.9%) |
| HEADACHE | n (%) | 16 ( 3.8%) | 16 ( 3.9%) | 8 ( 4.0%) | 39 ( 9.5%) |
| ATAXIA | n (%) | 0 | 3 ( 0.7%) | 0 | 24 ( 5.9%) |
| BALANCE DISORDER | n (%) | 1 ( 0.2%) | 5 ( 1.2%) | 1 ( 0.5%) | 10 ( 2.4%) |
| GASTROINTESTINAL DISORDERS | n (%) | 27 ( 6.3%) | 28 ( 6.8%) | 7 ( 3.5%) | 82 (20.0%) |
| NAUSEA | n (%) | 7 ( 1.6%) | 11 ( 2.7%) | 2 ( 1.0%) | 44 (10.8%) |
| VOMITING | n (%) | 5 ( 1.2%) | 4 ( 1.0%) | 1 ( 0.5%) | 27 ( 6.6%) |
| DIARRHOEA | n (%) | 5 ( 1.2%) | 4 ( 1.0%) | 1 ( 0.5%) | 9 ( 2.2%) |
| EYE DISORDERS | n (%) | 1 ( 0.2%) | 16 ( 3.9%) | 8 ( 4.0%) | 45 (11.0%) |
| DIPLOPIA | n (%) | 0 | 8 ( 1.9%) | 7 ( 3.5%) | 27 ( 6.6%) |
| VISION BLURRED | n (%) | 0 | 7 ( 1.7%) | 2 ( 1.0%) | 11 ( 2.7%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | n (%) | 15 ( 3.5%) | 16 ( 3.9%) | 8 ( 4.0%) | 33 ( 8.1%) |
| FATIGUE | n (%) | 5 ( 1.2%) | 4 ( 1.0%) | 1 ( 0.5%) | 16 ( 3.9%) |
| EAR AND LABYRINTH DISORDERS | n (%) | 3 ( 0.7%) | 6 ( 1.5%) | 4 ( 2.0%) | 16 ( 3.9%) |
| VERTIGO | n (%) | 1 ( 0.2%) | 6 ( 1.5%) | 4 ( 2.0%) | 15 ( 3.7%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | n (%) | 7 ( 1.6%) | 10 ( 2.4%) | 5 ( 2.5%) | 11 ( 2.7%) |
| RASH | n (%) | 0 | 2 ( 0.5%) | 5 ( 2.5%) | 5 ( 1.2%) |

Source: ISS Table 7.1.5.1



## 7.5.3 Drug-Demographic Interactions

The reader is referred to the current Clinical Pharmacology review for further details. The following conclusions were made by Dr. Veneeta Tandon in her Clinical Pharmacology review dated 3/29/09:

- No dose adjustment needed in elderly subjects with creatinine clearance >60 ml/min.
- Pharmacokinetics in pediatric subjects was not evaluated at this time in patients <18 years of age.
- No dosage adjustment based on gender needed.
- No dosage adjustment based on race needed based on a population pharmacokinetics analysis of 534 Caucasians, 77 Hispanics, and 12 Black. There were few Asian (N=6) to make adequate comparisons for this population.

*Comment: Of note, in the ongoing elderly epilepsy study 401, the Sponsor reported that almost half of the subjects (46%, 29/63) discontinued the study prematurely while only*

*27% (17/63) completed the study and 27% (17/63) are ongoing. The Sponsor reported that the most frequent (≥5%) TEAEs included dizziness, somnolence, bronchitis, and hyponatremia. This rate of discontinuations is much higher than in the Phase 3 Epilepsy Controlled Pool or the Nonepilepsy Double-blind Pool (up to 17.5%).*

*Furthermore, elderly patients are more likely to have a calculated creatinine clearance < 50 ml/min (or moderate renal impairment) and may require dose adjustments (see details in the next section of this review).*

The following tables summarize my analyses of the relative risk of TEAEs, SAEs, and DCs by various demographic characteristics including sex, age, race, region, BMI group, and concomitant AED for the Phase 3 Epilepsy Controlled Pool. I also performed analyses by age for the Nonepilepsy Double-blind Pool due to the higher percentage of elderly in these studies. Additional analyses for the adverse events of special interest by demographics are further described in the appropriate sections within Section 7.

While the overall relative risk of TEAEs, TEAEs leading to discontinuation, and SAEs were statistically significant, most of the within-category relative risks were not statistically significant (especially for the SAEs) due to small numbers. There may be a trend towards a higher relative risk of SAEs for females (vs males) and elderly (vs adults). However, with overlapping confidence intervals, it is difficult to draw any definitive conclusions regarding any of the demographic characteristics as risk factors for the development of adverse events with ESL use (compared to placebo).

**Table 138. Relative Risk of TEAEs by Demographics, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo | | ESL | | Relative Risk | 95% CI | |
|---|---|---|---|---|---|---|---|
| | n (%) | total | n (%) | total | | LL | UL |
| **Any TEAEs** | 244 | 426 | 744 | 1021 | 1.27 | 1.16 | 1.39 |
| **Sex:** | | | | | | | |
| Male | 114 | 212 | 353 | 504 | 1.30 | 1.14 | 1.49 |
| Female | 130 | 214 | 391 | 517 | 1.24 | 1.11 | 1.40 |
| **Age:** | | | | | | | |
| Adults (18-< 60 years) | 231 | 402 | 705 | 971 | 1.26 | 1.15 | 1.39 |
| Elderly (≥ 60 years) | 9 | 18 | 31 | 40 | 1.55 | 0.95 | 2.53 |
| **Age (Nonepilepsy Pool):** | | | | | | | |
| Adults (18-< 60 years) | 156 | 366 | 597 | 1059 | 1.32 | 1.16 | 1.51 |
| Elderly (≥ 60 years) | 59 | 141 | 390 | 696 | 1.34 | 1.09 | 1.64 |
| **Race:** | | | | | | | |
| Caucasian | 193 | 331 | 597 | 830 | 1.23 | 1.12 | 1.36 |
| Black | 9 | 14 | 27 | 33 | 1.27 | 0.83 | 1.94 |
| Asian | 22 | 46 | 65 | 87 | 1.56 | 1.13 | 2.16 |
| Hispanic | 2 | 7 | 10 | 12 | 2.92 | 0.88 | 9.67 |
| Other | 18 | 28 | 45 | 59 | 1.19 | 0.87 | 1.62 |
| **Region:** | | | | | | | |
| Eastern Europe | 51 | 132 | 202 | 352 | 1.49 | 1.18 | 1.88 |
| Latin America | 62 | 90 | 192 | 234 | 1.19 | 1.02 | 1.39 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Western Europe | 35 | 58 | 118 | 144 | 1.36 | 1.09 | 1.70 |
| North America | 59 | 81 | 128 | 155 | 1.13 | 0.97 | 1.32 |
| Rest of the World | 37 | 65 | 104 | 136 | 1.34 | 1.07 | 1.69 |
| **BMI Group:** | | | | | | | |
| <18 kg/m$^2$ (underweight) | 7 | 16 | 24 | 33 | 1.66 | 0.92 | 3.01 |
| 18-30 kg/m$^2$ | 188 | 333 | 595 | 816 | 1.29 | 1.16 | 1.43 |
| >30 kg/m$^2$ (obese) | 48 | 75 | 122 | 169 | 1.13 | 0.93 | 1.37 |

Source: Created by the reviewer using JReview (ADEVENTX and ADSL: SEX, AGEGRP, RACEGRP, REGION, BMIGRP)

**Table 139. Relative Risk of TEAEs Leading to Discontinuation by Demographics, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo | | ESL | | Relative Risk | 95% CI | |
|---|---|---|---|---|---|---|---|
| | n (%) | total | n (%) | total | | LL | UL |
| **Any TEAEs leading to DC** | 28 | 426 | 179 | 1021 | 2.67 | 1.82 | 3.91 |
| **Sex:** | | | | | | | |
| Male | 12 | 212 | 71 | 504 | 2.49 | 1.38 | 4.49 |
| Female | 16 | 214 | 108 | 517 | 2.79 | 1.69 | 4.61 |
| **Age:** | | | | | | | |
| Adults (18-< 60 years) | 27 | 402 | 172 | 971 | 2.64 | 1.79 | 3.89 |
| Elderly (≥ 60 years) | 1 | 18 | 6 | 40 | 2.70 | 0.35 | 20.8 |
| **Age (nonepilepsy pool):** | | | | | | | |
| Adults (18-< 60 years) | 19 | 366 | 129 | 1059 | 2.35 | 1.47 | 3.74 |
| Elderly (≥ 60 years) | 12 | 141 | 128 | 696 | 2.16 | 1.23 | 3.80 |
| **Race:** | | | | | | | |
| Caucasian | 17 | 331 | 146 | 830 | 3.42 | 2.11 | 5.57 |
| Black | 3 | 14 | 4 | 33 | 0.57 | 0.15 | 2.20 |
| Asian | 4 | 46 | 17 | 87 | 2.25 | 0.80 | 6.29 |
| Hispanic | 0 | 7 | 2 | 12 | 2.33 | 0.12 | 44.8 |
| Other | 4 | 28 | 10 | 59 | 1.19 | 0.41 | 3.45 |
| **Region:** | | | | | | | |
| Eastern Europe | 7 | 132 | 37 | 352 | 1.98 | 0.91 | 4.34 |
| Latin America | 6 | 90 | 42 | 234 | 2.69 | 1.19 | 6.11 |
| Western Europe | 2 | 58 | 39 | 144 | 7.85 | 1.96 | 31.5 |
| North America | 9 | 81 | 35 | 155 | 2.03 | 1.03 | 4.02 |
| Rest of the World | 4 | 65 | 26 | 136 | 3.11 | 1.13 | 8.53 |
| **BMI Group:** | | | | | | | |
| <18 kg/m$^2$ (underweight) | 0 | 16 | 8 | 33 | 7.76 | 0.47 | 127 |
| 18-30 kg/m$^2$ | 21 | 333 | 141 | 816 | 2.74 | 1.76 | 4.26 |
| >30 kg/m$^2$ (obese) | 7 | 75 | 28 | 169 | 1.78 | 0.81 | 3.88 |

Source: Created by the reviewer using JReview (ADEVENTX: DISC=1 and ADSL: SEX, AGEGRP, RACEGRP, REGION, BMIGRP)

**Table 140. Relative Risk of SAEs by Demographics, Phase 3 Epilepsy Controlled Pool**

| Category | Placebo | | ESL | | Relative Risk | 95% CI | |
|---|---|---|---|---|---|---|---|
| | n (%) | total | n (%) | total | | LL | UL |
| **Any SAEs** | 12 | 426 | 54 | 1021 | 1.88 | 1.01 | 3.47 |
| **Sex:** | | | | | | | |
| Male | 7 | 212 | 24 | 504 | 1.44 | 0.63 | 3.30 |
| Female | 5 | 214 | 30 | 517 | 2.48 | 0.98 | 6.32 |
| **Age:** | | | | | | | |
| Adults (18-< 60 years) | 12 | 402 | 50 | 971 | 1.73 | 0.93 | 3.20 |
| Elderly (≥ 60 years) | 0 | 18 | 4 | 40 | 3.60 | 0.20 | 64.6 |
| **Age (nonepilepsy pool):** | | | | | | | |
| Adults (18-< 60 years) | 5 | 366 | 21 | 1059 | 1.45 | 0.55 | 3.82 |
| Elderly (≥ 60 years) | 2 | 141 | 35 | 696 | 3.55 | 0.86 | 14.6 |
| **Race:** | | | | | | | |
| Caucasian | 11 | 331 | 43 | 830 | 1.56 | 0.81 | 2.99 |
| Black | 1 | 14 | 1 | 33 | 0.42 | 0.03 | 6.32 |
| Asian | 0 | 46 | 3 | 87 | 3.17 | 0.16 | 62.0 |
| Hispanic | 0 | 7 | 1 | 12 | 1.17 | 0.04 | 30.5 |
| Other | 0 | 28 | 6 | 59 | 5.69 | 0.33 | 98.4 |
| **Region:** | | | | | | | |
| Eastern Europe | 4 | 132 | 17 | 352 | 1.59 | 0.55 | 4.65 |
| Latin America | 3 | 90 | 10 | 234 | 1.28 | 0.36 | 4.55 |
| Western Europe | 2 | 58 | 9 | 144 | 1.81 | 0.40 | 8.14 |
| North America | 3 | 81 | 8 | 155 | 1.39 | 0.38 | 5.11 |
| Rest of the World | 0 | 65 | 10 | 136 | 9.56 | 0.57 | 161 |
| **BMI Group:** | | | | | | | |
| <18 kg/$m^2$ (underweight) | 0 | 16 | 2 | 33 | 1.94 | 0.09 | 40.58 |
| 18-30 kg/$m^2$ | 8 | 333 | 42 | 816 | 2.14 | 1.02 | 4.51 |
| >30 kg/$m^2$ (obese) | 4 | 75 | 10 | 169 | 1.11 | 0.36 | 3.42 |

Source: Created by the reviewer using JReview (ADEVENTX: AESER='Y' and ADSL: SEX, AGEGRP, RACEGRP, REGION, BMIGRP)
*Using zero correction factor of 0.5

Concomitant Carbamazepine
The following table summarizes my analyses of the relative risk of TEAEs by concomitant AED for the Phase 3 Epilepsy Controlled Pool. Of note, most of the total ESL group was being treated at baseline with 2 AEDs (68.7%), fewer with only 1 AED (28.2%) and fewest with 3 AEDs (3.0%). Analyses for SAEs were not performed due to small numbers.

For TEAEs leading to discontinuation, while there is a higher relative risk with concomitant carbamazepine use (vs nonuse), there are even larger relative risks with concomitant valproic acid use (vs nonuse) and phenytoin/phenobarbital use (vs nonuse). However, for TEAEs in the SOC Nervous system disorders (particularly in the dizziness group) and SOC Eye disorders, the largest relative risk occurred with concomitant carbamazepine use vs nonuse (while other AEDs such as

phenytoin/phenobarbital and valproic acid had lower relative risks for concomitant use vs nonuse). This trend was reversed for TEAEs in the somnolence group. However, with overlapping confidence intervals, it is difficult to draw any definitive conclusions regarding concomitant AED use as a risk factor for the development of adverse events with ESL use (compared to placebo).

**Table 141. TEAEs by Concomitant AED (during the baseline period), Phase 3 Epilepsy Controlled Pool**

| Category | Placebo | | Total ESL | | **Relative Risk** | 95% CI | |
|---|---|---|---|---|---|---|---|
| | n (%) | total | n (%) | total | | LL | UL |
| **TEAEs** | | | | | | | |
| Carbamazepine use | 116 | 198 | 396 | 524 | **1.29** | 1.14 | 1.46 |
| No CBZ at baseline | 128 | 228 | 348 | 497 | **1.25** | 1.10 | 1.42 |
| Lamotrigine use | 62 | 108 | 175 | 245 | **1.24** | 1.04 | 1.49 |
| No LTG use at baseline | 182 | 318 | 569 | 776 | **1.28** | 1.15 | 1.42 |
| Levetiracetam use | 53 | 91 | 130 | 178 | **1.25** | 1.03 | 1.52 |
| No levetiracetam use | 191 | 335 | 614 | 843 | **1.28** | 1.15 | 1.41 |
| Valproic acid use | 42 | 95 | 149 | 218 | **1.55** | 1.21 | 1.97 |
| No VPA use at baseline | 202 | 331 | 595 | 803 | **1.21** | 1.10 | 1.34 |
| Phenytoin, phenobarbital use | 47 | 84 | 123 | 166 | **1.32** | 1.07 | 1.63 |
| No PHT or PBT use | 197 | 342 | 621 | 855 | **1.26** | 1.14 | 1.39 |
| **TEAEs leading to DC** | 28 | 426 | 179 | 1021 | **2.67** | 1.82 | 3.91 |
| Carbamazepine use | 14 | 198 | 110 | 524 | **2.97** | 1.74 | 5.05 |
| No CBZ at baseline | 14 | 228 | 69 | 497 | **2.26** | 1.30 | 3.93 |
| Lamotrigine use | 4 | 108 | 28 | 245 | **3.09** | 1.11 | 8.58 |
| No LTG use at baseline | 24 | 318 | 141 | 776 | **2.41** | 1.59 | 3.64 |
| Levetiracetam use | 5 | 91 | 23 | 178 | **2.35** | 0.92 | 5.98 |
| No levetiracetam use | 23 | 335 | 156 | 843 | **2.70** | 1.77 | 4.10 |
| Valproic acid use | 2 | 95 | 26 | 218 | **5.67** | 1.37 | 23.4 |
| No VPA use at baseline | 26 | 331 | 153 | 803 | **2.43** | 1.63 | 3.60 |
| Phenytoin, phenobarbital use | 4 | 84 | 27 | 166 | **3.42** | 1.24 | 9.44 |
| No PHT or PBT use | 24 | 342 | 152 | 855 | **2.53** | 1.68 | 3.82 |
| **Nervous System Disorders** | | | | | | | |
| Carbamazepine use | 66 | 198 | 292 | 524 | **1.67** | 1.35 | 2.06 |
| No CBZ at baseline | 67 | 228 | 201 | 497 | **1.38** | 1.10 | 1.73 |
| Lamotrigine use | 35 | 108 | 111 | 245 | **1.40** | 1.03 | 1.90 |
| No LTG use at baseline | 98 | 318 | 382 | 776 | **1.60** | 1.33 | 1.91 |
| Levetiracetam use | 22 | 91 | 74 | 178 | **1.72** | 1.15 | 2.57 |
| No levetiracetam use | 111 | 335 | 419 | 843 | **1.50** | 1.27 | 1.77 |
| Valproic acid use | 23 | 95 | 85 | 218 | **1.61** | 1.09 | 2.38 |
| No VPA use at baseline | 110 | 331 | 408 | 803 | **1.53** | 1.29 | 1.81 |
| Phenytoin, phenobarbital use | 31 | 84 | 81 | 166 | **1.32** | 0.96 | 1.82 |
| No PHT or PBT use | 102 | 342 | 412 | 855 | **1.62** | 1.35 | 1.93 |
| **Dizziness group** | | | | | | | |
| Carbamazepine use | 28 | 198 | 206 | 524 | **2.78** | 1.94 | 3.98 |
| No CBZ at baseline | 24 | 228 | 99 | 497 | **1.89** | 1.25 | 2.87 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lamotrigine use | 15 | 108 | 80 | 245 | **2.35** | 1.42 | 3.89 |
| No LTG use | 37 | 318 | 225 | 776 | **2.49** | 1.81 | 3.44 |
| Levetiracetam use | 7 | 91 | 36 | 178 | **2.63** | 1.22 | 5.67 |
| No levetiracetam use | 45 | 335 | 269 | 843 | **2.38** | 1.78 | 3.17 |
| Valproic acid use | 11 | 95 | 41 | 218 | **1.62** | 0.87 | 3.02 |
| No VPA use | 41 | 331 | 264 | 803 | **2.65** | 1.96 | 3.59 |
| Phenytoin, phenobarbital use | 9 | 84 | 46 | 166 | **2.59** | 1.33 | 5.03 |
| No PHT or PBT use | 43 | 342 | 259 | 855 | **2.41** | 1.79 | 3.24 |
| **Eye Disorders** | 25 | 426 | 160 | 1021 | **2.67** | 1.78 | 4.01 |
| Carbamazepine use | 13 | 198 | 108 | 524 | **3.14** | 1.81 | 5.45 |
| No CBZ at baseline | 12 | 228 | 52 | 497 | **1.99** | 1.08 | 3.65 |
| Lamotrigine use | 14 | 108 | 46 | 245 | **1.45** | 0.83 | 2.52 |
| No LTG at baseline | 11 | 318 | 114 | 776 | **4.25** | 2.32 | 7.78 |
| Levetiracetam use | 5 | 91 | 21 | 178 | **2.15** | 0.84 | 5.51 |
| No levetiracetam use | 20 | 335 | 139 | 843 | **2.76** | 1.76 | 4.34 |
| Valproic acid use | 3 | 95 | 18 | 218 | **2.61** | 0.79 | 8.67 |
| No VPA at baseline | 22 | 331 | 142 | 803 | **2.66** | 1.73 | 4.09 |
| Phenytoin, phenobarbital use | 5 | 84 | 20 | 166 | **2.02** | 0.79 | 5.20 |
| No PHT or PBT use | 20 | 342 | 140 | 855 | **2.80** | 1.78 | 4.40 |
| **Somnolence group** | | | | | | | |
| Carbamazepine use | 32 | 198 | 103 | 524 | **1.22** | 0.85 | 1.75 |
| No CBZ at baseline | 25 | 228 | 115 | 497 | **2.11** | 1.41 | 3.16 |
| Lamotrigine use | 17 | 108 | 49 | 245 | **1.27** | 0.77 | 2.10 |
| No LTG at baseline | 40 | 318 | 169 | 776 | **1.73** | 1.26 | 2.38 |
| Levetiracetam use | 7 | 91 | 36 | 178 | **2.63** | 1.22 | 5.67 |
| No levetiracetam use | 45 | 335 | 269 | 843 | **2.38** | 1.78 | 3.17 |
| Valproic acid use | 9 | 95 | 43 | 218 | **2.08** | 1.06 | 4.10 |
| No VPA at baseline | 48 | 331 | 175 | 803 | **1.50** | 1.12 | 2.01 |
| Phenytoin, phenobarbital use | 15 | 84 | 40 | 166 | **1.35** | 0.79 | 2.30 |
| No PHT or PBT use | 42 | 342 | 178 | 855 | **1.70** | 1.24 | 2.32 |

Source: Created by the reviewer using JReview (ADEVENTX: AEDECOD and ADSL: CARBA, LAMOTRI, VALPACID, LEVETIR, PHENYTOI, PHENOBAR)

### 7.5.4 Drug-Disease Interactions

The reader is referred to the Clinical Pharmacology review for further details. The following conclusions were made by Dr. Veneeta Tandon in her Clinical Pharmacology review dated 3/29/09:

Hepatic Impairment

- Moderate hepatic impairment did not affect the pharmacokinetics of eslicarbazepine and dosage adjustment is not necessary.
- The pharmacokinetics of eslicarbazepine has not been evaluated in the severe hepatic impairment subjects.

Renal Impairment

- Dose reductions are recommended in the patients with moderate and severe renal impairment (<50 mL/min creatinine clearance) due to increased systemic exposure

to eslicarbazepine by 62%, 116%, and 154% in the mild, moderate, and severe renal impairment group, respectively, in comparison to that of the healthy subjects.
- Repeated hemodialysis was effective in removing the SEP-0002093 metabolites from the systemic circulation.
- Proposed dosing recommendations by renal impairment category:

**Table 142. Dosing Schedule for Renal Impairment**

| Dosing Recommendations | Normal (Clcr >80 ml/min) | Mild (Clcr 50-80ml/min) | Moderate (Clcr 30-49 ml/min) | Severe (Clcr 15-29 ml/min) |
|---|---|---|---|---|
| Initial | 400 mg QD<br><br>Weekly increments to the next dose | 400 mg QD<br><br>Weekly increments to the next dose | 300 mg QD<br><br>Weekly increments to the next dose | 200 mg QD<br><br>Weekly increments to the next dose |
| Maximum | 1200 mg QD | 1200 mg QD | 600 mg QD | 600 mg QD |

Source: Clinical Pharmacology Review, Dr. Veneeta Tandon 3/29/09

*Comment: Estimated creatinine clearance (CrCl) should be known before initiating treatment with ESL, particularly in the elderly in whom CrCl < 50 ml/min (or moderate renal impairment) is more common. This information should be included in the prescribing information for ESL.*

### 7.5.5 Drug-Drug Interactions

The reader is referred to the Clinical Pharmacology review for further details. Drug-drug interactions were evaluated in individual *in vitro* studies, studies in healthy volunteers and in a population PK analysis based on the Phase 3 epilepsy studies. The following conclusions were made by Dr. Veneeta Tandon in her Clinical Pharmacology review dated 3/29/09:

- Based on *in vitro* studies:
  - ESL is an inhibitor of CYP2C9 and CYP2C19.
  - ESL is not a substrate of CYP isoenzymes.
  - ESL is not an inducer of CYP3A4.
  - ESL is not an inducer of Phase II enzymes involved in glucuronidation and sulfation of 7-hydroxy coumarin.
- Based on *in vivo* studies in healthy volunteers:
  - Food had no effect on the pharmacokinetics of ESL.
  - No dose adjustment needed for digoxin, metformin, lamotrigine, or topiramate.
  - Alternative or additional non-hormonal birth control should be used (due to significant AUC decreases of ethinylestradiol [42%] and levonorgestrel [37%]).
  - Patients on coumadin should have INR values closely monitored (due to a 23% decrease in the AUC of S-warfarin while on concomitant ESL).
  - Phenytoin dose should be decreased (due to a 35% increase in the AUC of phenytoin while on concomitant ESL).

  - Higher dose of ESL needed while on concomitant phenytoin.
  - Serum lipid profiles should be monitored while on simvastatin and rosuvastatin due to decreased plasma exposures with coadministration of ESL (reported by the Sponsor for Study 124 and 150 – please see Clinical Pharmacology review for the current NDA submission for further details).
- Based on population PK analyses only:
  - No dose adjustment needed for carbamazepine, phenobarbital, valproate, levetiracetam, or gabapentin while on concomitant ESL.
  - Higher dose of ESL may be necessary while on concomitant carbamazepine or phenobarbital.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

In the preclinical studies, the Sponsor reported that there was an increase in the incidence of hepatocellular adenomas and carcinomas in mice. In the *in vitro* genotoxicity studies, the Sponsor reported that ESL and the major human metabolite, eslicarbazepine, were not mutagenic in the Ames test. The reader is referred to the Pharmacology, Toxicology review by Dr. Christopher Toscano for further details regarding these preclinical studies.

Evaluation of deaths, serious AE, discontinuations due to AE and common AE under the MedDRA SOC Neoplasms benign, malignant and unspecified (including cysts and polyps) in the ESL clinical program did not suggest an increased risk of malignancy in subjects taking ESL.

In the Phase 3 Epilepsy Controlled Pool, 1 ESL subject (and 0 placebo subjects) developed a malignant neoplasm (follicular lymphoma). Additionally, there were 3 benign conditions reported during these trials (breast fibroadenoma, verrucae seborrhoicae, angiomyolipoma). In the epilepsy OLE studies, the following additional malignant neoplasms were reported: insulinoma (1), bile duct cancer/colorectal cancer (1), and astrocytoma (1).

In the Nonepilepsy DB Pool (including Study 206), PTs in the SOC Neoplasms occurred in 10 ESL subjects (versus 0 placebo subjects). None of the malignant cancers occurred in more than 1 subject: prostate and renal cancer (both in same subject), basal cell and squamous cell carcinoma (both in same subject), peritoneal metastases, lung carcinoma, gastric cancer, and breast ductal carcinoma in situ. The only term that occurred in 2 or more subjects was a benign condition (melanocytic naevus).

In the nonepilepsy OLE studies, the following additional malignant neoplasms were reported in ESL subjects: tonsillar carcinoma (1), mantle cell lymphoma (in the same

subject who reported basal cell and squamous cell carcinoma during the DB portion of the study), and basal cell carcinomas (2).

In the Phase 1 studies and epilepsy Phase 2 studies, there were no PTs reported in the SOC Neoplasms. The following table summarizes the malignant neoplasms in the Neoplasm SOC.

**Table 143. Malignant Neoplasms, All Studies Pool (including 303)**

| Subject # | Age, Sex, Race | ESL Dose | Adverse event | Study day of ESL | Prior history? |
|---|---|---|---|---|---|
| 302-395-80794 | 61,F, W | 800 mg | Follicular lymphoma* | Day 47 (cont'd until Day 285) | No |
| 301-141-90181 | 39, F, W | 800 mg | Bile duct cancer<br>Colorectal cancer | Day 294 (cont'd until Day 475) | No |
| 302-338-80164 | 24, M, B | 400 mg | Insulinoma | Day 150 (cont'd until Day 337) | Low serum glucose |
| 303-611-70327 | 54, M, W | 400 mg | Astrocytoma* | Day 62 | Astrocytoma |
| 207-211-211008 | 73, M, W | 800 mg | Mantle cell lymphoma<br>(Basal cell carcinoma<br>Squamous cell CA) | 90 days after last ESL dose (after 259 days) | Basal cell |
| 207-210-21002 | 77, M, W | 1200mg | Tonsil cancer | Day 214 | No |
| 210-501-501013 | 60, F, W | 800 mg | Breast ductal carcinoma in situ (right) | Day 47 | Breast biopsy (R) |
| 207-222-222011 | 76, M, W | 400 mg | Oesophageal stenosis<br>Gastric cancer* | Day 15 | GERD |
| 207-206-206014 | 64, M, W | 400 mg | Lung neoplasm malignant* | Day 1 | No |
| 206-763-763013 | 75, M, W | 600 mg | Prostate cancer*<br>Renal cancer | Day 41 | Prostate adenoma |
| 206-566-566029 | 70, F, W | 600 mg | Metastases to peritoneum | Day 9 | Abdominal symptoms |
| 207-101-101002 | 72, F, W | 1200mg | Basal cell carcinoma | Day 250 | No |
| 207-385-385004 | 83, M, W | 800 mg | Basal cell carcinoma | Day 200 | Basal cell |

Source: Created by the reviewer using narratives provided by the Sponsor and JReview Graphical Patient Profile using ADSL and ADEVENTX datasets
*Resulted in death (of note for subject 302-395-80794, information regarding the death was missing from the narrative provided in this NDA resubmission. The death was reported in the narrative provided in the original NDA's 120-day safety update 8/28/09 Appendix 13.1. See Section 7.3.1 of this review for further details)

In the ongoing studies, the Sponsor reported the following TEAEs in the Neoplasms SOC in 7 ESL subjects: fallopian tube cancer/ovarian cancer (1), prostate cancer (1), glioblastoma multiforme (1), parathyroid tumour benign (1), angiofibroma (1), basal cell carcinoma (1), uterine leiomyoma (1) (Safety Information Amendment 7/1/13). The following TEAEs occurred in the blinded treatment group: brain neoplasm (1), glioblastoma multiforme (1), cholesteatoma (1), skin papilloma (1), uterine myoma (1).

Additional TEAEs in the ESL group included basal cell carcinoma (1), prostate cancer (1), uterine leiomyoma (1).

In the postmarketing database, the Sponsor reported no additional neoplasm SAEs in the table of all SAEs (Safety Information Amendment 4/19/13). As for TEAEs in the SOC Neoplasms, the Sponsor confirmed that there have been no postmarketing reports (Safety Information Amendment 7/1/13).

*Comment: In the All Studies Pool (including 303), there were a total of 13 cases of malignant neoplasms. Most (62%) were either diagnosed early in the study (n=1) or diagnosed in subjects with related symptoms or a cancer diagnosis prior to ESL exposure (n=7). Of the resulting 5 cases without prior history, it is difficult to establish a pattern to these neoplasms with only single cases of tonsil, basal cell, and bile duct/colorectal cancer except for the 2 cases of lymphoma (follicular and mantle cell). These cases of 2 different types of lymphoma occurred in older subjects (61 and 73 years of age, respectively). In conclusion, with only a few cases of malignant neoplasms, it is difficult to establish a causal role of ESL in carcinogenicity.*

### 7.6.2 Human Reproduction and Pregnancy Data

The Sponsor proposes that ESL be classified as Pregnancy Class C, noting that preclinical studies demonstrate reproductive toxicity but that there are no data from adequate and well-controlled trials in pregnant women that allow an evaluation of the effects of ESL on reproduction and fetal development. The Sponsor recommends that ESL "should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." Furthermore, for nursing mothers, the Sponsor recommends that "a decision should be made about whether to discontinue nursing or to discontinue ESL in nursing women, taking into account the risk and benefit of ESL to the mother."

In the preclinical studies, the Sponsor reported that ESL did not cause fetal malformations in mice, rats or rabbits. However, maternal toxicity and secondary fetal toxicity was seen with an increased number of post-implantation loss along with lower offspring survival, developmental delays, delayed ossification, and reduce fetal weight. The reader is referred to the Pharmacology, Toxicology review by Dr. Christopher Toscano for further details regarding the preclinical studies.

There was minimal data on the use of ESL in pregnant women as the protocols for the epilepsy studies required that female participants of child-bearing potential to be abstinent or to use at least one medically acceptable method of contraception.

In ISS Section 5.4.1, the Sponsor reported a total of 8 pregnancies (ESL-exposed, treatment-emergent pregnancies) in 8 subjects in the entire safety database. The Sponsor based this total on available information from blood pregnancy tests (beta HCG), urine pregnancy tests, AE reports, SAE reports, or discontinuations due to

pregnancy. (Of note, the Sponsor's search also identified 3 subjects with positive tests but were confirmed not to be pregnant and 8 subjects who were not exposed to ESL at any time [3 placebo subjects and 5 subjects screened but not randomized]). The following stratifies the pregnancies by study pool:

- Epilepsy studies: 6 pregnancies
- Nonepilepsy studies: 1 pregnancy
- Phase 1 studies: 1 pregnancy

The 8 pregnancies resulted in the following outcomes:

- 4 (50%) healthy births - described in more detail in the following Table
- 4 (50%) induced abortions

*Comment: I performed an independent search for pregnancies using the PTs abortion induced, abortion spontaneous, and pregnancy. I did not identify any additional pregnancies. However, I did identify additional pregnancies listed in the PSURs that the Sponsor submitted with the NDA. In response to the Division's information request to explain the additional pregnancies reported in the PSUR (dated 10/22/11-10/21/12) but missing from the ISS, the Sponsor submitted a Safety Information Amendment dated 7/1/13. The Sponsor stated that the 5 additional cases of pregnancy listed in the PSUR were not reported in Section 5.4.1 of the ISS "due to the different cut-off dates" (October 21, 2012 for the PSUR and the earlier cut-off of January 31, 2012 for the ISS). However, it is important to note that 3 out of these 5 pregnancies and deliveries occurred before the data cut-off date for the ISS (January 31, 2012). Furthermore, the Sponsor reported one additional pregnancy (304-303-30308) which was missing from their initial list of all pregnancies because this subject was "described in the section of the ISS describing deaths rather than the section describing pregnancies." These 6 additional pregnancies resulted in the following outcomes:*

- *4 healthy births - described in more detail in the following tables*
- *1 spontaneous abortion - described in the following table (ongoing trial)*
- *1 maternal death likely due to seizures 6 weeks after ESL discontinuation*

**Table 144. Description of Select Pregnancy Exposures to ESL, All Studies Pool (including 303)**

| Subject # | Study Treatment, Dose | Outcome | ESL exposure during pregnancy |
|---|---|---|---|
| 301-212-90237 | ESL 800-1200 mg | Healthy birth | Until third trimester |
| ESL was continued until the third trimester.<br>Outcome: delivery of normal male by Cesarean with normal Apgar scores 7-8.<br>Concomitant medications included carbamazepine and lamotrigine. | | | |
| 302-334-80101 | ESL 800 mg | Healthy birth | <4 weeks |
| ESL discontinued at end of 2 year trial (negative pregnancy test at discontinuation visit).<br>Four weeks later, pregnancy test positive.<br>Outcome: delivery of child with "skin in the middle of coccyx with foveal dimple" with normal spine MRI.<br>Concomitant medications included carbamazepine, clobazam, ethinylestradiol. | | | |

| | | | |
|---|---|---|---|
| 303-712-70064 | ESL 800 mg | Healthy birth | <4 weeks |
| ESL discontinued after positive pregnancy test (last menstrual period was ~1 month prior).<br>Outcome: delivery of normal female at 39 weeks gestation.<br>Concomitant medications included oxcarbazepine and valproate sodium. | | | |
| 304-044-04403 | ESL 800 mg | Healthy birth | ~5 weeks |
| ESL discontinued 9 days prior to positive pregnancy test (last menstrual period was ~6 weeks prior).<br>Outcome: delivery of normal healthy male without complications.<br>Concomitant medications included levetiracetam and carbamazepine. | | | |
| 301-123-90482 | ESL 800 mg | Healthy birth* | <4 weeks |
| Outcome: normal delivery of healthy child<br>Concomitant medications included carbamazepine and Epilan (phenytoin/phenobarbitone). | | | |
| 303-712-70062 | ESL 800 mg | Healthy birth* | <4 weeks |
| Outcome: normal delivery of healthy child<br>Concomitant medications included carbamazepine, clobazam, and diphenidol. | | | |

Source: Created by the reviewer using subject narratives provided by the Sponsor.
*Narratives and case reports submitted by the Sponsor in response to the Division's information request dated 6/19/13

Additionally in the ISS, the Sponsor reported 6 pregnancies in the ongoing studies and 4 pregnancies reported in the postmarketing data. These 10 pregnancies resulted in the following outcomes:

- 1 (10%) congenital anomaly - described in more detail in the following Table
- 3 (30%) spontaneous abortions - described in more detail in the following Table
- 2 (20%) healthy births - described in more detail in the following Table
- 1 (10%) induced abortions
- 3 (30%) outcome unknown (confirmed by the Sponsor in Safety Information Amendment dated 7/1/13 that these outcomes remained unknown).

**Table 145. Description of Select Pregnancy Exposures to ESL, Ongoing Studies and Postmarketing Database**

| Subject # | Study Treatment, Dose | Outcome | ESL exposure during pregnancy |
|---|---|---|---|
| 304-108-06 | ESL 800 mg | Congenital anomaly | <4 weeks |
| ESL discontinued after positive pregnancy test (last menstrual period was ~1 month prior).<br>Outcome: delivery of live infant with multiple congenital abnormalities (wide forehead, narrow bifrontal area, sparse eyebrows, arched palate, small mouth, micrognathia, short neck with excess posterior skin, supernumerary breast, heart murmur, low set ears, left ear deformity, reducible umbilical hernia, hands and feet in attitude of permanent flexion, camplodactilia with hypoplastic distal folds, single palm fold, plagiocephaly, flat pilonidal pit, hepatomegaly phimosis and curved spine).<br>Genetic testing revealed unbalanced structural chromosomopathy affecting one chromosome of the pair 18 (concluded as a "de novo" phenomenon with the parental karyotypes reportedly normal).<br>Concomitant medications included lamotrigine, ethinylestradiol/drospirenone, levothyroxine, lorazepam, and folic acid.<br>Obstetric history: 2 previous pregnancies with normal births<br>Past medical history: hypothyroidism, epilepsy | | | |

| | | | |
|---|---|---|---|
| 2012SP002971 | ESL 1200 or 1600 mg | Spontaneous abortion | <2 weeks |
| On Study Day 10, subject had a borderline positive hCG test. Five days later, she experienced vaginal bleeding and cramping and her hCG level was elevated. Event believed to be a spontaneous abortion.<br>Concomitant medications included gabapentin, lamotrigine, Adderall.<br>Obstetric history: no previous pregnancies<br>Past medical history: epilepsy, irritable bowel syndrome, migraine, depression, ADHD | | | |
| 311-01279 | ESL or CBZ | Healthy birth | <4 weeks |
| ESL discontinued after positive pregnancy test (last menstrual period was ~1 month prior).<br>Outcome: delivery of normal healthy female by Cesarean.<br>No concomitant medications were reported. | | | |
| BIA-01354 | ESL 1200 mg | Spontaneous abortion | 5 weeks |
| Subject was taking ESL for >5 years.<br>Outcome: spontaneous abortion at 5 weeks<br>Concomitant medications included lamotrigine, clobazam, and omeprazole.<br>Obstetric history: no previous pregnancies (and no family history of birth defects) | | | |
| BIA-01110 | ESL 800 mg | Spontaneous abortion | ~8 weeks |
| Outcome: spontaneous abortion at 8 weeks<br>Concomitant medications included levetiracetam, lacosamide, and clonazepam.<br>Obstetric history: no previous pregnancies (and no family history of birth defects) | | | |
| BIA-01293 | ESL 400 mg | Healthy birth | ≥ first trimester |
| Outcome: delivery of healthy child<br>Concomitant medications included carbamazepine (changed to ESL during first trimester). | | | |
| 050-6400-S002 | ESL 1600 mg | Healthy birth* | <4 weeks |
| Outcome: normal delivery of healthy child at 40 weeks gestation<br>Concomitant medications included lamotrigine. | | | |
| 050-0039-001 | ESL 1200 mg | Healthy birth* | ~5 weeks |
| Outcome: normal delivery of healthy child at full term<br>Concomitant medications included ciprofloxacin, valacyclovir, promethazine, diphenhydrinate, certirizine. | | | |
| 050-0003-001 | ESL 1600-2000 mg | Spontaneous abortion* | 6 weeks |
| Subject was taking ESL for almost 2 years.<br>Outcome: spontaneous abortion at 6 weeks<br>Concomitant medications included vitamins and supplements.<br>Obstetric history: G3 P1 (1 pregnancy termination and 1 “live birth”) | | | |

Source: Created by the reviewer using narratives provided by the Sponsor
*Narratives and case reports submitted by the Sponsor in response to the Division’s information request dated 6/19/13

In the ESL clinical database, ongoing studies, and postmarketing database, the Sponsor reported 1 case of congenital malformation (in Safety Information Amendment dated 7/1/13, the Sponsor confirmed that there were no additional cases of congenital malformations that have been identified). This mother was taking ESL for less than 4 weeks and also taking a concomitant Pregnancy Class D medication (lorazepam). Furthermore, the multiple malformations in this infant are consistent with a chromosomal abnormality (which was confirmed by the genetic testing results). Therefore, a causal link between ESL exposure during this subject’s pregnancy and

development of these congenital malformations cannot be definitely established. No other congenital malformations were reported in the healthy births by the Sponsor.

There were 4 cases of spontaneous abortions. One subject was taking a concomitant Pregnancy Class D medication (clonazepam) and 1 subject was taking a higher dose of ESL (≥1600 mg). However, with such a small number of pregnancies, the assessment of the causal relationship between ESL exposure and spontaneous abortions is difficult.

Of note, in the entire safety database, there were 3 ESL subjects with the following TEAEs coded to the SOC Congenital, Familial and Genetic Disorders: aplasia, dysplastic naevus syndrome, and type III hyperlipidaemia. These TEAEs occurred in adult subjects and were not due to ESL exposure during pregnancy.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable (intended population 18 years of age and above), and there were only 15 subjects in the entire database who were less than 18 years of age.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The effects of overdose with ESL will be discussed in this section. The reader is referred to the Controlled Substance Staff review by Dr. Alicja Lerner for further details regarding drug abuse potential and withdrawal/physical dependence, to the Pharmacology/Toxicology review by Dr. Christopher Toscano for details regarding the preclinical studies, and to Dr. Teresa Podruchny's review of efficacy for details regarding rebound epilepsy.

Overdose
In the ISS, the Sponsor reported a total of 2 cases of accidental overdose of ESL in the Phase III epilepsy studies (listed in the table below). Both were reported as SAEs. The Sponsor also noted that the 2012 data review revealed 2 cases of overdose in which both subjects took extra Dilantin not ESL (subjects 304-080-08002 and 304-301-30118). In the nonepilepsy studies, there was 1 case of intentional overdose of clonazepam not ESL.

*Comment: In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 7/1/13 to provide a tabular listing of all cases of overdose. The Sponsor reported that there were no additional cases of ESL overdose in the completed trials. In the ongoing trials, the Sponsor reported an additional 2 cases of ESL overdose (listed in the table below) and 1 case of "unspecified overdose."*

**Table 146. ESL Overdoses, All Studies Pool (including 303)**

| Subject # | ESL dose | TEAEs | Outcome | ESL course |
|---|---|---|---|---|
| 302-371-80534 | Accidental overdose on OLE Day 265 (dose not reported) | No TEAEs reported surrounding this event | SAE, Recovered | Continued |
| 304-307-30720 | Accidental overdose on DB Day 1 (800 mg qday instead of 400 mg) | Dizziness, tinnitus, nausea, vomiting, balance disorder, hyponatremia (Na=125 mEq/L) | SAE, Recovered | Interrupted but later restarted |
| 046-6028-S007* | Accidental overdose (dose not reported) | Dizziness, broken blood vessel in right eye, corneal abrasion, ALT increased | Resolved, no sequelae | Continued |
| 304-30714* | Accidental overdose of IP (dose not reported) | Vertigo, nasopharyngitis, somnolence, presyncope osteopenia, odynophagia, limb injury, excoriation, fall, contusion, cough, diplopia | Recovered | Continued |
| 304-75005* | Intentional overdose of IP (dose not reported) | Urinary tract infection | Recovered | Discontinued |

Source: ISS Section 5.5
*information submitted by the Sponsor in Safety Information Amendment 7/1/13

The largest intentionally administered dose of ESL was 3600 mg. In a Phase I Study 118, ESL doses of 3000 and 3600 mg administered for up to 2 days resulted in a high incidence of dizziness, nausea, headache, vomiting (led to discontinuation), and fatigue.

*Comment: Of note, in the All Studies Pool (including 303 using the ADEVENTX dataset), I identified 8 ESL subjects with the PT drug toxicity along with 4 ESL subjects with the PT poisoning (no ESL subjects were coded to the PTs medication error, drug administration error, drug dispensing error, or drug prescribing error). The verbatim terms are listed below (along with information regarding SAEs and TEAEs leading to DC). There were 2 subjects who were reported as taking overdoses of ESL in the narratives but were not reported by the Sponsor as cases of overdose in the ISS or in the Safety Information Amendment 7/1/13 in which the Sponsor was requested to provide a tabular listing of "all cases of overdose."*

*Drug toxicity:*

*"Impaired postural inbalance (associated with brief drug intoxication),"*
*"Carbamazepine toxicelled," "Toxic carbamazine"*
*"Phenytoin toxicity",*
*Carbamazepine toxicity (SAE, DC): 302-421-80778 developed "drug toxicity (carbamazepine)" along with dizziness, nausea, and vomiting on Day 54 of ESL. Carbamazepine dose was decreased and ESL was discontinued. Subject "recovered with sequelae" 6 days later.*
*Study drug intoxication (SAE): 301-171-90403 developed "drug toxicity" on Day 12 of ESL with symptoms of vertigo, vomiting, and diplopia. Subject was hospitalized and labs revealed hyponatremia. ESL dose was reduced and events resolved.*
*Intoxication medication (SAE): 302-362-80552 developed "drug toxicity" on Day 117 of ESL along with somnolence. ESL was continued and events resolved. About 2 months later, subject*

*experienced the SAE of psychotic disorder. ESL dose was decreased and the subject completed the OLE study 10 months later.*
*Intoxication with carbamazepine (SAE): 301-142-90178 developed "drug toxicity" on Day 14 of ESL with symptoms of nausea, vertigo, gait difficulties, diplopia, dizziness, and disturbance of equilibrium. Subject was hospitalized and labs revealed an elevated carbamazepine level. Carbamazepine dose was interrupted and later reduced. ESL was discontinued on Day 45 when the subject developed nystagmus. Outcome not reported.*
*Intoxication with AED's (SAE/DC): 301-141-90171 "**took a new dose of study medication** at the study site, under the investigator's supervision" and developed "intoxication" on Day 57 after the subject stated initially that he had missed taking ESL (and other concomitant medications such as lamotrigine) for 2 days. Thirty minutes later, the subject developed ataxia, difficulty walking, somnolence, and diplopia. The subject was pale with slightly lower BP 85/60 mmHg (compared to baseline values of 90/60-100-60 mmHg) and was hospitalized. ESL was discontinued. Events resolved and the subject was discharged 2 days later. Labs revealed elevated blood levels of lamotrigine. Later, the investigator received information that the subject had likely taken double doses of both ESL and the other concomitant medications because the subject had indeed taken his morning doses and again later at the study visit. **Of note, this subject was not included by the Sponsor in their list of overdoses (or coded to the PT hypotension even though the BP value met the Sponsor's criteria for adverse event which included any worsening of a pre-existing condition).***

*Poisoning:*
*"Intoxication" (n=4)*
*"Severe temperature-intoxication syndrome" (n=1)*
*"Intoxication (with SCO-BIA-2093)" (SAE/DC): 301-124-90357 taking ESL 1600 mg prescribed by the investigator "by mistake" instead of 800 mg per study protocol, and was hospitalized with "drug intoxication" on Day 28 of ESL. Symptoms included drowsiness, unsteady gait, and "brady psychic response." ESL was discontinued. Events resolved 16 days later. **Of note, this subject was not included by the Sponsor in their list of overdoses.***

An IND safety report submitted by the Sponsor on 6/13/13 included information regarding a 24 year old black male subject (2013SP000713) participating in the ongoing monotherapy Study 045 who experienced an accidental overdose after 5 weeks of ESL:

Subject with a history of epilepsy, skull fracture, diabetes, and depression received a second dose of blinded study medication (ESL 1200 mg or 1600 mg qday) within 3 hours. Then the subject experienced lightheadedness, twitching and loss of consciousness. The subject's cousin found the subject unresponsive, tremulous, and drooling. By the time the subject arrived at the hospital, the subject was awake and oriented (without memory of previous events). ECG revealed sinus tachycardia (106 bpm). Lab values were within normal limits. Urine drug screen was negative. The subject recovered and was discharged from the hospital within 24 hours. Concomitant medications included lacosamide and topiramate. The study medication was continued without any changes.
*Comment: These events most likely represent a seizure that was temporally related to the overdose of ESL (2400 mg or 3200 mg).*

In postmarketing reports through 10/21/12, the Sponsor reported a total of 35 cases of overdose. The Sponsor noted in the ISS that "according to BIAL convention, the term 'overdose' is coded whenever a patient, for whatever reason, is prescribed or takes more ESL than is prescribed or used in a manner not in accordance with approved prescribing information." The highest reported dose is 3200 mg (as a suicide attempt with no adverse outcome reported). One subject (BIAL-01616) was a completed suicide by overdose (dose unknown).

*Comment: In response to the Division's information request, the Sponsor submitted a Safety Information Amendment dated 7/1/13 to provide a tabular listing of all cases of overdose. In their response, the Sponsor reported a total of 24 postmarketing cases (instead of the 35 cases originally reported in the ISS). The cases were all described as either "overdose-nothing happened" or "overdose-no adverse event." None were reported as a serious event.*

*Comment: An additional case was reported by the Sponsor on July 30, 2013, of a subject (BIAL 02122) who was hospitalized "following an overdose of Zebinix which was suspected to be intentional." Of note, this adverse event was coded as "toxicity to various agents" rather than intentional overdose. The patient presented with drug intoxication under Zebinix (unknown dose), phenobarbital, and alcohol. He experienced arterial hypotension, bradycardia (global hypokinesia), calm and areflectic coma, myosis, closed and areactive pupils. The patient was treated in the intensive care unit with dobutamine, noradrenaline and intubated for ventilatory support. He underwent 1 hemodialysis session. He recovered on an unspecified date.*

### 7.7 Additional Submissions / Safety Issues

The Division made several request for information and additional analyses after the NDA resubmission on February 11, 2013. Review of the responses to the FDA requests for information has been incorporated throughout this review up to August 16, 2013.

# 8 Postmarket Experience

ESL was first granted marketing authorization on April 21, 2009 by the European Commission valid throughout the European Union for adjunctive therapy in adults with partial-onset seizures with or without secondary generalization. The Sponsor reports that ESL is currently approved in 36 countries and the marketing dossier is under evaluation in 2 countries (ISS Section 6).

The Sponsor identified October 21, 2012 as the data cut-off date for postmarketing data. The Sponsor stated that since October 21, 2012, none of the following actions relating to safety have been considered:

- Marketing authorization withdrawal or suspension
- Failure to obtain a marketing authorization renewal
- Restrictions on distribution
- Clinical trial suspension
- Dosage modification
- Changes in target population or indications
- Formulation changes
- Urgent safety restriction

The Sponsor calculated a crude estimate of the total number of patients exposed to ESL in the postmarketing period using combined worldwide sales volumes from April 21, 2009 to July 31, 2012. The Sponsor estimated the worldwide marketing exposure using data from the IMS prescription monitoring system and the assumption that each subscription unit (or number of tablets sold) was used in patients on a dosage regimen of 1 tablet per day where one subscription unit represents one 800 mg tablet taken per day. (b) (4)

The Sponsor calculated a total of (b) (4) subscription units sold during the reporting interval, representing 12,279 patient-years of exposure.

Postmarketing reports originated from spontaneous adverse event case reports from the following sources: consumers, health care professionals, health authorities, and scientific literature. These AE reports were held in the global safety database which was maintained by the licensor company, BIAL-Portela & Cª., S.A. The Sponsor reports that the database captures a unique report identifier, country of report origin, whether the event was medically confirmed, initial reporting date, a description of the adverse event, and when available, age, gender, therapy start and end dates, dose and event outcome. The postmarketing AE data presented by the Sponsor in the ISS were received by BIAL for ESL from April 21, 2009 through October 21, 2012.

During this reporting period, a total of 373 uniquely identified safety reports containing 720 individual adverse events (including 266 SAEs or 37%) were received by BIAL. Based on the Sponsor's population exposure estimates, the overall rate of reported events was 0.059 per patient-year. The following table summarizes the spontaneously reported AEs for ESL that were reported in ≥ 3 patients. The reporting rates were calculated by the Sponsor based on 12,279 patient-years exposure in the postmarketing period.

**Table 147. Postmarketing Adverse Events Reported in ≥3 Patients**

| Body System Class<br>Preferred Term | Serious | | Non-Serious | | Total* | | | |
|---|---|---|---|---|---|---|---|---|
| | Patients | Events | Patients | Events | Patients | Events* | Reporting Rate per Patient Year [1] | Reporting (Events) Rate per 10,000 patient years [2] |
| At Least One Event | 191 | 266 | 208 | 360 | 373 | 720 | 0.05864 | 587 |
| Blood and lymphatic system disorders | 8 | 9 | 1 | 1 | 9 | 10 | 0.00081 | 9 |
| Thrombocytopenia | 3 | 3 | 1 | 1 | 4 | 4 | 0.00033 | 4 |
| Ear and labyrinth disorders* | 4 | 4 | 13 | 13 | 19 | 19 | 0.00155 | 16 |
| Vertigo* | 4 | 4 | 12 | 12 | 18 | 18 | 0.00147 | 15 |
| Eye disorders | 3 | 3 | 16 | 18 | 19 | 21 | 0.00171 | 18 |
| Diplopia | 3 | 3 | 11 | 11 | 14 | 14 | 0.00114 | 12 |
| Vision blurred | 0 | 0 | 6 | 6 | 6 | 6 | 0.00049 | 5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Gastrointestinal disorders* | 6 | 6 | 22 | 31 | 33 | 43 | 0.00350 | 36 |
| Diarrhoea | 1 | 1 | 5 | 6 | 6 | 7 | 0.00057 | 6 |
| Nausea* | 1 | 1 | 9 | 9 | 13 | 13 | 0.00106 | 11 |
| Vomiting* | 2 | 2 | 3 | 3 | 8 | 8 | 0.00065 | 7 |
| General disorders and administration site conditions* | 11 | 15 | 29 | 33 | 48 | 59 | 0.00480 | 49 |
| Asthenia* | 1 | 1 | 2 | 2 | 4 | 4 | 0.00033 | 4 |
| Drug ineffective | 1 | 1 | 4 | 4 | 5 | 5 | 0.00041 | 5 |
| Fatigue* | 1 | 1 | 17 | 17 | 20 | 20 | 0.00163 | 17 |
| Malaise* | 0 | 0 | 1 | 1 | 4 | 4 | 0.00033 | 4 |
| Oedema* | 0 | 0 | 2 | 2 | 3 | 3 | 0.00024 | 3 |
| Oedema peripheral* | 0 | 0 | 2 | 2 | 4 | 4 | 0.00033 | 4 |
| Injury, poisoning and procedural complications | 1 | 1 | 58 | 58 | 59 | 59 | 0.00481 | 49 |
| Medication error | 0 | 0 | 30 | 30 | 30 | 30 | 0.00244 | 25 |
| Overdose | 0 | 0 | 24 | 24 | 24 | 24 | 0.00196 | 20 |
| Investigations* | 20 | 21 | 27 | 28 | 51 | 55 | 0.00480 | 45 |
| Blood sodium decreased** | 12 | 12 | 15 | 15 | 27 | 27 | 0.00220 | 22 |
| Gamma-glutamyltransferase increased* | 2 | 2 | 0 | 0 | 3 | 3 | 0.00024 | 3 |
| Weight increased | 0 | 0 | 7 | 7 | 7 | 7 | 0.00057 | 6 |
| Metabolism and nutrition disorders* | 84 | 87 | 14 | 18 | 98 | 107 | 0.00871 | 88 |
| Decreased appetite* | 0 | 0 | 4 | 5 | 6 | 7 | 0.00057 | 6 |
| Hyponatraemia** | 84 | 86 | 10 | 12 | 94 | 98 | 0.00798 | 80 |
| Nervous system disorders* | 61 | 73 | 42 | 65 | 108 | 156 | 0.01270 | 128 |
| Ataxia | 4 | 4 | 1 | 1 | 5 | 5 | 0.00041 | 5 |
| Burning sensation* | 0 | 0 | 1 | 1 | 3 | 3 | 0.00024 | 3 |
| Cognitive disorder | 0 | 0 | 3 | 3 | 3 | 3 | 0.00024 | 3 |
| Disturbance in attention | 0 | 0 | 5 | 5 | 5 | 5 | 0.00041 | 5 |
| Dizziness* | 5 | 5 | 20 | 20 | 30 | 30 | 0.00244 | 25 |
| Epilepsy | 2 | 3 | 1 | 1 | 3 | 4 | 0.00033 | 4 |
| Grand mal convulsion | 6 | 7 | 0 | 0 | 6 | 7 | 0.00057 | 6 |
| Headache* | 0 | 0 | 7 | 8 | 10 | 11 | 0.00090 | 9 |
| Partial seizures | 26 | 26 | 1 | 1 | 27 | 27 | 0.00220 | 22 |
| Somnolence* | 2 | 2 | 3 | 3 | 8 | 8 | 0.00065 | 7 |
| Speech disorder | 1 | 1 | 2 | 2 | 3 | 3 | 0.00024 | 3 |
| Status epilepticus | 4 | 4 | 0 | 0 | 4 | 4 | 0.00033 | 4 |
| Tremor | 1 | 1 | 3 | 4 | 4 | 5 | 0.00041 | 5 |
| Psychiatric disorders* | 6 | 7 | 14 | 21 | 22 | 34 | 0.00277 | 28 |
| Aggression | 1 | 1 | 4 | 4 | 5 | 5 | 0.00041 | 5 |
| Confusional state* | 0 | 0 | 1 | 1 | 3 | 3 | 0.00024 | 3 |
| Depression | 1 | 1 | 3 | 3 | 4 | 4 | 0.00033 | 4 |
| Depressed mood* | 0 | 0 | 2 | 2 | 3 | 3 | 0.00024 | 3 |
| Respiratory, thoracic and mediastinal disorders* | 4 | 5 | 5 | 6 | 12 | 15 | 0.00122 | 13 |
| Dyspnoea* | 2 | 2 | 3 | 3 | 7 | 7 | 0.00057 | 6 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Skin and subcutaneous tissue disorders* | 13 | 16 | 32 | 41 | 46 | 85 | 0.00692 | 70 |
| Erythema* | 0 | 0 | 0 | 0 | 3 | 3 | 0.00024 | 3 |
| Pruritus* | 0 | 0 | 4 | 4 | 12 | 12 | 0.00098 | 10 |
| Rash | 3 | 3 | 12 | 12 | 15 | 15 | 0.00122 | 13 |
| Rash erythematous | 3 | 3 | 3 | 3 | 6 | 6 | 0.00049 | 5 |
| Rash generalised | 2 | 2 | 1 | 1 | 3 | 3 | 0.00024 | 3 |
| Rash pruritic* | 1 | 1 | 6 | 6 | 7 | 8 | 0.00065 | 7 |
| Surgical and medical procedures | 0 | 0 | 6 | 6 | 6 | 6 | 0.00049 | 5 |
| Off label use | 0 | 0 | 6 | 6 | 6 | 6 | 0.00049 | 5 |
| Vascular disorders* | 3 | 6 | 3 | 3 | 9 | 15 | 0.00122 | 13 |
| Poor peripheral circulation* | 0 | 0 | 2 | 2 | 4 | 4 | 0.00033 | 4 |

[1] Reporting Rate per Patient Year equals the total number of events divided by 12279 patient years of exposure.
[2] Reporting rate (events) per 10,000 patient years of exposure equals Reporting Rate per Patient Year times 10,000 patient years, rounded up to the nearest integer.
*Some events determined to be a symptom of a diagnosis term do not have seriousness criteria assigned; therefore the total is more than the sum of serious and non-serious counts shown in the table.
**The 21Apr2009 to 31 July2012 post marketing database of spontaneous reported cases used in this ISS contains 121 cases with 125 events of the preferred terms Hyponatremia or Blood sodium decrease. Previously submitted PSURs have identified 119 cases with 125 events of Hyponatremia or Blood sodium decrease.
Source: ISS Table 107

The System Organ Classes with the most AEs (≥50) reported were the following:

- Nervous system disorders (n=156; 30 dizziness and 27 partial seizures)
- Metabolism and nutrition disorders (n=107; 98 hyponatremia)
- Skin and subcutaneous tissue disorders (n=85; 15 rash)
- Injury, poisoning and procedural complications (n=59; 30 medication error and 24 overdose)
- General disorders and administration site conditions (n=59; 20 fatigue)
- Investigations (n=55; 27 blood sodium decreased)

Most individual AEs were reported fewer than 10 times. The following AEs were reported ≥10 times: hyponatraemia (98), dizziness (30), medication error (30), blood sodium decreased (27), partial seizures (27), overdose (24), fatigue (20), vertigo (18), rash (15), diplopia (14), pruritus (12), nausea (13), and headache (11).

*Comment: The Sponsor noted that "according to BIAL convention, the term 'overdose' is coded whenever a patient, for whatever reason, is prescribed or takes more ESL is prescribed or used in a manner not in accordance with approved prescribing information."*

The SOCs with the most SAEs (≥20) were metabolism and nutrition disorders (87, due to hyponatraemia), nervous system disorders (73), and investigations (21, due to blood sodium decreased). SAEs reported ≥5 times were hyponatremia (86), partial seizures (26), blood sodium decreased (12), grand mal convulsion (7), and dizziness (5). More specific details of spontaneously reported serious adverse events (especially of adverse

events of special interest) are described in the appropriate sections throughout this review.

The Sponsor also performed a review and analysis of published literature. The search covered ESL and also the related compounds, oxcarbazepine and racemic licarbazepine (an active metabolite of oxcarbazepine). The electronic oxcarbazepine search was limited to epilepsy or bipolar disorder. There were 173 published eslicarbazepine acetate articles and 17 licarbazepine articles where administration to humans in a clinical setting was identified. The oxcarbazepine clinical literature included 1,335 literature articles. The Sponsor stated that no unanticipated safety issues were identified in published literature.

In conclusion, the postmarketing spontaneous reports to BIAL did not reveal any new safety concerns. The most frequently reported AEs appear to be associated with the underlying conditions under treatment or were consistent with the safety profile observed in clinical studies.

# 9 Appendices

See following pages.

## 9.1 Literature Review/References

Literature citations have been incorporated into the body of this review as footnotes.

## 9.2 Labeling Recommendations

Draft labeling recommendations will be added to a working document in the e-room.

## 9.3 Advisory Committee Meeting

The Division did not present the eslicarbazepine acetate NDA to an Advisory Committee.

# Appendix 1: Description of Eslicarbazepine Acetate Clinical Studies

## Table 148. Description of ESL Epilepsy Studies

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Duration of Treatment |
|---|---|---|---|---|---|---|
| PK Safety and Efficacy | BIA-2093-201 | Safety and efficacy of ESL as adjunctive therapy in patients with refractory partial epilepsy. ESL PK | Double-blind, randomised, placebo controlled study | ESL or placebo tablets.<br>W 1 – 4:<br>- 400 mg QD<br>- 200 mg BID<br>W 5 – 8:<br>- 800 mg QD<br>- 400 mg BID<br>W 9 – 12:<br>- 1200 mg QD<br>- 600 mg BID<br>Placebo. | 143 M/F<br>(ESL QD n=50<br>ESL BID n=46<br>Placebo n=47)<br>(110completed) | 12 weeks + 1 week tapering off |
| PK Efficacy and Tolerability | BIA-2093-202 | ESL PK in children and adolescents. Efficacy and tolerability of ESL as add-on therapy in children and adolescents with refractory partial epilepsy | Phase IIA, open- label, single-center, multiple-dose study | ESL suspension, PO.<br>Group 1 suspension (50 mg/mL)<br>Groups 2 and 3 tablets.<br>All Groups:<br>Weeks 1–4: 5 mg/kg/day QD<br>Weeks 5–8: 15 mg/kg/day QD<br>Weeks 9–12: 30 mg/kg/day QD or 1800 mg/day QD, whichever is less | 30 planned<br>(10 per group)<br>31 enrolled<br>(2-6 yr N=12;<br>7-11 yr N=8;<br>12-17 yr N=11)<br>26 complete<br>(2-6 yr N=9,<br>7-11 yr N=7;<br>12-17 yr N=10) | 12 weeks |
| Efficacy and Safety<br>Tolerability<br>Drug-drug Interaction<br>QOL | BIA-2093-301 Part 1 | Efficacy of ESL versus placebo as adjunctive therapy in patients with refractory partial epilepsy. Safety and tolerability. Maintenance of therapeutic effects of ESL. Drug-drug PK interactions between ESL and concomitant AEDs. Health-related QOL and depressive symptoms. | Phase III, Parallel-group, randomized, placebo-controlled. 8-week single- blind placebo baseline, 2-week titration 12-week maintenance 4- week tapering- off. | ESL tablets, PO.<br>Part 1: ESL 400 mg, 800 mg, 1200 mg or placebo tablets, QD<br>Part 2: ESL 400 mg to 1200 mg QD | 400 planned<br>402 randomized<br>(ESL 1200 mg N=102<br>ESL 800 mg N=98<br>ESL 400 mg N=100<br>Placebo N=102)<br>330 completed | 26 weeks |
| | BIA-2093-301 Part 2 | | 1- year OLE trial after Part 1 | ESL 400 to 1200 mg QD | 314 enrolled<br>239 completed | 52 weeks |
| | BIA-2093-301 Part 3 | | OLE trial after Part 2 | ESL tablets, PO. ESL 400 mg to 1200 mg QD | 95enrolled<br>81 complete | 52 weeks |
| | BIA-2093-301 Part 4 | | OLE trial after Part 3 | ESL tablets, PO. ESL 400 mg to 1200 mg QD | 71 enrolled<br>49 complete | unlimited |

| | | | | | | |
|---|---|---|---|---|---|---|
| Efficacy and Safety Tolerability Drug-drug Interaction QOL | BIA-2093-302 Part 1 | Efficacy of ESL QD vs placebo as adjunctive therapy in patients with refractory partial epilepsy. Safety and tolerability. Maintenance of therapeutic effects of ESL. Assess drug-drug PK interactions between ESL and concomitant AEDs. Health-related QOL and depressive symptoms. | Phase III, Parallel-group, randomized, placebo-controlle d. 8-week baseline 2-week titration 12-week maintenance | ESL tablets, PO. ESL 400 mg, 800 mg, 1200 mg or placebo tablets, QD | 400 planned 503 enrolled 395 randomized (ESL 400 mg N=96 ESL 800 mg N=101 ESL 1200 mg N=98 Placebo N=100) 325 completed | 22 weeks |
| | BIA-2093-302 Part 2 | | Patients completing Part 1 may enter a 1-year open-label extension; patients completing Part 2 could participate in a further study extension by continuing until marketing authorization was obtained or clinical development was discontinued. | ESL 400 to 1200 mg QD | N=325 M/F (223 completed) | 52 weeks |
| | BIA-2093-302 Part 3 (Argentina, Germany and Sweden) | | To continue subjects where a compassiona te program was not possible for patients to continue treatment until ESL was available on the marked | ESL 400 to 1200 mg QD | 20 enrolled | unlimited |

| | | | | | | |
|---|---|---|---|---|---|---|
| Efficacy and safety<br>Tolerability<br>Drug-drug interaction<br>QOL | BIA-2093-303<br>Part 1 | Efficacy of ESL QD vs placebo as adjunctive therapy in patients with refractory partial epilepsy Safety and tolerability. Maintenance of therapeutic effects of ESL Assess drug-drug PK interactions between ESL and concomitant AEDs. Health-related QOL and depressive symptoms | Parallel-group, randomized, placebo-controlle d. 8-week baseline 2-week titration 12-week maintenance 4-week tapering- off. | ESL tablets, PO ESL 800 mg, 1200 mg or<br>Placebo tablets, QD | 252 planned<br>253 randomized<br>(ESL 1200 mg N=80<br>ESL 800 mg N=85<br>Placebo N=88)<br>197 completed | 26 weeks |
| | BIA-2093-303<br>Part 2 | | Patients completing Part 1 may enter a 1-year OLE; patients completing Part 2 could participate in a further study extension by continuing until marketing authorization was obtained or clinical development was discontinued. | ESL 400 mg to 1200 mg QD | 194enrolled<br>150 completed | 52 weeks |
| Therapeutic Confirmatory Efficacy and Safety<br>Tolerability<br>Drug-drug Interaction<br>QOL | BIA-2093-304<br>Part 1 | Efficacy and safety of ESL as adjunctive therapy for refractory partial seizures in epileptic adult patients treated with 1-2 AEDs. | Phase III, multi-national, randomized, double-blind, placebo-controlle d, parallel-group study. Part 1: 8 week baseline period, double-blind 2-week titration period, 12-week maintenance period. | ESL tablets or matching placebo, PO<br>ESL 800 mg QD, or ESL 1200 mg QD. | 615 planned<br>653 randomized<br>(ESL 800 mg N=216<br>ESL 1200 mg N=211<br>Placeb N=226)<br>504 completed | 22 weeks |
| | BIA-2093-304<br>Part 2 | | 1-year OLE trial after Part 1. | ESL tablets, PO ESL 400-1600 mg QD. | 495 enrolled<br>46 completed | 52 Weeks |
| | BIA-2093-304<br>Part 3 | | 2-year OLE trial after Part 2. | ESL tablets, PO ESL 400-1600 mg QD. | 2 enrolled | 104 Weeks |

Source: ISS Appendix 7.1 Table 1

## Table 149. Description of ESL Nonepilepsy Studies

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| Efficacy and Safety. Tolerability | BIA-2093-203 | Efficacy of ESL in acute manic episodes. Tolerability and safety | Phase II, double-blind, dose-titration, randomized placebo-controlled. | ESL tablets, PO<br>Group I: 800 mg up to 2400 mg (dosing interval: 800 mg), QD<br>Group II: 600 mg up to 1800 mg (dosing interval: 600 mg), QD<br>Group III: Placebo tablets, QD | 160 planned<br>162 randomized<br>123 completed | Bipolar Patients | 3 weeks |
| Efficacy and Safety. Tolerability | BIA-2093-204 | Efficacy of ESL in acute manic episodes. Tolerability and safety | Phase II, double-blind, fixed multiple-dose, randomized placebo-controlled | ESL tablets, PO<br>600 mg or<br>1200 mg or<br>1800 mg QD or<br>Placebo tablets QD | 160 planned<br>38 randomized (study terminated early)<br>28 completed | Bipolar Patients | 3 weeks |
| Efficacy and Safety. Tolerability | BIA-2093-205 | Efficacy of ESL in recurrence prevention of bipolar disorder. Tolerability and safety | Phase II, extension of 2093-203 and 2093-204<br>Part 1:<br>2 weeks, all patients received open-label treatment with ESL tablets 900 mg.<br>Part 2:<br>A double-blind, parallel-group design | ESL tablets, PO<br>Part 1:<br>900 mg QD<br>Part 2:<br>300 mg or<br>900 mg or<br>1800 mg QD | 160 planned<br>104 enrolled (Part 1)<br>87 randomized (Part 2)<br>35 completed | Bipolar Patients | Part 1: 2 weeks<br>Part 2: up to 15 months |

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| PK Safety, and Efficacy (painful diabetic neuropathy) | BIA-2093-206 Part 1 | Efficacy and safety of eslicarbazepine acetate as therapy for patients with painful diabetic neuropathy | Phase II, multi-national, randomized, double-blind, double-dummy, placebo-controlled study. 2-week baseline period, double-blind 1-week titration period, 12-week maintenance period, and 2-week safety follow-up. | ESL and placebo tablets, PO ESL 400 mg BID, 800 mg QD, 600 mg BID, 1200 mg QD, 800 mg BID, or placebo. | 540 planned 557 randomized 419 completed | ≥18 years male or female with diagnosis of painful diabetic neuropathy (PDN) for 1 year prior to enrollment | 12 weeks |
| | BIA-2093-206 Part 2 | | Patients completing Part 1 may enter a 1-year open-label extension | ESL and placebo tablets, PO ESL 400 mg QD, 400 mg BID, 800 mg QD, 600 mg BID, 1200 mg QD, 800 mg BID, or placebo. | 159 enrolled 125 completed | | 52 weeks |
| Efficacy and Safety | BIA-2093-307 Part 1 | Efficacy in painful diabetic neuropathy, tolerability and safety | Phase III, multinational, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, confirmatory study. 3-week titration period, 12-week maintenance period and 3-week tapering-off/4-week follow-up period | ESL and matching placebo tablets, PO ESL 800 mg QD, 1200 mg QD, 1600 mg QD or placebo | 468 planned 333 randomized 182 completed | ≥18 years male or female with diagnosis of painful diabetic neuropathy for 1 year prior to enrollment | 20 to 23 wks (up to 2w washout, 1 to 2w baseline, 3w titration, 12w maintenance, 4w follow-up) |
| | BIA-2093-307 Part 2 | | Patients completing Part 1 may enter 36-week open-label phase | ESL tablets, PO ESL 800-1600 mg QD | 169 enrolled 6 completed | | 36 weeks |

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| Safety, and Efficacy (postherpetic neuralgia) | BIA-2093-207 Part 1 | Efficacy and safety of eslicarbazepine acetate as therapy for patients with postherpetic neuralgia. | Phase II, multi-national, randomized, double-blind, double-dummy, placebo-controlled study. 2-week baseline period, double-blind 1-week titration period, 8-week maintenance period, and 2-week safety follow-up. | ESL and placebo tablets, PO ESL 400 mg BID, 800 mg QD, 600 mg BID, 1200 mg QD, 800 mg BID, or placebo. | 540 planned 567 randomized 438 completed | ≥18 years male or female with diagnosis of postherpetic neuralgia (PHN) and neuropathic pain >3 months after healing of the herpes zoster skin rash | 13 weeks (2w baseline, 1w titration, 8w maintenance, 2w follow-up) |
| | BIA-2093-207 Part 2 | | Patients completing Part 1 may enter a 1-year open-label extension | ESL and placebo tablets, PO ESL 400 mg QD, 400 mg BID, 800 mg QD, 600 mg BID, 1200 mg QD, 800 mg BID, or placebo. | 151 enrolled 97 completed | | 52 weeks |
| Efficacy and Safety | BIA-2093-308 Part 1 | Efficacy in post-herpetic neuralgia, tolerability and safety | Phase III, Multinational, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, confirmatory study. 3-week titration period, 12-week maintenance period and 3-week tapering-off/4-week follow-up period | ESL and matching placebo tablets, PO ESL 800 mg QD, 1200 mg QD, 1600 QD or placebo | 392 planned 244 randomized 128 completed | ≥18 years male or female with diagnosis of postherpetic neuralgia and neuropathic pain >3 months after healing of the herpes zoster skin rash | 20 to 23 weeks (up to 2w washout period, 1 to 2w baseline, 3w titration, 12w maintenance, 4w follow-up) |
| | BIA-2093-308 Part 2 | | Patients completing Part 1 may enter 36-week open-label phase | ESL tablets, PO ESL 800-1600 mg QD | 100 enrolled 8 completed | | 36 weeks |

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| Therapeutic Exploratory, Efficacy, and Safety | BIA-2093-209 | Efficacy versus placebo in prophylaxis of migraine headaches in adults with migraine.<br>Safety and tolerability. | Phase II, randomized, double-blind, placebo-controlled, parallel-group, multi-center study.<br>4-week single-blind baseline period, double-blind 2-week titration period, 12-week maintenance period, and 4-week safety follow-up. | ESL and matching placebo tablets, PO<br>ESL 800 mg QD, 1200 mg QD, or placebo QD. | 515 planned<br>410 randomized<br>355 completed | Male and female adult subjects with diagnoses of migraine headaches for 1 year prior to enrollment | 22 weeks |
| Therapeutic Exploratory, Efficacy, and Safety | BIA-2093-210 | Efficacy of ESL versus placebo in adults with fibromyalgia.<br>Safety and tolerability. | Phase II, randomized, double-blind, placebo-controlled, parallel-group, multi-center study.<br>2-week baseline period, double-blind 1-week titration period, 12-week maintenance period, and 2-week safety follow-up. | ESL and matching placebo tablets, PO<br>ESL 400 mg QD, 800 mg QD, 1200 mg QD, or placebo QD. | 480 planned<br>528 randomized<br>386 completed | Male and female adult subjects with diagnosis of fibromyalgia (FMS) and meets the ACR 1990 diagnostic criteria for FMS (widespread pain for at least 3 months and pain in at least 11 of 18 tender points). | 17 weeks |

Source: ISS Appendix 7.1 Table 1

## Table 150. Description of Other ESL Studies

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| Pediatric Cognition, Safety, and Efficacy | BIA-2093-208 Part 1 | Effect of ESL on cognitive function in epileptic children with partial onset seizures ages 6-16, treated with 1-2 AEDs. | Phase II, multi-center, randomized, double-blind, placebo-controlled, parallel-group study. | ESL 200 mg tablets or matching placebo tablets, PO<br>Part 1: Patients randomized in a 1:2 ratio to receive placebo or ESL 10 to 30 mg/kg/day (maximum 1200 mg QD) | 90 planned<br>116 randomized<br>65 completed | Pediatric patients with epilepsy | Part 1: 12 weeks<br>Part 2: 52 weeks |
| | BIA-2093-208 Part 2 | | Patients completing Part 1 may continue to receive ESL in a 1-year open-label extension. | ESL 10 mg/kg/day to 30 mg/kg/day (maximum 1200 mg QD). | 65 enrolled<br>0 completed | | 52 weeks |
| Pediatric Efficacy, PK, and Safety | BIA-2093-305 Part 1 | Efficacy of ESL as adjunctive therapy therapy for refractory partial seizures in epileptic children (2-16 years) treated with 1-2 AEDs. | Phase III, multi-national, randomized, double-blind, placebo-controlled, parallel-group study.<br>Part 1: 8-week baseline period, double-blind 6-week titration period, 12-week maintenance period, tapering-off period, and a 4-week observational follow-up period. | ESL tablets, (200 mg; 7-16 years) PO and oral suspension (50mg/mL; 2-6 years) PO or matching placebo tablets and oral suspension, PO<br>placebo or ESL 10 to 30 mg/kg/day (maximum 1200 mg QD) | 315 planned<br>283 randomized<br>193 completed | Pediatric patients with epilepsy | Up to 34 weeks |
| | BIA-2093-305 Part 2 | | Patients completing Part 1 may continue to receive ESL in a 1-year open-label extension. | ESL 10 mg/kg/day to 30 mg/kg/day (maximum 1200 mg QD). | 150 enrolled<br>79 completed | | 52 weeks |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | BIA-2093-305 Part 3 | | Patients completing Part 2 may continue to receive ESL in a 1-year open-label extension. | ESL 10 mg/kg/day to 30 mg/kg/day (maximum 1200 mg QD). | 68 enrolled | | 52 weeks |
| | BIA-2093-305 Part 4 | | Patients completing Part 3 may continue to receive ESL in a 1-year open-label extension. | ESL 10 mg/kg/day to 30 mg/kg/day (maximum 1200 mg QD). | 38 enrolled | | 52 weeks |
| Safety and Efficacy (elderly) | BIA-2093-401 | Safety and efficacy of ESL as adjunctive therapy for partial seizures in elderly patients | Phase III, multi-center, open-label study. 8-week baseline period, 26-week treatment period, and a 4-week follow-up period. | ESL tablets, PO ESL 400-1200 mg QD | 100 planned 63 enrolled 17 completed | Elderly patients with epilepsy | 26 weeks |

Source: ISS Appendix 7.1 Table 1

## Table 151. Description of ESL Monotherapy Trials

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| Safety and Efficacy | BIA-2093-311 | Non-inferiority of ESL monotherapy in newly diagnosed adult epileptic patients experiencing partial-onset seizures compared to CBZ-CR<br>Further demonstrate efficacy and safety of ESL as monotherapy<br>Health-related QOL and depressive symptoms | Phase III, multinational (non-US), randomized, double-blind, active-controlled, parallel group. | ESL tablets, PO<br>ESL tablets (over-encapsulated) 800 mg QD, 1200 mg QD, 1600 mg QD<br><br>Carbamazepine-CR commercial tablets, PO (over-encapsulated) 200 mg BID, 400 mg BID, 600 mg BID | 900 planned<br>172 randomized<br>0 completed | ≥18 years with newly diagnosed partial onset epilepsy | 29 to 163 weeks |
| Safety and Efficacy Monotherapy | SEP093-045 | Efficacy of ESL versus historical control as monotherapy in subjects with partial epilepsy not well controlled by current AED.<br>Safety and tolerability<br>Population PK .<br>Health-related QOL and depressive symptoms | Phase III, double-blind Multicenter,<br>8-week baseline,<br>2-week titration,<br>16-week maintenance,<br>1-week taper | ESL tablets, PO<br>1200 and 1600 mg QD<br>(administered as over-encapsulated 400, 600, or 800 mg tablets) | 202 planned<br>96 randomized<br>40 completed | Subjects with partial onset epilepsy not well controlled with current AED | 18 weeks |
| Safety and Efficacy Monotherapy | SEP093-046 | Efficacy of ESL versus historical control as monotherapy in subjects with partial onset epilepsy not well controlled with current AED.<br>Safety and tolerability<br>Population PK.<br>Health-related QOL and depressive symptoms | Phase III, double-blind Multicenter,<br>8-week baseline,<br>2-week titration,<br>16-week maintenance,<br>1-week taper | ESL tablets, PO<br>1200 and 1600 mg QD<br>(administered as over-encapsulated 400, 600, or 800 mg tablets) | 202 planned<br>158 randomized<br>47 completed | Subjects with refractory partial onset epilepsy | 18 weeks |
| Long-term Safety and Efficacy | SEP093-050 | Maintenance of therapeutic effect, quality of life, suicidality, and depressive symptoms over a 1-year and post-1-year period as monotherapy | Phase III, open-label, Multicenter 1-year and post-1-year extension study of 093-045 and 093-046 | ESL tablets, PO<br>Open-label flexible dose (800 to 2400 mg QD) | 348 planned<br>126 enrolled<br>4 completed | Subjects with refractory partial onset epilepsy who participated in study 093-045 or study 093-046 and willing to continue receiving eslicarbazepine acetate. | > 1 year |

Source: ISS Appendix 7.1 Table 1

## Table 152. Description of ESL Phase 1 Studies

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| **5.3.1 Reports of Biopharmaceutic Studies** | | | | | | | |
| **5.3.1.1 Bioavailability (BA) Study Reports** | | | | | | | |
| BA – Food effect and dosage form proportio-nality | BIA-2093-103 | Effect of food on ESL PK. Tolerability and safety | Phase I, open-label, randomized, 2-way cross-over study | ESL tablets, PO. Single dose of 800 mg either after a high-fat meal or after 10 hrs of fasting | 12 planned<br>12 completed | Healthy Male Subjects | Single Dose |
| BA Tolerability Safety | BIA-2093-104 | ESL and oxcarbazepine (OXC) PK.<br>Tolerability and safety | Phase I, open-label, randomized, 2-way cross-over study | ESL or OXC tablets, PO. Single dose of 900 mg or OXC 900 mg. | 12 planned<br>13 randomized<br>12 completed | Healthy Subjects | Single Dose |
| BA Tolerability Safety | BIA-2093-110 | ESL and OXC PK. Tolerability and safety | Phase I, open-label, randomized, 3-way cross-over study | ESL or OXC tablets, PO.<br>ESL 900 mg QD or<br>ESL 450 mg BID or<br>OXC 450 mg BID | 12 planned<br>12 randomized<br>10 completed | Healthy Subjects | 8 Days |
| BA Tolerability Safety | BIA-2093-115 | ESL and metabolites PK Tolerability and safety | Phase I, open-label, randomized, single-center study | ESL, BIA 2-194 and BIA 2-195 tablets, PO.<br>Group 1: ESL 900 mg QD<br>Group 2: BIA 2-194 450 mg + BIA 2-195 450 mg QD<br>Group 3: BIA 2-194 450 mg QD<br>Group 4: BIA 2-195 450 mg QD | 32 planned<br>32 randomized<br>28 completed | Healthy Subjects | Single Dose + Multiple Dose (7 days) |
| BA – Food effect and dosage form proportionali ty | BIA-2093-117 | Effect of food on ESL PK. Dosage form proportionality Tolerability and safety | Phase I, open-label, randomized, gender-balanced, 3-way cross-over study | ESL tablets, PO. Single dose of 800 mg, fasting conditions; single dose of 800 mg, fed conditions; single dose of 2 tablets x400 mg, fasting conditions | 18 planned<br>18 randomized<br>17 completed | Healthy Subjects | Single Dose |

| 5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports | | | | | | | |
|---|---|---|---|---|---|---|---|
| BA/BE Tolerability Safety | BIA-2093-109 | BA/BE of 3 different formulations Tolerability and Safety. | Phase I, open-label, randomized, 3-way cross-over study to determine BE of 3 different formulations | ESL tablets and suspension, PO. Single dose of 800 mg. Test 1: 16 mL oral suspension 50 mg/mL Test 2: 4 tablets x 200 mg Reference: 1 tablet x 800 mg | 18 planned 18 randomized 18 completed | Healthy Subjects | Single Dose |
| BA/BE Tolerability Safety | BIA-2093-122 | BA/BE of formulation used in pivotal clinical trials and commercial tablet formulation. Tolerability and safety | Phase I, open-label, randomized, 2-way cross-over study | ESL tablets, PO. Group 1: ESL: Reference: single dose of 400 mg clinical trial formulation (CTF) Test: single dose of 400 mg to-be-marketed (TBM) formulation Group 2: ESL: Reference: single dose of 600 mg CTF Test: single dose of 600 mg TBM formulation Group 3: ESL: Reference: single dose of 800 mg CTF Test: single dose of 800 mg TBM formulation | 60 planned 60 randomized 59 completed | Healthy Subjects | Single Dose |
| BA/BE Tolerability Safety | BIA-2093-130 | Bioequivalence (BE) between two active product ingredient (API) sources of eslicarbazepine acetate (ESL) at two dosage strength (400 mg and 800 mg), tolerability and safety | Phase I, open-label, randomized, 2-way cross-over | Oral tablets 400 mg and 800 mg Zebinix® marketed formulations Oral tablets Corresponding 400 mg 800 mg to be marketed formulations (new API source) | 40 planned 38 completed | Healthy Volunteers | Single Dose |
| BE, PK Safety and Tolerability of crushed tablet vs. whole tablet | SEP093-155 | BA/BE Comparison ESL Administered Orally as Either Crushed or Whole Tablets in Healthy Male and Female Subjects; safety and tolerability | Single-center, randomized, open-label, two way cross-over single day administration of crushed and whole tablet | Oral tablets 800 mg QD for 1 day (D1 and D8 of study), crushed or whole tablets | 28 planned 28 randomized 27 completed | Male and female healthy volunteers | Single dose. |

**5.3.3 Reports of Human Pharmacokinetic (PK) Studies**

**5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| PK Tolerability Safety | BIA-2093-101 | ESL PK Clinical EEG Tolerability and safety | Phase I, double-blind, randomized, placebo-controlled, single ascending dose study | ESL tablets, PO. Single doses: 20 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, 900 mg, 1200 mg Placebo tablets. | 64 planned (8 per group; 6 ESL+ 2 placebo) 64 completed | Healthy Male Subjects | Single Dose |
| PK Tolerability Safety | BIA-2093-102 | ESL PK Clinical EEG Tolerability and safety | Phase I, double-blind, randomized, placebo-controlled, multiple ascending dose study | ESL tablets, PO. 200 mg BID 400 mg QD 800 mg QD 1200 mg QD Placebo tablets | 32 planned (8 per group; 6 ESL+ 2 placebo) 32 completed | Healthy Male Subjects | 8 Days |
| PK Tolerability Safety | BIA-2093-113 | ESL PK. Tolerability and safety | Phase I, double-blind, randomized, placebo-controlled study | ESL tablets, PO. Phase A: Single dose of 1800 mg or 2400 mg. Phase B: Multiple doses of 1800 mg or 2400 mg QD for 7 days Placebo tablets | 18 planned (ESL: n=6+6 Placebo: n=3+3) 18 completed | Healthy Male Subjects | Single Dose + Multiple Dose (7 days) |
| MTD Tolerability | BIA-2093-118 | Maximum tolerated dose in healthy subjects. ESL PK. | Phase I, double-blind, randomized, placebo-controlled. Sequential multiple ascending dose study | ESL tablets, PO 3600 mg QD for 2 days; 3000 mg QD for 2 days | 32 planned 16 enrolled 0 completed | Healthy Subjects | Single dose + Multiple Dos (7 days) |
| QQT/QTc | BIA-2093-116 | Effect of ESL on cardiac repolarization. ESL PK Tolerability/safety | Phase I, double-blind, randomized, placebo-controlled, and open-label active-controlled 4-period cross-over study. | ESL and moxifloxacin tablets, PO. ESL 1200 mg QD for 5 days; ESL 2400 mg QD for 5 days; placebo tablets. Moxifloxacin 400 mg single dose | 67 planned 67 randomized 55 completed | Healthy Subjects | Single Dose + Multiple Dose (5 days) |
| PK, Safety, and Tolerability | BIA-2093-127 | Evaluation of steady-state cerebrospinal fluid versus plasma concentrations following oral administration of ESL and oxcarbazepine | Phase I, single-center, open-label, randomized, parallel study to evaluate the pharmacokinetics and tolerability of multiple doses of ESL and OXC in healthy subjects. | ESL tablets and OXC, PO Group A: ESL 600 mg QD (AM) from Day 1 to 3 and ESL 1200 mg QD (AM) from Day 4 to 9. Group B: OXC 300 mg BID (AM and PM) from Day 1 to 3 and OXC 600 mg BID (AM and PM) from Day 4 to 9 (AM only). | 12 planned (6 M, 6 F) 14 enrolled 13 completed | Healthy Subjects | 9 days |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **5.3.3.2 Patient PK and Initial Tolerability Study Reports** | | | | | | | |
| PK Efficacy and Tolerability | BIA-2093-202 | ESL PK in children and adolescents. Efficacy and tolerability of ESL as add-on therapy in children and adolescents with refractory partial epilepsy | Phase IIA, open-label, single-center, multiple-dose study | ESL suspension, PO. Group 1 suspension (50 mg/mL) Groups 2 and 3 tablets. All Groups: Weeks 1–4: 5 mg/kg/day QD Weeks 5–8: 15 mg/kg/day QD Weeks 9–12: 30 mg/kg/day QD or 1800 mg/day QD, whichever is less | 30 planned (10 per group) 31 enrolled (2-6 yr N=12; 7-11 yr N=8; 12-17 yr N=11) 26 complete (2-6 yr N=9, 7-11 yr N=7; 12-17 yr N=10) | Pediatric patients with refractory epilepsy | 12 weeks |
| **5.3.3.3 Intrinsic Factor Study Reports** | | | | | | | |
| Gender balanced | BIA-2093-105 | ESL PK in elderly versus young healthy subjects. Tolerability and safety | Phase I, open-label, parallel group, non-randomised, gender- balanced study | ESL tablets, PO. Phase A: Single dose of 600 mg. Phase B: Multiple doses of 600 mg for 8 days | 24 planned 30 enrolled (≥65 yrs N=14 18–40 yrs N=16) 24 completed | Young and Elderly Healthy Subjects. | Single Dose + Multiple Dose (8 days) |
| Hepatic Impairment | BIA-2093-111 | ESL PK in patients with moderate hepatic impairment versus healthy subjects. Tolerability and safety | Phase I, open-label, multiple-dose, study. Group 1: Subjects with moderate hepatic impairment (Child-Pugh classification) Group 2: Healthy controls | ESL tablets, PO. 800 mg QD for 8 days | 20 planned 17 randomized (Healthy Subjects N=8 Patients N=9) 16 completed (healthy subjects N=8; Patients N=8 subjects) | Healthy Subjects and Patients | Multiple Dose (8 days) |
| Renal Impairment | BIA-2093-112 | ESL PK in patients with renal impairment versus healthy subjects. Tolerability and safety | Phase I, open-label, single-dose, study. Group 1: normal renal function (creatinine clearance>80 mL/min) Group 2: mild renal impairment (creatinine clearance 50-80 mL/min) Group 3: moderate renal impairment (creatinine clearance 30-50 mL/min) Group 4: severe renal impairment (creatinine clearance<30 mL/min) Group 5: ESRD requiring hemodialysis | ESL tablets, PO. Single dose of 800 mg | 40 planned (8 subjects per group) 40 completed | Healthy Subjects and Patients | Single Dose |

| 5.3.3.4 Extrinsic Factor Study Reports | | | | | | | |
|---|---|---|---|---|---|---|---|
| Drug-drug Interaction | BIA-2093-107 | Effect of ESL on the digoxin PK. Tolerability and safety | Phase I, multiple-dose, double-blind, randomized, placebo-controlled, 2 way cross-over study | ESL tablets and digoxin, PO. ESL 1200 mg QD or matching placebo concomitantly with 0.5 mg digoxin QD Day 1-2 and 0.25 mg digoxin QD Day 3-8 | 12 planned<br>13 randomized<br>12 completed | Healthy Subjects | Multiple Dose (8 days) |
| Drug-drug Interaction | BIA-2093-108 | Effect of ESL on the warfarin PK. Tolerability and safety | Phase I, multiple-dose, open-label, single-period study.<br>Phase A: Warfarin dose-finding<br>Phase B: Warfarin PK<br>Phase C: Warfarin treatment alone | ESL tablets and warfarin, PO. Phase A: Warfarin alone to determine dose that stabilized INR between 1.3-1.8 (16 to 21 days of treatment)<br>Phase B: ESL tablets 1200 mg QD + warfarin dose defined in Phase A, for 7 days<br>Phase C: Warfarin alone for 7 days | 12 planned<br>15 enrolled<br>13 completed | Healthy Subjects | Multiple Dose |
| Drug-drug Interaction | BIA-2093-114 | Effect of ESL on the PK of a combined (Ethinyloestradiol and levonorgestrel) oral contraceptive. Tolerability and safety | Phase I, single-center, 2-way cross-over, randomized, open-label study | ESL tablets and combined contraceptive, PO.<br>ESL 1200 mg QD<br>Subjects received an oral single-dose of a combined contraceptive 30 µg ethinylestradiol + 150 µg levonorgestrel on 2 occasions:<br>-once alone as reference;<br>-once after pretreatment with ESL 1200 mg QD for 15 days | 20 planned<br>20 randomized<br>17 completed | Healthy Female Subjects | Single dose<br>Single dose + Multiple Dose (15 days) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Drug-drug Interaction | BIA-2093-119 | Drug-drug PK interaction between ESL and lamotrigine. Tolerability and safety | Phase I, single-center, multiple-dose, open-label, one-sequence | ESL tablets and lamotrigine, PO.<br>Group 1: ESL 600 mg QD on Days 1 and 2 followed by 1200 mg QD from Day 3 to 27. Lamotrigine tablets: 50 mg QD on Days 9 and 10 followed by 150 mg QD from Day 11 to 27.<br>Group 2: Lamotrigine tablets: 50 mg QD on Days 1 and 2 followed by 150 mg QD from Day 3 to 27. ESL 600 mg QD on Days 9 and 10 followed by 1200 mg QD from Day 11 to 27 | 32 planned<br>32 enrolled<br>28 completed | Healthy Male Subjects | Multiple Dose |
| Drug-drug Interaction | BIA-2093-120 | Drug-drug PK interaction between ESL and topiramate. Tolerability and safety. | Phase I, single-center, multiple-dose, open-label, parallel group, one-sequence design study | ESL tablets and topiramate, PO.<br>Group A: ESL 600 mg QD on Days 1-2 followed by 1200 mg QD on Days 3-27. Topiramate tablets: 100 mg QD on Days 9-10 followed by 100 mg BID on Days 11-12 and 200 mg QD on Days 13-27<br>Group B: Topiramate tablets: 100 mg QD on Days 1-2 followed by 100 mg BID on Days 3-4 and 200 mg QD on Days 5-27. ESL 600 mg QD on Days 9-10 followed by 1200 mg QD on Days 11 to 27 | 32 planned<br>32 enrolled<br>27 completed | Healthy Male Subjects | Multiple Dose |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Drug-drug Interaction | BIA-2093-121 | Drug-drug PK interaction between ESL and phenytoin. Tolerability and safety | Phase I, single-center, multiple-dose, open-label, parallel group, one-sequence design study | ESL tablets and phenytoin, PO. Group 1: ESL 600 mg QD on Days 1 and 2 followed by 1200 mg QD from Day 3 to 27. Phenytoin tablets: 100 mg QD on Days 9 and 10 followed by 300 mg QD from Day 11 to 27<br>Group 2: Phenytoin tablets: 100 mg QD on Days 1 and 2 followed by 300 mg QD from Day 3 to 27. ESL 600 mg QD on Days 9 and 10 followed by 1200 mg QD from Day 11 to 27 | 32 planned<br>32 enrolled<br>28 completed | Healthy Male Subjects | Multiple Dose |
| PK Tolerability | BIA-2093-106 | Effect of ESL on the phenytoin PK. Tolerability and safety | Phase I, Phase A: Open label.<br>Phase B: Multiple-dose, double-blind, randomized, placebo-controlled, 2-way cross-over | ESL tablets and phenytoin, PO.<br>Phase A: ESL 1200 mg single dose<br>Phase B: ESL 600 mg daily for 7 days followed by 1200 mg for 7 days (or Placebo for 14 days)<br>Phenytoin as usual care | 12 planned<br>4 enrolled<br>4 completed | Healthy Subjects | Phase A: single dose<br>Phase B: multiple dose (14 Days) |
| Drug-drug Interaction (simvastatin) | BIA-2093-124 | Effect of repeated administration of ESL 800 mg QD on the PK of simvastatin(S) 80 mg (substrate of CYP3A4) | Phase I, single-center, 2-way cross-over, randomized, open-label study | ESL tablets and simvastatin, PO<br>80 mg of simvastatin alone or after 14 days of pretreatment with 800 mg ESL QD | 24 planned<br>30 enrolled<br>24 completed | Healthy Male and Female Volunteers | Oral single-dose of simvastatin 80 mg on two occasions: once administered alone and once after tx with an oral QD dose of 800 mg of SEP-0002093 for 14 days |

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|---|---|---|---|---|---|---|---|
| Drug-Drug Interactions (metformin) | BIA-2093-125 | Drug-drug PK interaction between ESL and metformin. Tolerability and safety | Phase I, single-center, 2-way cross-over, randomized, open-label | ESL and metformin tablets, PO. Group A: ESL 1200 mg QD on Days 1-6 with a single dose of 850 mg metformin concomitantly on Day 5. A single dose of 850 mg metformin followed a 14-day wash-out. Group B: A single dose of 850 mg metformin followed by a 14-day wash-out. ESL 1200 mg QD on Days 1-6 with a single dose of 850 mg metformin concomitantly on Day 5. | 20 planned 20 randomized 19 Completed | Healthy Subjects | Single Dose + Multiple Dose (6 days) |
| Drug-Drug Interactions (gliclazide) | BIA-2093-126 | Drug-drug PK interaction between ESL and gliclazide. Tolerability and safety | Phase I, single-center, 2-way cross-over, randomized, open-label study | ESL and gliclazide tablets, PO. Group A: ESL 600 mg QD on Days 1-3, ESL 1200 mg QD on Days 4-16 with a single dose of 80 mg gliclazide concomitantly on Day 14, followed a ≥14-day wash-out, then a single dose of 80 mg gliclazide. Group B: A single dose of 80 mg gliclazide followed by a ≥14-day wash-out. ESL 600 mg QD on Days 1-3, ESL 1200 mg QD on Days 4-16 with a single dose of 80 mg gliclazide concomitantly on Day 14. | 20 planned 20 randomized 19 completed | Healthy Subjects | Multiple Dose |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Drug-drug Interaction (contra-ceptive) | BIA-2093-128 | Effect of ESL 800 mg QD on combined oral contraceptive (ethinylestradiol and levonorgestrel) PK; Tolerability and safety | Phase I, single-center, 2-way cross-over, randomized, open-label study | ESL tablets, PO Microginon® coated tablets Single oral dose of a combined contraceptive containing 30 µg ethinyloestradiol and 150 µg levonorgestrel (Microginon®) on 2 occasions (once as such and once after pretreatment with an oral QD dose of 800 mg of ESL for 15 days. | 20 planned 20 randomized 19 completed | Healthy Female Subjects | Levonorgestrel once alone ESL 800 mg QC for 15 days plus levonorgestrel once on Day 15 |
| Pharmacology, PK and Safety | BIA-2093-129 | Interaction between ESL and carbamazepine; safety and tolerability of combination. | Phase I, single-center, randomized, open-label, 2-way parallel group | ESL tablets, PO: Group A: 800 mg QD (days 1-35) Group B: 800 mg QD (days 29-35) Tegretol; PO: Group A: Tegretol (Carbamazepine) 200 mg QD (D: 8-14) 400 mg QD (D: 15-21) 400 mg BID (D: 22-35) Group B: 200 mg QD (D: 1-7) 400 mg QD (D: 8-14) 400 mg BID (D: 15-35) | 40 planned 43 enrolled 38 completed | Healthy male and female volunteers | 35 days |
| PK, Safety and Tolerability | SEP093-150 | Effect of multiple doses of ESL on rosuvastatin 40 mg (a CYP2C9 substrate); safety and tolerability | Phase I, single center, open-label, fixed-sequence. All subjects will receive 2 treatments (A and B) sequentially | ESL tablets, PO Oral tablets 400 mg QD for 7 days (D5-11), 800 mg QD for 7 days (D12-18), and 1200 mg QD for 14 days (D19-32) Also, 1200 mg QD administered on D33-35 Rosuvastatin 40mg PO Treatment A: single dose of rosuvastatin Treatment B: single dose of rosuvastatin on 14th day of ESL 1200mg administration. | 33 planned 33 enrolled 30 completed | Male and female healthy volunteers | Treatment A: single dose Treatment B: ESL 400/088 mg titration (2 weeks), ESL 1200 mg (2 weeks) plus rosuvastatin 40 mg single dose |

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| **5.3.4 Reports of Human Pharmacodynamic (PD) Studies** | | | | | | | |
| **5.3.4.1 Healthy Subject PD and PK/PD Study Reports** | | | | | | | |
| PK/PD Tolerability | BIA-2093-123 | PD effects and safety of ESL in healthy volunteers | Phase I, single-center, single-blind, fixed-order, single- and multiple-dose study | ESL and placebo tablets, PO. Single dose of ESL 900 mg followed by placebo QD for 7 days followed by ESL 800 mg QD for 7 days followed by ESL 1200 mg QD for 7 days | 20 planned 26 enrolled (ESL 900 mg N=26 Placebo N=26 ESL 800 mg N=24 ESL 1200 mg N=23) 22 completed | Healthy Subjects | Single Dose + Multiple Dose (3 Weeks) |
| Abuse Potential, Safety and Tolerability | SEP093-153 | Abuse potential of ESL in recreational CNS depressant users compared to placebo, and alprazolam | Phase I, single center, randomized, double-blind, placebo- and active-controlled, cross-over study | ESL tablets, PO Oral tablets 800 mg, 1600 mg, 2000 mg, and 2400 mg QD Alprazolam 1.5 mg and 3.0 mg PBO | 49 planned 53 randomized 44 completed | Male and female recreational CNS depressant users who have passed a pharmacologic qualification | Qualification period: alprazolam 2 mg for 2 doses, PBO for 2 doses Treatment period: single dose |

Source: ISS Appendix 7.1 Table 1

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MARY DOI
09/06/2013

SALLY U YASUDA
09/06/2013

**Deputy Office Director Decisional Memo**

| | |
|---|---|
| **Date** | 30 April 2010 |
| **From** | Ellis F. Unger, M.D.<br>Deputy Director, Office of Drug Evaluation-1 |
| **Subject** | Deputy Office Director Decisional Memo |
| **NDA/BLA #**<br>**Supplement #** | 22-416<br>0000 |
| **Applicant Name** | Sepracor, Inc. |
| **Date of Submission** | 3/29/09 |
| **PDUFA Goal Date (post-extension)** | 4/30/10 |
| **Proprietary Name /**<br>**Established (USAN) Name** | Stedesa<br>Eslicarbazepine acetate |
| **Dosage Forms / Strength** | 400, 600, and 800 mg tablets |
| **Proposed Indication(s)** | adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy |
| **Action:** | Complete Response |

| **Material Reviewed/Consulted** | **Names of discipline reviewers** |
|---|---|
| Regulatory Project Manager | Dorothy Demczar |
| Cross-Discipline Team Leader Review | Norman Hershkowitz |
| Clinical Review | Teresa Podruchny |
| Biostatistics Review | Xiang Ling |
| Pharmacology Toxicology Review | Christopher Toscano |
| Chemistry Manufacturing Controls (CMC) Review | Charles Jewell |
| Clinical Pharmacology Review | Veneeta Tandon, Kofi Kumi |
| Clinical Pharmacology Review (Drug-Drug Interactions) | Kofi Humi |
| Controlled Substances Staff | Alicja Lerner |
| Division of Scientific Investigations | Antoine (Tony) El-Hage |
| Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology | Latoya Toombs |
| QT Interdiciplinary Team | Joo Yeon Lee, Lihan Yan, Joanne Zhang, Monica Fiszman, Christine Garnett, Norman Stockbridge |

**Concurrence**

I concur with the recommendation of Dr. Russell Katz, Director, Division of Neurology Products, on a Complete Response action for eslicarbazepine, NDA 22-416. The review team is aware of the planned action, and is aligned on this decision.

As summarized by Drs. Hershkowitz and Katz, the review team has discovered a number of important deficiencies in the conduct and analysis of the pivotal studies, which can be divided into two categories: 1) improper study conduct and documentation (non-compliance with federal regulations and commonly accepted good clinical practice), as identified by DSI inspectors; and 2) inadequate and/or inaccurate presentation of the data in the application, as discovered during the review process.

These inadequacies undercut our confidence in the veracity of the data submitted in the application, and render impossible an adequate, independent review.

As noted, Study 303 was not found to be in compliance with Good Clinical Practice requirements when audited by Sepracor. Of the 35 total sites in Study 303, 10 were in Mexico, and the applicant audited 6 of these sites. The applicant's audit reports include infractions, deviations, and omissions that are both profound and widespread. A partial list includes: inadequate or missing documentation of study enrollment criteria, admission of subjects who did not meet enrollment criteria, missing medical history charts, lack of drug accountability logs, discrepancies between source documents and case report forms, un-dated case report forms, missing start and stop dates for anti-epileptic drugs, lack of reporting for numbers of seizures, seizure diaries that were not reviewed until well after a visit, missing electrocardiograms, and potential adverse events described in the source documents that were not included in the CRFs.

The applicant has taken the position that data from Study 303, although not adequate to support efficacy, can be used to support safety. The review team argues that these data are inadequate to support either safety or efficacy, and I concur. A safety analysis is fundamentally a non-inferiority analysis, and random noise, as one might expect from poor study execution, tends to obscure differences. Moreover, if the shortcomings of study 303 are non-random in nature, that is, if there were fraudulent activities, then inclusion of the data would be even more misleading.

The specific deficiencies discovered by DSI are described in detail in reviews by Drs. Podruchny and Hershkowitz, and also summarized by Dr. Katz. They are clearly beyond the importance and scope of those typically found during inspections in other applications. DSI argued strongly that the data were not to be trusted. Specifically, they noted: "In light of the issues noted during FDA audits, the audit reports submitted by Sepracor to the NDA are not considered sufficient in scope and detail to assure confidence of the data."

At various stages of the review, Dr. Podruchny discovered various anomalies and inconsistencies in the data listings and tables of the application. When brought to the applicant's attention, some issues were found to be due to misunderstandings, but in other cases, the applicant noted important errors that mostly served to weaken the team's confidence in the data.

Reviewers' comments on the efficacy and safety data should be construed as preliminary, therefore, given the data integrity issues. The demonstration of efficacy was fairly

straightforward and more or less robust to exploration, with one notable issue. The study design was such that subjects were not asked to place notations in their diaries to indicate the absence of seizures. Thus, by design, a blank diary was tantamount to having had no seizure, and it was not possible to discriminate missing data from lack of seizures. Presumably, this design flaw would have been avoided had the studies been performed under IND and the protocols reviewed by our staff.

The chief problem regarding safety is the potential for underreporting of adverse events. Based on site audits and Dr. Podruchny's review, it is possible that some adverse events went unreported or underreported, weakening our confidence in the results. On face, the data submitted do not suggest that there are safety issues that could not be addressed through labeling, but again, this conclusion is based on data deemed to be unreliable. There are some lingering concerns regarding multiorgan hypersensitivity syndrome, hepatic toxicity, and blood dyscrasias, as individual cases suggest potential signals. The review team also would like a better assessment of the relationship of eslicarbazepine and sudden death in epilepsy (SUDEP).

Overall, it is unfortunate that these shortcomings could not have been identified at an early date, such that the Division could have taken a Refuse to File action on this application. Ultimately, this action would have made the review process more efficient for the Division and the development process more efficient for the applicant. Unfortunately, these issues came to light as a result of the discovery process during the review, and were largely unknown at the time of the filing review.

**Applicant's Path Forward**

DSI has a number of requests for audits, outlined in their review and the Complete Response letter. It is not clear, however, that the sponsor can adequately "resurrect" the data. It is possible that an additional study or studies may need to be performed, and the applicant has been made aware of our concern. It is worth noting that it would be of value for the applicant to obtain domestic data. We accept foreign data when they meet our standards; in this case, however, they largely did not.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22416 | ORIG-1 | SEPRACOR INC | SEP-0002093 ESLICARBAZEPINE ACETATE |

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ELLIS F UNGER
04/30/2010

**Addendum to clinical review of NDA 22416:**

Regarding the use of the safety data in study 303, I recommend this data be viewed only for signals of serious events on a case-by-case basis, if necessary, and not be used to support the safety database otherwise. The sponsor notes GCP issues that were significant and noted a failure to "consistently (prospectively) assure subject safety" and control of the investigational product (p.64/75 of the clinical overview).

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22416 | ORIG-1 | SEPRACOR INC | SEP-0002093 ESLICARBAZEPINE ACETATE |

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TERESA A PODRUCHNY
04/30/2010

NORMAN HERSHKOWITZ
04/30/2010

# Cross-Discipline Team Leader Review

| | |
|---|---|
| **Date** | 4/30/10 |
| **From** | Norman Hershkowitz MD, PhD |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA # Supplement#** | 22416 (000) |
| **Applicant** | Sepracor Inc. |
| **Date of Submission** | 3/29/09 |
| **PDUFA Goal Date** | 4/30/10 |
| | |
| **Proprietary Name / Established (USAN) names** | STEDESA/ Esclicarbazepine Acetate |
| **Dosage forms / Strength** | 400, 600 and 800 mg |
| **Proposed Indication(s)** | Partial Onset Seizures |
| **Recommended:** | *Complete Response* |

Cross Discipline Team Leader Review Template

# 1. Introduction

Esclicarbazepine acetate (ESL) is a dibenz[b,f]azepine antiepileptic drug, the chemical family of which also includes the anticonvulsants carbamazepine and oxcarbazepine. All such agents block the voltage-gated sodium channel (and perhaps calcium gated channels), which is believed to be their mechanism of anticonvulsant action. Many other anticonvulsants (e.g. phenytoin and lamotrigine) are believed to act through a similar mechanism. ESL is actually very similar to oxcarbazepine. ESL may be considered a prodrug. Thus, it is rapidly and almost completely metabolized to S-licarbazepine (eslicarbazepine); small proportions of R-licarbazepine and oxcarbazepine are also produced. Both S-licarbazepine and R-licarbazepine are thought to possess the predominant "sodium channel blocking" anticonvulsant activity of this compound in humans. Oxcarbazepine produces the same active metabolites, but in different proportions. Thus the proportion of S-licarbazepine to R-licarbazepine, following oral administration of eslicarbazepine acetate, is 21:1, whereas the proportion following oxcarbazepine oral administration is 4:1.

The present application is for the approval of ESL as adjunctive treatment in partial onset seizures (POS). Well over 11 agents are presently marketed for the same indication. This includes those that are structurally and mechanistically similar (oxcarbazepine and carbamazepine), as well as a number of other agents with similar presumed mechanisms (e.g. phenytoin and lamotrigine), and others with potentially different mechanisms (valproic acid, gabapentin, vigabatrin).

# 2. Background

Eslicarbazepine acetate was developed by Bial-Portela & Ca.S.A. Sepracor is the U.S. sponsor of eslicarbazepine and the sponsor of this NDA. Development of this drug started in the year 2000 and mostly occurred outside and prior to the establishment of an FDA IND. The phase 3 clinical drug development program was wholly outside the United States. Two pre-NDA meetings occurred, one with Bial and another with Sepracor. One of the crucial issues discussed at these meetings was the absence of US data. The Sponsor was requested to provide an adequate justification for the exclusive use of non-US data in their NDA application.

ESL has recently been given a favorable EMEA review and is to be marketed in Europe under the brand name of Zebinix.

## 3. CMC/Device

The CMC reviewer, Charles Jewell, recommends approval. He notes that the drug substance was adequately characterized with respect to chemical purity, stereo-chemical purity, stability, physical properties and consistency in manufacture. He also noted that the manufacturing process for the drug product was adequately studied and the drug is produced in a controlled and consistent fashion. The product proved to have adequate quality and stability. (b) (4)

All production sites were inspected and reviewed and given an "acceptable decision."

## 4. Nonclinical Pharmacology/Toxicology

Dr Toscano performed the pharmacology/toxicology review. Dr. Toscano notes that, with the exception of one deficiency, the application contained an adequate non-clinical assessment of the pharmacology and toxicology of ESL. He notes that ESL demonstrated to be a carcinogen and teratogen in non-clinical studies, this effect was not different from some other anticonvulsants that are presently approved. He also notes that ESL's overall nonclinical profile is similar to other approved anticonvulsants and should be approved with appropriate labeling. He does recommend a PMR to further investigate the genotoxicity, as the original studies utilized rat microsomes. Such studies were inadequate as rats metabolite ESL differently from humans. He therefore recommends that the Sponsor, "be required to conduct an *in vitro* mammalian mutagenicity assay and an *in vitro* chromosomal aberration assay on the main human metabolite, BIA 2-194 (eslicarbazepine)." Dr Freed, the Pharm/Tox team leader, believes that only one of these studies are required, as we are no longer interested in using such studies for the purpose of predicating carcinogenicity, but to better understand its carcinogenic potential.

## 5. Clinical Pharmacology/Biopharmaceutics

Drs. Veneeta Tandon and Kofi Kumi performed the Clinical Pharmacology review. Both concurred that the PK studies were adequate and the application can be approved.

The to-be marketed formulation and the formulation used in the pivotal clinical trials were considered bioequivalent. Dosage strengths were determined to be equivalent. The DSI inspection results were acceptable. No food effect was apparent.

As noted above oral ESL can be considered a prodrug to S-licarbazepine, which represents 95% of the circulating species, and is believed to exert it's predominate anticonvulsant action. Metabolism is believed to occur by hydrolytic first-pass metabolism in the presence of hydrolase; other active metabolites produced in substantially smaller amounts include R-licarbazepine and oxcarbazepine. Additional inactive metabolites are produced and account for a small percentage of that circulating (3%). Bioavailability is high. Tmax of S-licarbazepine occurs in about 1-4 hours. Protein binding is relatively low (<40%).

ESL metabolites are predominately eliminated by the kidney, mostly in the form of free S-licarbazepine (approximately two-thirds) and conjugated S-licarbazepine (one third). The T1/2 in epilpsy patients is 13 to 20 hours.

Pharmacokinetic studies indicated dose proportionality in the range of 400 to1200 mg/day, doses equivalent to Sponsor recommended labeled dose (400 to 1200 mg/day).

The clinical pharmacology reviewer notes that the extent of systemic exposure ($AUC_{0-\infty}$) to S-licarbazepine was increased by 62%, 116%, and 154% in the mild, moderate, and severe renal impairment group, respectively. Because of this dose reduction is recommended in patients with moderate and severe renal failure. The clinical pharmacology reviewer recommends the following dosing in patients with renal failure.

| Dosing Recommendations | Normal (Clcr >80 ml/min) | Mild (Clcr 50-80 ml/min) | Moderate (Clcr 30-49 ml/min) | Severe (Clcr 15-29 ml/min) |
|---|---|---|---|---|
| Initial<br><br>(Need better info who rapid an increase and what are the increments?) | 400 mg QD<br><br>Weekly increments to the next dose | 400 mg QD<br><br>Weekly increments to the next dose | 300 mg QD<br><br>Weekly increments to the next dose | 200 mg QD<br><br>Weekly increments to the next dose |
| Maximum | 1200 mg QD | 1200 mg QD | 600 mg QD | 600 mg QD |

(b) (4)

(b) (4)

The QD dosing regimen recommended by the clinical pharmacologist results in greater superimposability of curves in the modeling. The Clinical Pharmacology reviewer is recommending that a 200 mg tab be developed for QD dosing, but is not requiring this for approval. I agree with this, and would underscore that this should be made mandatory. While there is a small pharmacokinetic advantage, there is no hard evidence to indicate that this regimen would be advantageous from a therapeutic point of view. (b) (4)

Moderate hepatic impairment did not affect the pharmacokinetics of eslicarbazepine and dosage adjustment is not necessary.

No significant change in the pharmacokinetics was apparent in the elderly with creatinine clearance > 60 mL/min. Children were not studied.

With regard to general drug-drug interaction Clinical Pharmacology reviewers agrees with the Sponsor that Eslicarbazepine is an inhibitor of CYP2C19. Significant reduction in levels of oral contraceptives and warfarin was noted that will require cautionary labeling. With regard to its effect on other anticonvulsants, while all were not studied, the only significant interaction was an increase in phenytoin exposures, which may require a reduced phenytoin dose. Also noted is observation that phenytoin, carbamazepine and phenobarbital may increase ESL exposure, requiring a reduced ESL dose.

Metabolism did not appear to be significantly affected by race (black versus Caucasian) or sex.

Approval is recommended and no post marketing commitments or requirements are noted. As noted above, there is a recommendation for the development of lower tablet strength for dosing in patients with moderate renal failure.

## 6. Clinical Microbiology

Not applicable.

## 7. Clinical/Statistical- Efficacy

Dr. Podruchny performed the medical review and Dr. Ling performed the statistical review.

Three phase 3 randomized, placebo-controlled, and multi-center trials (studies 301, 302 and 303) were designed to serve as pivotal trials to support adjunctive treatment in partial onset epilepsy. Studies were wholly performed outside the US in Eastern Europe, Western Europe, Latin America, Australia and South Africa. Only two of these (studies 301 and 302, with an n's of 402 and 302, respectively) were submitted by the Sponsor to support efficacy because of data integrity issues in the third study (study 303, see the section on "Other Relevant Regulatory Issues). Study 303 (n = 253) was to be considered as supportive. Because of this, studies 301 and 302 will be discussed in greater detail than study 303.

Studies 301 and 302 were of relatively typical design for studies that examine adjunctive treatment of epilepsy. Patients were recruited and entered into an 8-week prospective placebo period. Only subjects who fulfilled minimal frequency requirements during the baseline period was randomized to one of four treatment groups (placebo or ESL 400mg, 800mg or 1200mg qd) and entered the experimental phase of the study. The experimental phase consisted of a 2 week titration period followed by a 12 week maintenance period.

The primary analysis was performed on the dataset that was defined as all randomized patients with at least one administration of study medication and at least one post-baseline (maintenance period) seizure frequency assessment. The primary endpoint was absolute logarithmically transformed seizure frequency[1] during maintenance, which was compared among the treatment groups by using an analysis of covariance (ANCOVA) that models seizure frequency as a function of baseline seizure frequency and treatment. The "last observation carried forward" during the maintenance phase was used. Patients who dropped out during the titration phase were not included in this analysis. Dunnett's multiple comparison procedure was used for the comparison of each active treatment group to the placebo group and corrected for multiple comparisons. This method of analysis is relatively routine, except that it is more common to include the titration as well as the maintenance period in this calculation and eliminates any potential bias for patients dropping out early. Using the titration phase maintains randomization and is closer to a true ITT analysis. The logarithmic transformation is performed to normalize the data.

[1] Natural logarithm transformation was carried out according to the following formula: Ln(standardized seizure frequency+4). The standardized seizure frequency for a period was calculated as: (number of seizures/days in the period*28).

*Study 301*

No obvious demographic or baseline differences were apparent across treatment groups. All patients were categorized as Caucasian. Data and analyses (from the statistical review).for the primary endpoint are presented in the table below

**Study 301: Seizure Frequency per 4 Weeks over the Maintenance Period (Sponsor updated result)**

| | **Placebo** | **Eslicarbazepine Acetate Dose Group** | | |
|---|---|---|---|---|
| | | **400 mg** | **800 mg** | **1200 mg** |
| N | 99 | 97 | 93 | 92 |
| LSmean (SE) | 7.5 (0.67) | 6.7 (0.60) | 5.6 (0.58) | 5.4 (0.56) |
| 95% CI | 6.3, 8.9 | 5.6, 8.0 | 4.6, 6.9 | 4.4, 6.6 |
| Log Difference in LSMean (SE) | | -0.07 (0.055) | -0.18 (0.055) | -0.20 (0.056) |
| 95% CI for Difference in LSMean | | -0.20, 0.06 | -0.31, -0.05 | -0.33, -0.07 |
| p-value | | 0.4067 | 0.0041 | 0.0009 |

Source: Sponsor's response to October 8, 2009 Request for information and is confirmed by FDA reviewer. Without imputation, baseline AED as covariate

Only the 800 mg/day and 1200 mg/day group were determined to be statistically significantly different from placebo. The percent reductions in seizure frequency over placebo in these two groups, based upon the Sponsor's calculation, were 16.5% and 18.1% for ESL 800mg/day and 1200mg/day, respectively.

The Sponsor concludes that doses of 800 and 1200 mg/day produced statistically significant effects. Similar results were observed in the Sponsor's analysis of 50% responder rates, a secondary endpoint, with only the 800 and 1200 mg/day dose producing a statistically significant effect (adjusted for multiple comparisons) as compared to placebo (ESL 1200 mg group =44.6% and the ESL 800 mg group = 35.5% compared to the placebo group = 20.2%).
.
The statistics reviewer notes that the data provided by the Sponsor was "hardcoded" to correct for errors that were introduced in the original datasets. These hardcode corrected for these errors. The reviewer examined this issue and determined that this hardcoding affected 559 data-points. Some of these hardcodes resulted from an unblinded review. Such problems were evenly distributed across treatment groups. A sensitivity analysis, with removal of the hardcodes, produced similar results as that observed with the hardcodes. While the statistics reviewer did not believe the degree of hardcoding affected the final conclusions she did believe that such a degree was unusual and that it reflected on the poor conduct of the study (see the section on "Other Relevant Regulatory Issues").

Another issue noted by the statistics reviewer is that while it is routine for patients to maintain record of seizures by updating a diary, which serves as the source of the primary endpoint calculation, subjects were instructed to update their diary only on days when they had seizures. This meant that diary cards that were not filled out or returned were assumed to represent days

without seizures. Moreover, the last diary returned was assumed to represent the last day in the trial and used to calculate the denominator for frequency. However a worst case scenario sensitivity evaluation was, according to the statistics reviewer, "still favorable."[2]

Another issue considered by the statistician was the use of only patients who reached the maintenance phase. This, as noted above, is not a typical ITT analysis. The statistician performed a sensitivity analysis and found that this did not influence the final conclusion.

The statistics reviewer considered two additional issues in the Sponsor's analysis of this study, including her observation that : 1) logarithmic transformation should have used a slightly different analytic manipulation, 2) the original SAP ANCOVA's analysis identified only frequency and treatment as covariates, but the Sponsor added the "number of concomitant AEDs" as a third covariate. The FDA statistician recalculated data performing a correction for these factors and found similar statistical significance for the two highest doses.

The statistician also performed a calculation of the primary endpoint excluding site 112, which was determined to be problematic by inspection, and observed a similar statistical significance of the two highest doses.

*Study 302*

Demographic variables in this study tended to be well distributed over the treatment groups except for slightly fewer Caucasians in the 1200 mg/day treatment group and fewer males in the 400 mg/day treatment group. Baseline characteristics were similar except for a trend toward slightly lower baseline seizure frequency in the placebo groups (thus median baseline frequencies were 7.4, 8.2, 9.1, and 9.3 seizures per 4 weeks in the placebo and ESL 400 mg, 800 mg and 1200 mg groups, respectively). These differences, however, were small and the analysis statistically corrects for baseline.

The Sponsor's statistical evaluation of the primary endpoint revealed that the dose groups of 800 and 1200 mg/day were statistically significantly different from the placebo group (see table below, from the statistical review). The treatment effect in the 400 mg/day dose group was not determined to be statistically significant. These calculations were confirmed by the FDA statistician. These data translate into percent reductions in seizure frequency over placebo of 16.5% and 13.9 % for the 800 mg/day and 1200 mg/day groups, respectively. A worse case scenario analysis[3] to correct for the patient diary reporting problem (see study 301) was still "favorable" to an effect. The 50% responder rate exhibited a similar result as the primary endpoint evaluation.

[2] The worst case scenario calculation revealed a p-value of 0.0599 for the 800 mg group and from 0.0009 for the 1200 mg group.

[3] The worst case scenario calculation revealed a p-value of 0.031 for the 800 mg/day group and 0.078 for the 1200 mg/day group.

| | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg |
| N | 99 | 94 | 87 | 81 |
| LSmean (SE) | 10.0 ( 0.67) | 9.2 ( 0.65) | 7.6 ( 0.59) | 8.0 ( 0.62) |
| 95% CI | 8.7, 11.3 | 7.9, 10.5 | 6.5, 8.8 | 6.8, 9.2 |
| Log Difference in LSMean (SE) | | -0.06 ( 0.061) | -0.18 ( 0.062) | -0.15 ( 0.063) |
| 95% CI for Difference in LSMean | | -0.20, 0.08 | -0.33, -0.04 | -0.30, 0.00 |
| p-value | | 0.6524 | 0.0095 | 0.0420 |

Similar to study 301, the statistics reviewer performed analyses adjusting the logarithmic formula, covariates, and use of only patients during maintenance to define an ITT population. These analyses indicted that the 800 mg/day group maintained its effect, but statistical significance was lost in the 1200 mg/day group. . Hardcoding was not as much an issue in this study, as their use was more transparent. A sensitivity analysis, examining the affect of hardcoding, indicated that it did not influence the final conclusion of efficacy.

*Study 303*

As noted elsewhere in the review, the data in this study were considered suspect and are therefore not considered in the evaluation of efficacy. Study 303 was similar in design to those studies noted above, however study 303 examined only three experimental groups (placebo, 800 mg/day and 1200 mg/day) and was carried out at sites in Mexico, with some in Spain and Portugal. Analysis revealed that both experimental drug groups exhibited a statistically significant reduction in seizures as compared to the placebo control group. The analysis was confirmed by the FDA statistician. A reanalysis of the data, which was updated to incorporate changes in deriving the efficacy variable resulted in statistical significance only in the 1200 mg/day group.

*Subgroup analysis*

As per the statistical reviewer, no obvious sex, age or racial factors appeared to influence the drugs effect. These data were limited, however, by small numbers of patients older then 60 years old and who was not Caucasian. The number of patients of both sexes was adequate.

Whereas the statistical reviewer did not perform an analysis of sub-categories of partial onset seizures by type (simple partial, complex partial and partial secondary generalized), the Sponsor presents such an analysis in one of their tables in the integrated summary of efficacy, shown below. Only patients having a particular seizure subtype during baseline were analyzed, leaving the conclusions open to bias resulting from the loss of randomization and

sampling error. Nonetheless, while the table indicates favorable trends (and even statistical significance) in two seizure subtypes (simple partial and complex partial seizures), no trend is indicated in the partial secondarily generalized seizures. With the understanding that such analysis is flawed, I believe the Sponsor should be asked to explain this unexpected result.

**Table 3.4.2.1-5: Analysis of Relative Change in Standardized Seizure Frequency During the 12-Week Maintenance Period for the Pooled Pivotal Phase III Studies 2093-301 and 2093-302 by Seizure Type (Model 1, without Interaction) - ITT Analysis Set**

| Seizure Type | ANCOVA Statistic[a] | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|---|
| | | | 400 mg | 800 mg | 1200 mg |
| Simple Partial | N | 92 | 85 | 86 | 85 |
| | LS Mean (SE) | 39.6 (13.41) | 3.8 (13.86) | -22.2 (13.74) | -20.2 (14.21) |
| | 95% CI | 13.2, 66.0 | -23.5, 31.1 | -49.2, 4.8 | -48.1, 7.7 |
| | Diff in LS Mean (SE) | | -35.8 (16.83) | -61.8 (16.68) | -59.8 (16.73) |
| | 95% CI for Diff in LS Mean | | -75.6, 4.0 | -101.2, -22.4 | -99.3, -20.3 |
| | p-value[a] | | 0.0885 | 0.0007 | 0.0012 |
| Complex Partial | N | 144 | 137 | 131 | 137 |
| | LS Mean (SE) | 1.2 (8.23) | -20.6 (8.45) | -27.0 (8.81) | -23.4 (8.40) |
| | 95% CI | -14.9, 17.4 | -37.2, -4.1 | -44.3, -9.7 | -39.9, -6.8 |
| | Diff in LS Mean (SE) | | -21.9 (9.81) | -28.2 (9.87) | -24.6 (9.78) |
| | 95% CI for Diff in LS Mean | | -45.0, 1.3 | -51.5, -4.9 | -47.7, -1.5 |
| | p-value[a] | | 0.0686 | 0.0124 | 0.0333 |
| Partial Evolving to Secondarily Generalized | N | 75 | 66 | 62 | 64 |
| | LS Mean (SE) | -54.8 (24.08) | -9.2 (24.26) | -29.1 (25.57) | -55.0 (24.53) |
| | 95% CI | -102.2, -7.3 | -57.0, 38.6 | -79.4, 21.3 | -103.3, -6.7 |
| | Diff in LS Mean (SE) | | 45.6 (28.20) | 25.7 (28.62) | -0.2 (28.44) |
| | 95% CI for Diff in LS Mean | | -21.3, 112.4 | -42.1, 93.5 | -67.4, 67.1 |
| | p-value[a] | | 0.2567 | 0.7052 | >0.9999 |
| Unclassified | N | 24 | 19 | 22 | 21 |
| | LS Mean (SE) | -65.2 (15.77) | -38.2 (18.15) | -52.5 (18.00) | -52.4 (17.28) |
| | 95% CI | -96.6, -33.8 | -74.3, -2.1 | -88.3, -16.6 | -86.8, -18.0 |
| | Diff in LS Mean (SE) | | 27.0 (20.89) | 12.7 (20.77) | 12.8 (20.67) |
| | 95% CI for Diff in LS Mean | | -23.1, 77.1 | -37.1, 62.5 | -36.7, 62.4 |
| | p-value[a] | | 0.4338 | 0.8748 | 0.8704 |

Abbreviations: ANCOVA=analysis of covariance; LS=least squares; SE=standard error of the mean; CI=confidence interval; Diff=difference.

a ANCOVA model with fixed effects for treatment, study, baseline standardized seizure frequency, and number of concomitant AEDs at baseline, without the treatment by study interaction.



*Summary of Effect*

The statistics reviewer prepared the following summary tables of their own analysis for all three studies, which corrects for the ITT analysis (using titration data for patients without maintenance data). This includes the primary endpoint, 50% responder rate and percent reduction from baseline.

**Primary endpoint: maintenance seizure frequency**

| | | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|---|
| | | | 400 mg | 800 mg | 1200 mg |
| 301 | LSmean | 6.9 | 6.2 | 5.2 | 4.8 |
| | p-value | | 0.5136 | 0.0125 | 0.0007 |
| 302 | LSmean | 9.2 | 8.2 | 6.8 | 7.5 |
| | p-value | | 0.5368 | 0.0072 | 0.1143 |
| 303 | LSmean | 6.8 | | 5.3 | 5.0 |

| | | | | | |
|---|---|---|---|---|---|
| | p-value | | | 0.0887 | 0.0335 |

**Secondary endpoint: percent of responder during maintenance**

| | | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|---|
| | | | 400 mg | 800 mg | 1200 mg |
| 301 | n/N (%)a | 20/102 ( 19.6 ) | 23/ 98 ( 23.5 ) | 34/ 98 ( 34.7 ) | 42/ 97 ( 43.3 ) |
| | Chi-square p-value | | 0.6225 | 0.0249 | 0.0006 |
| 302 | n/N (%)a | 18/100 ( 18.0 ) | 20/ 96 ( 20.8 ) | 33/ 98 ( 33.7 ) | 32/ 94 ( 34.0 ) |
| | Chi-square p-value | | 0.7483 | 0.0183 | 0.0169 |
| 303 | n/N (%)a | 21/ 84 ( 25.0 ) | | 29/ 84 ( 34.5 ) | 34/ 77 ( 44.2 ) |
| | Chi-square p-value | | | 0.2375 | 0.0167 |

Unadjusted p-value from pair wise test of each active treatment group compared to placebo.

**Percent reduction from baseline**

| | | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|---|
| | | | 400 mg | 800 mg | 1200 mg |
| 301 | LSmean | -7.7 | -15.9 | -28.4 | -29.6 |
| | p-value | | 0.6391 | 0.0373 | 0.0262 |
| 302 | LSmean | 3.6 | -10.8 | -17.9 | -5.3 |
| | p-value | | 0.2773 | 0.0521 | 0.6574 |
| 303 | LSmean | -2.0 | | -19.3 | -18.8 |
| | p-value | | | 0.3165 | 0.3522 |

Based upon the above the data the statistical reviewer concludes that the 800 mg/day dose is no better then the 1200 mg/day dose.

*Conclusion*

I agree with the statistics reviewer that, at face, the data indicates efficacy for doses of 800 mg/day with the 1200 mg/day dose offering no additional protection, on average, than the 800 mg/day dose. The effect size is similar to what I have seen for other anticonvulsants, albeit on the low side. Two observations are noteworthy. The first is that the 800 mg/day dose failed to show a statistically significant effect in study 303. If, indeed, this study was performed in the absence of good GCP guidelines false negatives would not be completely unexpected considering the increase variability introduced by the studies poor performance. Therefore, one must view such results as noncontributory. The other issue is the absence of a statistically significant effect when the true ITT population is evaluated in the 1200 mg/day group in study 302. This is likely a result of including patients who dropped out during titration but where still in the titration phase, thereby having low exposures. Supporting the effect at 1200 mg/day is the effect observed in the 1200 mg/day group in study 301 and the "supportive study" 303 as well as relatively consistent effects observed for 800 mg/day groups (with the exception of study 303). Lastly, as noted above, there is some question as to whether partial onset secondarily generalized seizures are also suppressed by the medication, although such subgroup analyses should be interpreted with caution.

While in sum these results suggest that ESL possesses anticonvulsant activity this conclusion can only be considered as tentative because the larger overarching issue of data integrity.

Nonetheless, it should be pointed out that conclusions regarding efficacy may be less problematic then those of safety when GCP practice is not adhered to. That is, these problems would cause an increase in background noise (variability) which may make it more difficult to conclude a statistically significant effect. Nonetheless, efficacy was concluded from the data. On the other hand the increase in noise may also increase the difficulty in detecting a safety signal. This is particularly important when one considers that rare, but significant, safety events may be missed.

# 8. Safety

**General Safety Review**

The safety review was performed by Dr. Podruchny.

Because of serious data integrity issues (see Other Relevant Regulatory Issues) a full safety review was not completed. However, the process of an initial review permitted the reviewer, Dr. Podruchny, to identify a number of data integrity issues. The review included the adequacy of the database, deaths, serious adverse events and discontinuations. Dr Podruchny notes that the safety data, like the efficacy data, must be interpreted with caution. I agree; any conclusions drawn from this data must be considered as tentative because of the data integrity issues and are open to change following the Sponsor's response to what will be a CR letter.

The present safety database included phase 1, phase 2 and phase 3 studies. The development program of this drug included studies targeted to examine its effect on patients with partial onset epilepsy (phase 2 and 3), pain (herpetic neuralgia and diabetic neuropathy) as well as manic depression. The epilepsy database include the 3 phase 3 trials in POS, but as noted in other parts of their review, study 303 was determined to have a number of GCP issues.

A total 1889 unique patients were exposed to drug. Examining the Sponsor's safety update table, the Sponsor achieves exposures to approximately 600 patient for 6 months or greater, at the mean dose of 600 to 900 mg/day; few patients were exposed to greater mean doses for this duration (n=25). Moreover, there was a substantial number of exposures one year or greater at mean dose of 600 to 900mg/day (n= 582), but few one-year exposures are observed at higher doses (n=1). While mean dose exposures were presented by the Sponsor as a range, my calculations indicate that at least half of the patients noted in the 600 to 900 mg/day dose were exposed to 800 mg/day or more. These data are generally sufficient to satisfy ICH guidelines, with the caveat that there was minimal long-term exposure at the high dose. One caveat to consider is that these values include study 303, the efficacy data of which was determined by the Sponsor to be untrustworthy because of significant deviations from GCP. Dr. Podruchny and I see no reason to accept such data for safety if they are rejected it for efficacy. Indeed, as previously noted, the use of this study may be more problematic when it comes to safety then when we consider efficacy. An initial re-analysis by Dr. Podruchny, which excludes study 303, reveals 6 month and one year exposures at doses greater or equal to 800 mg/day to be 463 and 307, respectively. The exposure appears to be adequate, but on resubmission the Sponsor

should provide an update of exposures that includes only that data from studies that are deemed adequate: other studies may be found inadequate on a more thorough analysis.

*Deaths*

Sixteen deaths were identified in the database, 2 on placebo and 14 on drug. No deaths on drug were identified during the control phase of the phase 3 epilepsy trials. Of these deaths one was in a phase 1 study, one was in a bipolar study, four were in trials of either post-herpetic neuralgia or diabetic neuropathy, and 8 are from extensions phases of the phase 3 epilepsy studies. Three deaths in the epilepsy trials were from drowning, with 2 of these occurring at least 3 weeks after drug discontinuation. Such deaths are likely more a reflection of the general quality of seizure control in these patients then a reflection of a drug effect. Of the remaining deaths in the epilepsy studies three were associated with seizure events (status or cluster seizures), one from reoccurrence of an astrocytoma and one from sudden death in a patient with severe atherosclerosis. Three additional deaths in other therapeutic trials resulted from neoplasms (lung, prostate, gastric), all in patients who were over 60 years old and in all but one case the diagnosis was made in less then one month after drug was initiated. I believe these cases do not represent a signal. One death, in a manic depression protocol, occurred as a result of suicide. Although Dr Podruchny did not carry out an analysis of Sudden Unexplained Death in Epilepsy (SUDEP) rate, I would note that the numerator in the analysis would include either one, including only the cardiovascular death, or 4, adding the three seizure related deaths. This absolute number is within that which we have seen in other studies and cannot therefore be attributable easily to a drug effect. The Sponsor should perform an analysis and compare their rate to background rates.

*Non-fatal Serious Adverse Events*

The Sponsor reports that 88/1977 (4.5%) ESL-treated subjects experienced 125 non-fatal SAEs. In the blinded epilepsy studies 1.4% of patients in the placebo group as compared to 4.5% of patients in drug treatment groups experienced serious adverse events; 6.9% of epilepsy patients in open label studies experienced SAEs. These rates where generally similar to that observed in the controlled bipolar studies. Examination of epilepsy trials did not reveal an obvious dose/response relation for serious adverse events.

The most common adverse event “System Organ Class” in the controlled epilepsy studies were “Nervous System Disorders” followed by “Gastrointestinal Disorders.” Most events in the “Nervous System Disorders” consisted of events with preferred terms of abnormal movements, ataxia, dizziness and various preferred terms for seizures (convulsions, grand mal seizures etc). Nervous disorders were also the most common SAEs observed in the open label epilpsy trials, however in this case such episodes consisted of predominately seizures. It is noteworthy that, at least in some patients, coding to different preferred term may have diluted adverse event reporting. Thus, reading narratives indicted patients who were ataxic were coded to ‘drug toxicity” and “coordination abnormal.” Vomiting was the most common gastrointestinal serious adverse event. Serious adverse events of particular interest in the controlled epilpsy studies identified by Dr Podruchny include the following: 1) One subject with hyponatremia (Na 123 mM) associated with vomiting and “abnormal movements” that

resolved when dechallenge, 2) one subject with vasculitis that may have had this as a preexisting condition , 3) One patient with a rash, fever, elevated CRP, leukopenia, anemia, thrombocytopenia, and increased LDH, AST, and GGT (normal bilirubin), which the Sponsor reports as viral in nature, but I believe may be suspicious for a multiorgan hypersensitivity, 4) one patient (without a psychiatric history) was reported to have psychotic behavior after treatment which resolved with drug discontinuation. Cases of interest in the open label phase of the epilepsy trials included: 1) One case of hyponatremia (Na 124mM) associated with UTI, 2)hepatitis which resolved even with drug continuation , making it less likely to be medication related, 3) Dr Podruchny notes 6 cases were reported that contained some form of psychotic type behaviors, 4) One case of epilepsy suggested the onset of a non-preexisting seizure subtype (atonic). The Sponsor should be queried in the CR letter to perform a more careful analysis of the potential to produce new form of seizure and analyze the potential psychiatric effects of ESL. No obvious other signals were identified in other epilepsy trials (including a phase 2 pediatric study) except for a serious rash in an ongoing trial that still remains blinded. More information will need to be provided on this case.

No obvious drug related SAEs could be indentified in the phase 1 ISS database (4 total SAEs reported). There was one case of a drop in neutrophils; however, that may be related to an EBV infection. However, latter submissions, provided by the Sponsor as a result of the divisions request for data clarification, identified an additional 2 cases in the phase 1 database, one of which was somewhat worrisome. That case involved a patient on Lamictal who may have experienced a serious skin reaction.

SAEs were reported in the Bipolar phase 2 studies which generally added little additional information to the previous data, although some issue were unclear and should be clarified by the Sponsor as recommended by Dr Podruchny. Thus Subject 203-301/203215 had hyponatremia (Na 128) and a mild leukopenia. This same patient was noted to have elevated bilirubin at two visits, but little other information is provided. One serious adverse event was described as with “anemia,” and esophageal stenosis with little other information gleaned by Dr Podruchny. The Sponsor should provide more information on this patient.

Additional SAEs were reported in what Dr Podruchny describes as “ongoing and clinically completed but not reported studies” in submissions provided by the Sponsor on 2-4-10 and 1-25-10. These studies included patients being studied for pain associated with diabetic neuropathy and post-herpetic neuralgia. As pointed out by Dr Podruchny, a number of cardiac events were observed. While such events could be expected in an older group some of whom are diabetic, no such events were observed in the placebo group. The Sponsor should further explore this issue. One serious rash was noted. In general Dr Podruchny notes that the presentation of this data was suboptimal and needs clarification.

Dr Podruchny notes that it was difficult to have confidence in the data because of a number of reasons, which she enumerates as, follows:

- “Small number of placebo SAES reported” - The small numbers in the placebo group, as compared to other similar drug applications, may indicate incomplete SAE reporting.

- "data quality issues at DSI inspection" (see Other Regulatory Issues)
- "Several significant events (bipolar 203058, phase 1, 119-04 and 110-11) have not been adequately presented."
- "it appears that several significant events (bipolar 203058, phase 1, 119-04 and 110-11) have not been adequately presented and this includes one event that meets regulatory standards for serious that is not classified as such."
- "Some narratives are content poor in terms of clinical descriptions and bolded event headings may be the stated reasons for the SAE or DC, but do not do not optimally represent the data". For example, many of the pertinent positive and negative signs, symptoms and laboratories were not discussed.
- "some CRFs are difficult to follow with multiple data clarification forms and/or corrections"
- There was not "infrequently internal inconsistency or incomplete information when trying to cross-reference between listings and tables and narratives that make it difficult to feel confident that the data were adequately quality control checked."

From what can be gleaned from the data, which Dr Podruchny feels is flawed, she conclude that "certain serious events are seen across development phases and/or in more than one population. These include rash, a spectrum of drug toxicity reactions or side effects to include ataxia, vertigo, diplopia, and vomiting, hyponatremia, possibly GI motility disorders (obstipation, esophageal stenosis)."

*Discontinuations*

In the complete study database approximately 11 % of patients on drug discontinued due to adverse events; this compares to 3.4% on placebo. Similar values were observed in the controlled phase of the combined pivotal epilepsy studies 301 and 302. Thus, 4%, 8.7%, 14.6%, and 23% of the placebo, eslicarbazepine 400 mg/day, 800 mg/day and 1200 mg/day groups, respectively, discontinued secondary to an AE. Higher rates of discontinuation were observed in the placebo group and lower rates in the drug treatment groups in study 303. Dr Podruchny notes that the most common cause of discontinuations in pivotal trials, greater than placebo, resultied from adverse events under the organ class "Nervous System Disorder." These included dizziness, abnormal coordination, and somnolence. Other preferred terms, such tremors, vertigo and ataxia, although not occurring at as great a frequency as the latter terms, really should have been included under the same rubric as the latter preferred terms (e.g. vertigo and dizziness may have been classified together[4]). GI adverse events of nausea and somnolence were also quite common. Diplopia and blurred vision were also noted to be common and greater in the drug group. All such events are relatively commonly observed in this class of drugs (sodium blocking anticonvulsants). Dr Podruchny notes that some patients who experienced a constellation of symptoms (e.g. nausea vomiting and dizziness) were also described as having discontinued because of "drug toxicity." Examination of Dr Podruchny's tables indicated quite a large number of cases of discontinuations from rash like phenomena described as exanthema, rash, erythema nodosum and facial edema in studies 301 and 302. To

[4] I know of no attempt to define 'dizziness' by differentiating it into to either true vertigo from light headedness.

me this seems like a large number of such events. One case of rash was associated with an elevation in LFTs without increases in bilirubin. Additional events leading to discontinuations seen in more then one patient receiving ESL in studies 301 and 302 was tremor, constipation and hyponatremia. A number of patients discontinued in the controlled epilepsy studies for psychiatric complications, one of these was due to "psychotic disorder" and 3 for depression (and an additional subject with crying).

Sixty to 71 additional patients discontinued because of AEs in the open label phase of the 3 phase 3 epilepsy studies, depending on what source document was being evaluated. Reasons for discontinuations were similar as those described in the controlled trial. Of interest, there were 2 cases of discontinuation because of hyponatremia and one for pancreatitis (but confounded with the use of valproic acid). Six subjects discontinued for psychiatric reasons, 3 of whom experienced psychotic like behavior, and one for decrease blood cell counts (not specified in Dr Podruchny's review). Three subjects discontinued for decreased blood cell counts (not specified in Dr. Podruchny's review).

Reasons for discontinuations in phase 1 trials were similar to that for epilepsy. It is noteworthy that there were 11 discontinuations for the terms "hypersensitivity reaction," rash/urticaria/generalized rash, and one rash that include LFT elevations (110-000-11). This interprets into about 8% of patients in the phase 1 trial experiencing rashes. There was also one case of elevation of transaminase (ALT was 8 times normal).

Discontinuations in bipolar studies were similar in nature to those on other studies. The most notable discontinuations included: 1) a number discontinuations were noted for hypersensitivity with rash, 2) one case of nausea and vomiting along with transaminase elevations, with increase in bilirubin and minimal increase in alkaline phosphatase, which while suggestive of hepatic toxicity (or biliary stasis) is confounded by a significant history of pancreatitis, 3) one case of hepatic steatosis, 4) one case described as "leukopenia and hyponatremia." Abnormalities in these cases appear to have resolved on drug discontinuation.

Discontinuations in ongoing studies provided as a follow-up to questions poised by the FDA revealed a similar profile as above. Noteworthy were 8 cases of discontinuation from rash, pruritus or itching and 3 for what appeared to be angioedema with edema/ of face, eyelids, and/or tongue and 2 cases of hyponatremia.

**Formal QT Study**

The Sponsor performed a formal QT study in 67 subjects that was considered adequate in design by the TQT team. The TQT team determined that ESL fails to produce a significant QT prolongation. I have examined the tables in the TQT review (Table 10) and have noted a mild trend for QT shortening (double delta of -1 to -6 msec) that was not dose dependent. The significance of such shortening is not well understood. Moreover, a small, non-clinically significant prolongation in the PR interval and QRS duration was noted. Similar QT, PR and QRS changes have been noted with other sodium channel blocking anticonvulsant agents.

**Conclusions**

Data integrity issues, completeness of information and organization made the review of this application very difficult. Some of these issues are discussed in the section Other Regulatory Issues. It was not infrequent to discover an issue that needed clarification from the Sponsor following our own more granular review, which upon receipt required the reviewer to revise her approach to reviewing the application or an alteration in her conclusions. While this is not uncommon in reviewing application, it seemed to come up more frequently then usual and involve more significant new pieces of information (e.g. serious adverse events). This combined with data integrity issues discovered during the review and similar DSI findings (see Other Regulatory Issues) led us in believing that a complete definitive review would be impossible at this time. Thus, a complete review was not performed and the Sponsor will be asked to address those issues of data integrity and provide an updated analysis of safety (and efficacy).

The following safety issues are notable in my examination of the review for which tentative statements may proffered:

- There appears to be definite and significant signals which would require labeling in the Warnings and Precautions section of the Package Insert. These included hyponatremia, neuropsych effects and rash. The Sponsor has included this information in their present proposed label. It should, however, be noted, that serious rashes are not directly attributed to ESL in the label. This should likely be further explored.
- Suicide will have to be labeled in the Warnings and Precautions section, as it is for other anticonvulsants as part of class labeling. The Sponsor has included this in the label.
- There are other potential signals that have not been completely or appropriately examined in the Sponsor's application. Thus, while there is a hypersensitivity section in the Sponsor's application I do not feel that they used an adequate strategy to identify all potential cases of multiorgan hypersensitivity syndrome (also called DRESS). The Sponsor should also include additional separate sections where they analyze potential hepatic toxicity and blood dyscrasias, as there are individual cases that suggest a potential signal.
- The Sponsor should provide a section on the relationship of ESL treatment and SUDEP.

Moreover many narratives contained sparse information, lacking significant positive and negative signs, symptoms and labs that would be required for complete understanding events.

## 9. Advisory Committee Meeting

Not requested.

## 10. Pediatrics

Because of the serious issues of data integrity and the resulting inability to definitively draw efficacy and safety conclusions it has been decided to defer pediatric issues (PPSR and PERC conference) to subsequent resubmissions.

# 11. Other Relevant Regulatory Issues

**Acceptability of non-US Data**

As noted previously this application was wholly performed outside of US (and Canada). Approximately 25% of the study was performed in countries for which the division has some experience with and include Australia, Austria, Belgium, Denmark, Germany, Portugal, South Africa, Spain, Sweden, Switzerland. The remainder of the sites were from less conventional locations including those in Eastern Europe (Czech Republic, Croatia, Hungary, Lithuania, Poland, Romania, Russia, and the Urkraine) and Latin America (Mexico, Argentina, Brazil). Because this was of some concern to this division the Sponsor was asked to present an argument for this division's acceptance of the applicability of such data to the US population. Dr Podruchny, the medical reviewer, addressed this. The argument is divided across two main areas, safety and efficacy, and is briefly discussed as follows:

- *Safety*: Thus, the Sponsor compared common adverse event rates for previously approved anticonvulsants with regard to how they were differentially reported across countries. Adverse events were noted to be lower in non-US sites in this analysis, but Sponsor argues that this may result from lower doses studies at these sites. They argued that the data from non –US sites is sufficiently representative. Nonetheless, AEs at such sites do tend to be lower on the whole (although Latin American sites appeared to be higher). More importantly Dr Podruchny performed a comparison of placebo phase 3 serious adverse event rates (also see below) in the ESL phase 3 study protocols with other prior anticonvulsant drug study and found them to be lower, suggesting a potential under reporting in the present study. Third party audits were also used to investigate this issue. Such audits did result in the exclusion of a complete trial (study 303) from efficacy consideration by the Sponsor. The Sponsor, however, deemed the remaining studies to be adequate. Notwithstanding the Sponsor's findings, the FDA's inspections (see below) revealed number of critical problems. Thus, 2 (site 112-301 and site 395-302) of 4 sites that were audited by the Sponsor were found by the FDA to have serious flaws (see below).

- *Efficacy*: The Sponsor describes how the present studies are similar to those which were used in the approval of prior anticonvulsants, which were performed in both US and non-US populations. Thus, they compared the demographics, including seizure etiology, concomitant medication, baseline seizure rates, age etc.), and trial design (including inclusion/exclusion criteria, definition of epilepsy etc) across trials and countries. They conclude that their present pivotal phase 3 program and population is similar to that of other drug development programs used for prior drug approval. Dr.

Podruchny agrees with this argument, and I concur. There are however GCP issues regarding the performance of the trials (see below).

**Data Integrity**

A number of crucial issues were raised regarding data integrity by the medical reviewer, the statistics reviewer and by the DSI reviewer. These are described below.

*Issues uncovered by DSI*

Dr El Hage, performed the DSI review and participated in one of the inspections.

Inspections were requested in a total of 4 sites, 2 each from studies 301 and 302. Sites were in Zagreb Croatia (#112 in study 301), Odessa Ukraine (#213 in study 301), Sao Paulo Brazil (# 338 in study 302) and Madrid Spain (#395 in study 302). Inspection site selection was mostly determined by the number of patients recruited, although other factors played a part including the desire to investigate Croatian sites (as DSI has limited experience in this country) and therapeutic effect size (although no individual site solely contributed to the final statistical significance for efficacy).

The US Sponsor, Sepracor, informed FDA of GCP problems with sites in study 303 at the pre-NDA meeting and subsequently excluded this study from efficacy analysis, but included it in the safety database. Sepracor indicated these significant GCP compliance deficiencies were consistent with findings made during previous audits by Bial. Because of limited resources a decision was made not to audit sites from this study. Of note, the Sponsor argued that issues that were problematic with study 303 were restricted to Mexico and limited to the CRO that monitored only Mexican sites. Although this site was excluded from efficacy consideration, the Sponsor included the safety data for consideration. Dr Podruchny, the medical reviewer, as well as the SDI reviewer questions whether it is justifiable to exclude a site from efficacy consideration, but still use it in safety determination.

The following issues were identified as problematic at 2 of the 4 inspected sites:

- *Dr Danilo Hodoba, at site 112, in study 301 in Zagreb, Croatia (18 patients studied):* Inspection revealed major problems in drug accountability and inadequate record keeping. For example record keeping errors included: 1) typed "medical charts and source documents …were not labeled or signed" and had contained "handwritten notes and sticky notes," 2) "some typed progress notes had newly handwritten entries added to them with no initials as to who made the entries," 3) "records were found out of sequence." Drug accountability problems included: 1) "there was no identification of the investigational product kit assigned to the subject or lot numbers on the drug accountability log," 2) "… drug products and related labeling...had been destroyed prior to the inspection," 3) records reviewed indicated "a lack of documentation for the returned test article that would allow reconciliation of the amount of placebo or test article given to study subjects," 4) "investigation found instances where the number of

tablets destroyed were greater than the number of tablets returned by the subjects, 5) there was one case where a subject assigned to receive one blister pack recived that of another. Additionally the DSI inspector notes instances were diaries were translated into English by an unidentified individual and were seizure counts were not recorded in the data listings. One case was identified where a patient was reported as an adverse event of leucopenia (WBC 2.66), but this event was not transferred to data listings as leucopenia, but as unacceptable adverse event. All such problems were considered by DSI to be problematic, but the issue of drug accountability was considered as the most important. A "483" was issues to the investigator.

- *Dr. Carmen Diaz-Obregon at site 395 in Martin Lagos, Madrid for study 302 (16 patients)*: DSI uncovered a number of problems that related to record keeping. Perhaps the most worrisome included the finding was that source documents related to the seizure counts (the primary endpoint) was missing and that even though 10 of the 15 subjects, included at this site, did not meet eligibility criteria, there was no adequate records justifying this inclusion. In general the DSI reviewer notes that the records were in great disarray with typed progress notes having newly handwritten entries added, with no initials as to who made such entries, or the rationale for the addition of new notes. The progress notes were not in sequence, which made it very difficult to follow the protocol required events. The study related documents were in such disarray, according to the DSI reviewer, making it difficult to "verify adequate conduct and, as such, the reliability of the data." A "483" was issued to the investigator.

Two additional sites 213 (n=28) in the Ukraine and 302 (n= 36) in Brazil were inspected, from study 301 and 302, respectively. Although minor irregularities were noted, no major issues were identified at these two sites.

Inspection of Sepracor in Marlborough, MA was performed. According to the DSI review this inspection was believed to be of limited value, at this time until. Additional information is needed on the "scope of inspection."

Both Bial and Sepracor contracted for third party audits ( (b) (4) on behalf of Bial, respectively). DSI notes that such audits are "inconclusive due to evaluation of a limited number of clinical sites with inadequate number of enrolled subjects audited." However DSI had the following conclusions upon examining these reports:

- The DSI reviewer noted that the audit revealed a "broad range of violations regarding subject safety, inclusion criteria, poor source documentation, discrepancies between source documents and what was recorded in the case report forms in terms of adverse events, use of concomitant medications, and inadequate drug accountability records suggesting a systemic problem across all three studies (301, 302, and 303)." The DSI reviewer notes that majority of discrepant AE observed in the audit remains unresolved.
- As noted above, audits reports were limited and there was no attempt to determine whether these problems were applicable to other sites, which were not audited, and determine what impact such issues may have on the application as a whole.

- While the audit report led to the discounting of efficacy data in study for site 303, the Sponsor included the safety study for support of this application's approval. However, it is unclear as to why the safety data should be included.

The DSI reviewer concludes from their findings that the original developer, Bial, did not practice adequate control over the performance study to assure data integrity. The audits performed by both Bial and Sepracor were not sufficient to allay the reviewers concern. The DSI reviewer recommends the following: "1) additional FDA clinical site inspections for a) Studies 301 and 302, b) clinical sites from Study 303, because the sponsor proposes to use the data from this study to support safety," 2) "Re-inspection of the sponsor, as a comprehensive inspection doesn't appear to have been conducted, and 3) Inspection of the " CROs responsible for monitoring the studies;" and 4) "a 3rd party audit by the Applicant with a request that the Agency review and comment upon the audit plan prior to the audit to ensure that a sufficient number of subjects and sites are audited, and a request that full audit reports are provided to the Agency for review."

*Issues Uncovered upon Medical Review*

As noted by the medical reviewer the initial audits by the US Sponsor of ESL indicted to them that sites in Mexico in study 303 were "determined to be non-compliant with Good Clinical Practices." Dr. Podruchny notes that problems included, improper activities relating to study conduct (PI oversight), inappropriate enrollment of randomized subjects, data integrity issues (absence of certain source documents to verify/support data entered into CDFs), and failure to consistently and prospectively assure subject safety. For this reason this phase 3 study was withdrawn from consideration, by the Sponsor, for use in the determination of efficacy. The Sponsor, however, still feels that it may still be adequate for consideration as part of the safety data pool. The medical reviewer believes that the safety data from study 303 is questionable in view of the data integrity issues for the efficacy data from that same study. I believe she is right to question the safety data, particularly in view of the significant data integrity issues uncovered in the application as a whole.

Notwithstanding the above, in reviewing the application as a whole, Dr Podruchny uncovered a number of issues that were problematic, which were not necessarily linked only to study 303. These are summarized as follows:

- Fifty-nine adverse events were described by the Sponsor in their safety update to occur during the controlled phase of the pivotal trials. Many of these did not appear to have been reported in the original ISS.
- Upon an inquiry on the interpretation of a table in the Safety update the Dr Podruchny noted that 31 additional serious adverse events were indentified by the Sponsor (these were separate from those described in the first bulleted item). The Sponsor notes that the reason these were not originally identified was because the data was "preliminary, unconfirmed, and subject to change in the final CSR." Dr Podruchny, however, notes that data from some of these studies were completed 2 years prior to the Safety update. One of these events included a death.

- The Sponsor's third part audits of sites resulted in a large number of discrepancies between source documents and CRFs. Some discrepant results were not included in the final analysis. Upon inquiry with the Sponsor noted that these adverse events were considered post ictal events and not associated with drug. Dr Podruchny examined these adverse events and did not believe that all appeared to be related to ictal or post-ictal states.
- Dr Podruchny notes that 9 SAEs occurring within a week after drug discontinuation were not "consistently reflected" in the tables provided in the ISS.
- There were inconstancies in presentation of discontinuations in various tables of the ISS. When this was investigated by the medical officer a number of patients were identified whose discontinuation was not provided in the main table relaying this information.
- Dr Podruchny notes discrepancies between FDA inspections and the Sponsor's audits.
    - She notes that site while records of drug accountability were considered adequate at 112 (study 301) by the Sponsor, the FDA inspection found them to be seriously lacking.
    - Dr Podruchny notes that subject 112-90393 in study 301 was discovered to have withdrawn because of a low WBC count (2.7) as per the investigator, but was reclassified as "withdrawal of consent."
- Dr Podruchny also noted numerous instances of internal inconsistency in adverse event reporting or coding within NDA. For example, reasons for discontinuation may vary depending on whether one is examining the datasets, CRFs, narratives and tabulated data. The Sponsor was requested to clarify these inconstancies. By the time the response was received, Dr. Podruchny notes, insufficient time remained to adequately review this response.

Additionally Dr Podruchny notes, data was presented in a fashion that was difficult to discern; for example, it was difficult to identify doses of drug in SAEs line listings in phase 2 studies.

*Issues Uncovered in the Statistical Review*

As noted in the efficacy section, the Statistical reviewer noted that the datasets were "hardcoded." That reviewer noted that "hardcoding over rides the database controls in the clinical data management systems and may compromise study data integrity." The statistics reviewer noted that from the extent of required hardcoding "that the study was not well conducted and the data quality/reliability was questionable." In talking to the statistics reviewer she notes that it is unusual to have this degree of hardcoding which she identified (particularly in study 301).

Moreover, data were problematic in that the diaries could not distinguish between forgotten recording of seizure-free days and true seizure-free days. An attempt was made to control for these factors utilizing a sensitivity analysis. This analysis suggested that these problems did not influence the final conclusion of efficacy.

**CSS and Drug Scheduling**

In their original review, dated 12/7/09, CSS concluded that ESL has "anxiolytic, sedative, and muscle relaxant properties, impairs memory and co-ordination, and produces physical dependence, as evidenced by the occurrence of withdrawal symptoms upon abrupt withdrawal." But, they also expressed concern that there were limitations in the data provided that precluded a definitive analysis of abuse potential. Thus, they note that non-clinical studies were limited as: 1) Ki parameters were not provided for $GABA_A$ subunit bindings; 2) most behavioral studies were performed on rat, a species that does not metabolize the drug into the active ingredient of eslicarbazepine; 3) mice cognitive studies did not provide serum levels, to allow clinical comparison; 4) withdrawal studies in dogs and rats were inappropriate as these species do not metabolize the drug like humans (see item 2); and 5) There were methodological problems in the monkey drug discrimination study. Clinical studies were also faulted for the following reasons: 1) there was a general underreporting of adverse events in the pivotal trials, an issue that a part of the overarching issue of that of data integrity; 2) inadequate and inaccurate reporting of abuse related terms and drug accounting; 3) the use of various versions of MedDRA during the development program, complicating the interpretation of the data. The CSS reviewer specifically points out that, in clinical trials there were a number of withdrawal phenomena including seizures, somnolence, headache, GI symptoms (e.g. nausea) and psychiatric symptoms (e.g. depression), making her conclude the possibility of a withdrawal syndrome. The CSS reviewer recommended: 1) an abuse potential trial; 2) that the Sponsor re-translate verbatim terms to MedDRA 10.0 and; 3) perform additional binding studies for $GABA_A$, Chloride TBIB, and sodium sites.

As a result of the above review a number of questions were provided to the Sponsor in communications on 1/4/10 and 1/13/10. The Sponsor provided a response on 2/10/10. CSS generated an addendum, to their original review on 3/19/10, responding to the Sponsor's correspondence and making their final recommendations. Briefly, the Sponsor contested all of CSS's points, except the inadequacy of the rat as a model. With exceptions CSS rejected the Sponsor's arguments. The exceptions included: 1) CSS deemed not to comment on the issue of $GABA_A$ binding, although they seem note it is immaterial,[5] 2) CSS deemed not to respond to the issue of the dog as an appropriate model for humans, 3) CSS is willing to take another look at the confounding effect of the different versions of MedDRA, as the Sponsor noted that this was considered in their evolutions.

With this in mind CSS believes that the available information is inadequate and does not permit scheduling. They have the following recommendations:

- "Conduct an appropriate and well designed human abuse potential study with eslicarbazepine. CSS is available to evaluate the protocol design and provide feedback prior to the start of the study.
- Conduct a two-week prospective evaluation of physical dependence at the conclusion of the new clinical efficacy study. CSS is available to evaluate the protocol design and provide feedback prior to the start of this phase of the study.

[5] Thus CSS notes that "the mechanism of action of a drug may be unknown, even after binding studies are complete."

- Update the reporting of adverse events in clinical studies to the most recent version of MedDRA used in the NDA (i.e., MedDRA 10.0) by using the verbatim descriptions that occurred during clinical trials.
- Provide an analysis of all abuse related AEs, using the terms provided previously by CSS."

I would note that identification of potentially significant abuse and dependence clinical behaviors is difficult in trials on anticonvulsants. Thus symptoms, which may suggest withdrawal or abuse potential, are not uncommon in this population and may result from the disease itself or concomitant medications (e.g. ataxia, sedation, seizures, headache depression, hallucinations etc). Indeed there are anticonvulsants (e.g. phenytoin and carbamazepine). , that are not scheduled, but whose effects (sedation, somnolence and ataxia) might be interpreted as indicating abuse potential. This was discussed at a meeting with CSS, who noted that indeed that is the problem: i.e. the present data alone do not provide adequate information to allow scheduling and additional data from studies will be required.

**Proprietary Name**

The proprietary name was found acceptable. DMEPA's analysis showed no significant risk of confusion with other marketed products. DDMAC did not consider the proprietary name as promotional.

**Financial Disclosure**

Dr Podruchny, the medical reviewer, examined the information provided in the original submission along with a later requested additional information (7/31/09) and concludes the information "appears acceptable."

# 12. Labeling

The label has been partially revised and provided to the Sponsor. As issues regarding clinical data are still unresolved, labeling review of those sections are being deferred

# 13. Recommendations/Risk Benefit Assessment

I do not agree with the present approval of the application. There is a general consensus between DSI and the clinical reviewer that data integrity issues preclude approval. I agree. These problems have already been described in the above review. The Sponsor will be asked to correct above noted problems. Additional third party audits will be requested, and it is agreed by both DNP and DSI that additional FDA inspections of clinical sites will be required. Additional recommendations of special analyses will also be made (see the section on Safety).

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22416 | ORIG-1 | SEPRACOR INC | SEP-0002093 ESLICARBAZEPINE ACETATE |

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/s/

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NORMAN HERSHKOWITZ
04/30/2010
CDTL Review

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 22416 |
| Priority or Standard | S |
| Submit Date(s) | 3-29-08 |
| Received Date(s) | |
| PDUFA Goal Date | 4-30-09 (extended by major amendment) |
| Division / Office | |
| Reviewer Name(s) | Teresa A. Podruchny |
| Review Completion Date | |
| Established Name | Eslicarbazepine acetate |
| (Proposed) Trade Name | Stedesa |
| Therapeutic Class | Antiepileptic |
| Applicant | Sepracor |
| Formulation(s) | Tablet |
| Dosing Regimen | Oral, daily |
| Indication(s) | Refractory partial onset seizures |
| Intended Population(s) | Patients with epilepsy |

Template Version: March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

Sepracor is the U.S. Sponsor of this NDA for eslicarbazepine acetate (Stedesa) for adjunctive treatment of partial-onset seizures in adults with epilepsy. The original sponsor was Bial (Portuguese company) and all phase 3 data are from clinical trials conducted outside of the U.S. Sepracor submitted three phase 3 studies of epilepsy. Two were designated as pivotal efficacy studies (studies 301 and 302). The third study, study 303, was noted to have significant Good Clinical Practice (GCP) issues (i.e., non-compliance) such that the study could be supportive only for safety and efficacy. Sepracor posited that these issues are essentially limited to one country in study 303 (Mexico) and to one Clinical Research Organization (CRO) charged with oversight of sites in that country. However, Sepracor indicated there were GCP issues at two other sites (Spain and Portugal), but not of the same magnitude.

In addition to sponsor-reported, significant non-compliance at one of three phase 3 studies (study 303), FDA's Division of Scientific Investigations reports significant non-compliance with federal regulations and GCP at two of the four inspected sites from the two other phase 3 studies (one for each pivotal study). The data at one of these two sites (study 301-site 112 and study 302-site 395) have been classified by DSI as unreliable and the data at the other site has received a preliminary classification as unreliable. DSI also reviewed audit reports submitted by the sponsor and considers that the audit reports are insufficient in scope and detail to provide assurance of data quality. It is notable that the sponsor audited the same four sites audited by DSI and did not conclude that data from any of the sites were unreliable.

My review of the submission revealed a number of issues that impeded the review process and undermined confidence in the submission quality and the data quality. Submission quality issues included a number of apparent inconsistencies in data presentations, presentations that are sometimes not comprehensive (for example, the section on special events, rash, does not cover all phases of development), and a paucity of clinical descriptions in some narratives such that one has to search study reports and/or datasets, and/or case report forms not to verify or reconcile data but to acquire details. The sponsor did provide corrections to data previously submitted, but some were submitted only as a response to FDA's request for clarification. These issues are described in section 3 of this review.

At times these submission quality issues lead to apparent discrepancies in data presentations or the appearance of a more significant event than was described. Considering the identified GCP issues and the possibility that these issues were not limited to one country and one CRO, I felt the most critical job was to establish that the data provided by the sponsor could be reviewed reliably.

As I note above, some submissions corrected data from previous submissions. For example, the 120-day safety update indicated that there were 83 adverse events (64 subjects) discovered during evaluation of open-label data that had an onset during the part 1 double-blind phase. These 83 events were reviewed by Sepracor on a case-by-case basis and resulted in the company pooling 59 additional adverse events (48 subjects) with adverse events from the original part one summaries submitted in the initial summary of safety (ISS). While attempting to review a table in the 120-day safety update (Table 9.2-1-listing of serious adverse events for trials considered ongoing or clinically completed but not reported), I realized that clarification was needed from the Sponsor because the table was difficult to read. The Sponsor provided clarification on the table, but also reported 31 additional serious adverse events that were identified as having been "inadvertently omitted" from Table 9.2-1 in the 120-day safety update.

In addition to the problem of difficulty reading Table 9.2-1, the 120-day safety update did not contained discontinuations due to an adverse event and seemed to indicate that the safety data presented for these ongoing or clinically completed trials were from the period between the cut-off of the first integrated summary of safety (ISS) and the 120-day safety update (SU). FDA requested the discontinuation events and information regarding possible events before the ISS cut-off. In the company's response to this request, other corrections were made to information from the original table 9.2-1. These were of less magnitude but they did correct errors in the table. The company also indicated that a death not reported in the safety update was being reported, although this event met the cut-off for the SU. Of note, this death was in a line listing of a previous submission but it is unclear that the Sponsor was aware as they reported including a "narrative for the new report of death" (p.5/35 of 2-4-10 submission).

As is the case with some of the DSI findings, the consideration of review submission findings is not limited to the data itself or the impact of the individual finding (adverse event) on the whole (safety dataset). Maybe the 59 events reported as delayed events are not serious and maybe the reason for the error is reasonable, but then there is the correction to a safety update table (31 SAEs reported 1-25-10), and then further corrections of the 1-25-10 submission in a 2-4-10 submission.

Overall (Or taken together), the GCP problems in study 303, the DSI inspection findings, my attempt to review the NDA, review issues noted in the Controlled Substance review, and the extensive hard-coding noted in the statistical review lead me conclude that even if it had been possible to review all data in all submissions, it would be difficult to reach a meaningful conclusion because of the DSI-GCP type issues. Also, given the seeming submission quality issues, it probably would be necessary to have the company re-evaluate all of the data for consistency and completeness and re-submit it for review. Otherwise, at this point, I think I would not be convinced that with another inquiry, FDA might not get different information. From a practical point, I have not completed the review of all submission, especially the more recent ones and have not integrated findings from all submissions. It is possible that if all submissions could

be reviewed, data verified and reconciled, perhaps some issues would be clarified, but even if this were the case, the more fundamental quality issues remain.

In addition to the potential, specific data integrity/quality issues in this application, there is the issue that this application has no domestic, phase 3 data and the vast majority of all exposure is from foreign trials. Regardless of the nominal similarities in trial design and diagnostic criteria, it seems clear from the sponsor's data and data from other development programs in epilepsy that there is a reporting difference in the incidence of reporting AES between US and non-US locations.

It seemed reasonable to try and evaluate whether this may be the case with serious adverse events and discontinuations secondary to adverse events. It seemed reasonable to use placebo rates for such a comparison as each antiepileptic drug (AED), although perhaps sharing similar toxicities, is a new molecular entity and may have a unique safety profile. Therefore, although it is arguably scientifically questionable to compare incidences of adverse events across development programs, the sponsor was asked to make this comparison for serious adverse events and discontinuations secondary to an adverse event (the sponsor had described common treatment emergent events in eslicarbazepine acetate (ESL) compared to other AED programs). Differences in the incidence of serious adverse event reporting in placebo groups are seen between the phase 3 studies of ESL and studies supporting five AED programs (lacosamide, pregabalin, zonegran, oxcarbazepine, and levetiracetam). Specifically, in two of the three ESL studies, there are no serious adverse events reported for the placebo groups. As per sponsor-provided data, the rates are 2.7% to 10.5% in studies supporting the five referenced AEDs.

I recommend the Division discuss a strategy for moving forward with respect to DSI and GCP issues (for example, would it be helpful to have CDER statisticians provide assistance in determining how many sites DSI might need to inspect to provide some assurance that findings are reflective of the whole and what specifically does the Division and DSI think is critical to acquire from the 3$^{rd}$ party audits to ensure the audits can be maximally informative) and that there be discussion of data from other studies contributing to the safety database in terms of audit reports. At this time, I tend to think the optimal path forward will require a new trial performed in the US or North America.

I think that it might be very difficult to perform a review of DSI-GCP issues and review the resultant data simultaneously. Also, to review the resultant data before addressing data quality may be inefficient use of FDA resources if the data are not considered reliable after the DSI and GCP issues are addressed and reviewed.

I recommend the company be issued a complete response letter. There are potential data integrity issues that require further investigation, but at this time are sufficient as to undermine confidence in the data. There are also submission quality issues that made review of the data difficult and suggest that there were inadequate quality control checks of documents integral to the review (integrated summaries of safety).

## 1.2 Risk Benefit Assessment

A conclusive risk-benefit assessment is deferred given the significant quality issues described above and in section 3 of this review. Preliminary safety findings are described below and limited to deaths, non-fatal serious adverse events (SAEs), and discontinuations secondary to an adverse event. In the opinion of the reviewer, the presentation of events by dose group should be interpreted with caution, not only because of the quality issues, but also because the classification of drug group may not reflect the actual dose on which an event occurred.

**Safety:** The database includes 2076 unique subjects in phase 1, phase 2, and phase 3 studies (as per the 120-day safety update (SU), clinical summary of safety document (CSS). 527 were exposed to placebo, 289 to an active control, and 1889 to eslicarbazepine. These numbers do not include subjects in ongoing studies or studies, classified by the sponsor, as clinically completed but not reported although the death and non-fatal SAE information below does include these subjects. Discontinuations from this group are not included (2-4-10 submission, not fully reviewed).

**Death**: 16 deaths in the development program are reported through NDA submissions dated 2-4-10. 14 were in patients who had been exposed to ESL and 2 were in placebo patients. An additional death of an ESL treated patient is known from an IND safety report.

One of the two placebo deaths was in an epilepsy trial (301). The subject was “found dead” on the street and died from hypothermia. The second placebo death was in a bipolar study and was due to an ischemic stroke.

Of the 14 ESL deaths, none are reported as occurring in the controlled phases of the three phase 3 epilepsy studies. One death was in a phase 1 study, one was in a bipolar study, four were in trials of either post-herpetic neuralgia or diabetic neuropathy, and 8 are from extensions phases of the phase 3 epilepsy studies.

The non-epilepsy ESL deaths were attributed by the sponsor to acute occlusion of a coronary artery and signs of sudden cardiovascular death (in the phase 1 subject), suicide (in the bipolar trial), and differing forms of cancer (gastric, lung, prostate in neuropathy or neuralgia subjects).

The phase one subject was a 65 year old male with a reported history that included atrial fibrillation and in whom autopsy findings are described as acute occlusion of the left circumflex coronary artery and signs of sudden cardiovascular failure. The suicide is reported to have occurred after stopping ESL (how long after is uncertain, see below).

The three subjects who died from cancers have fairly short exposure times to ESL or short times between beginning ESL and diagnosis or death. For the subject with lung neoplasm, his exposure was about 5 weeks and his death about 13 weeks from first

exposure. For the subject with gastric cancer, he was admitted to a hospital with gastric stenosis on day 33 of exposure. Study medication was stopped. He died 43 days later. This subject also had a history of peptic ulcer and of having a resection of the esophagus with a stomach tube replacement secondary to Boerhaave syndrome. One source notes that medically treated peptic ulcer does not appear to be associated with an increased risk of gastric cancer and references that patients who have undergone distal gastrectomy have been reported to have a 5-fold risk many years after the procedure (Holland-Frei Cancer Medicine-8$^{th}$ ed (2010), online). The subject who died from prostate cancer was 75 years old and was exposed to ESL for about 4 weeks before he experienced "lumbalgia", reported as due to prostate cancer. He died within 2 months of first taking ESL.

For the deaths in the epilepsy trials, three are reported as secondary to drowning, 3 are reported as directly related to a seizure/status epilepticus, one is reported as a recurrence of an astrocytoma, and one is reported as sudden death and severe coronary atherosclerosis in one subject (30 year old male, autopsied). There also is a death from respiratory failure about 6.5 months after the last dose of ESL. The respiratory failure sounds like the terminal event in a patient with follicular lymphoma that presented in part 1 on day 56 with a neck mass.

Of the deaths described as drowning, two are reported as occurring after stopping eslicarbazepine (21 and 45 days). One subject who drowned also had other injuries on autopsy, although these were not considered as causally related to his death. The subjects who died from seizure related events were a child who experienced cluster seizures and cardiac arrest, an adult subject whose death is reported as secondary to brain edema following an epileptic seizure, and an adult who is reported as dying from status epilepticus.

To illustrate the interface of the quality issues with the review of data, please note the following. The suicide in a bipolar subject is reported as either 5 days (p. 454/582 of the ISS) or 11 days (p. 98/582) after the last dose of ESL. The issue may not be the impact of the differences in the information on interpretation but death is, from a regulatory sense, one of the most significant types of safety information.

**Non-fatal SAEs:**

For phase 1 through 3 studies, the sponsor reports 3/528 (0.6%) placebo subjects with 3 non-fatal SAEs and 88/1977 (4.5%) ESL treated subjects with 125 non-fatal SAEs.

At this time it appears there may have been at least one serious rash (301-111-90341) and rash was fairly common. At least 8 subjects in phase 1 discontinued with a rash as one event in the discontinuation. Some are reported as on concomitant AEDS. At least two of these events seemed to have required steroid use.

Hyponatremia was seen and was a serious event in some cases.

**Discontinuations secondary to an AE**:
Overall, in the safety database (does not include the ongoing and clinically completed but not reported studies), 18/528 (3.4%) of placebo subjects and 226/1997 (11.4%) of ESL subjects discontinued secondary to an AE.

Epilepsy: Rash and hypersensitivity reactions include one involved with liver function test elevations and one with facial edema and paresthesia. Facial edema can be consistent with angioedema.

Liver enzyme elevations were also seen in another subject without rash and reported as discontinuation due to "Gamma glutamyltransferase Increased" in the narrative. This patient also had increased AST and ALT (about 2x and 1.5x ULN respectively) with bilirubin lower or within reference range (not meeting Hy's law).

Cardiac events of angina pectoris and Wolf-Parkinson-White (WPW) Syndrome led to discontinuation of one subject each, although for the WPW, WPW syndrome is reported at pre-dosing, but seems to have worsened. Events of hypertension led to discontinuation in two subjects (one with hypertensive crisis) and hypotensive events were involved in the discontinuation of two other subjects.

Constipation led to discontinuation in two subjects (302-331-80152 on 400 mg and 302-393-80415 on ESL 800 mg).

Two discontinuations, one of which was also an SAE, involved hyponatremia (302-306-80614-SAE and 303-703-70231).

In some patients, there is a constellation of symptoms consistent with drug toxicity or called simply "drug toxicity" or with the term "drug toxicity" as part of the description. The term "Cerebellar Syndrome" was used for a patient who discontinued in study 303 (303-703-70374). This was also a serious adverse event.

There were singular event terms of dysarthria, aphasia, dystonia, and vasculitis cerebral

*Comment:*
*Thyroid function assessment is not adequate as there was no measure of TSH in pivotal epilepsy trials.*

*Pending resolution of data quality issues, the Sponsor should submit synthesized presentation of rash, possible hepatotoxicity events, possible significant hematologic events, and psychiatric events from all development phases. Also the sponsor should clarify verbatim terms as noted in foreign data section of this review.*

**Efficacy:** The sponsor submitted 3 phase 3 studies of epilepsy, two designated were designated as determinate for efficacy purposes (301 and 302) and one was designated as supportive for efficacy purposes (due to GCP issues). Additionally, a phase 2

epilepsy study was submitted. This study evaluated twice-a-day dosing compared to once-day-dosing and is not further described in this section, although there is discussion in the appendix of this document.

The phase 3 trials were multi-center, double-blind, placebo-controlled, parallel group, studies of adjunctive therapy in adult subjects with refractory partial-onset seizures. In general, the three phase 3 trials included a 12 week maintenance phase preceded by a 2 week titration (handled differently in each trial) and in all three, an 8 week baseline period. The baseline was observational in studies 302 and 303 and as a single-blind, placebo baseline in study 30. In two of the three studies, patients were tapered off drug and one there was no taper (study 302). The studies were conducted in Latin America (including Mexico), Western Europe (included South Africa), and Eastern Europe.

Subjects were to have ≥ 4 partial seizures in each 4-week period during the 8-week baseline, with a seizure-free period of no longer than 21 days. Subjects were randomized equally to placebo, ESL 400 mg, ESL 800 mg, and ESL1200 mg in studies 301 and 302 and to placebo, ESL 800 mg and ESL 1200 mg in study 303.

The primary endpoint was standardized seizure frequency per 4 weeks over the 12-week maintenance period. Secondary endpoints included proportion of patients with a ≥ 50% reduction in seizure frequency during the 12-week maintenance period compared with the 8-week baseline (responders).

Study 301: The statistical reviewer indicates that there was extensive hardcoding of the data. FDA statistical review team indicates this suggests that the study was not well conducted and that the data quality is questionable. In study 301, there were blinded and unblinded reviews of the seizure data. The statistical review indicates some hardcodes were generated from the unblinded review. A sensitivity analysis was performed removing the hardcoding. No difference was observed in data interpretation or conclusions.

The statistical review describes missing seizure data. Given that subjects were instructed to update seizure diary data only when they experienced a seizure, if a diary is blank, it is difficult to know if the blank is a true 0 (no seizures) or a missing data (failure to record a seizure). The statistical review indicates that a worst-case-scenario analysis was performed by the sponsor to asses the effect of the part of missing data that was caused by unreturned diary cards. The FDA requested worst-case-analysis was not doable because the period of time for which the diaries was missing could not be determined. An analysis of the worst-case imputation was favorable.

468 subjects were enrolled into study 301, 402 were randomized, and 330 completed part 1 (included the double-blind phase).

The statistical review indicates there were no relevant differences between the treatment groups in demographics. The average age of placebo subjects was 37 years

± 12 years (youngest group) and in the ESL 800 mg group was 41 years ± 12 years (oldest group). Gender distribution ranged from 44% male in the 1200 mg group to 55% male in the ESL 800 mg group.100% of subjects were Caucasian.

Subjects had been diagnosed with epilepsy from about 19 years (±12.6 years) to about 23 years (±13.5 years) and the most common etiology of epilepsy was "other" in 35% to 39% of the placebo through ESL groups. The mean seizure frequency standardized to 4 weeks ranged from 11.2 (±11.2) to 12.4 (±17.94). Most subjects were taking two other concomitant antiepileptic drugs (60 % to 68%). The most common concomitant antiepileptic drugs was carbamazepine (56% to 62% of subjects) followed by either lamotrigine (overall). The percentage of subjects using either lamotrigine or/and valproic acid was very similar.

The statistical reviewer's analysis of the primary endpoint was performed using completers (with a maintenance assessment), with the ITT population and conservative imputation, and with the ITT population and non-conservative imputation. In all three analyses, the 400 mg group was not statistically different from the placebo group and the 800 mg and 1200 mg groups were (ITT conservative imputation, p-value of 0.018 for the 800 mg group and 0.001 for the 1200 mg group).

Given the problems at site 112, the site was dropped from analyses. The results remained similar.

The statistical reviewer analyzed the percent responder data by two methods. The results of the analysis of this endpoint by both methods supported the primary endpoint.

The statistical reviewer also conducted an analysis of the % change from baseline. This analysis indicated that the 400 mg group was not statistically positive (p value 0.64, difference in LS mean % change of -8.24). For the 800 mg and 1200 mg groups, the results were statistically significant (p of about 0.04 and 0.3 for the groups respectively with differences in the LS mean of about -21% and -22%).

Study 302:

The statistical review reports that similar issues were identified for the data in this study as in study 301 except that review of the seizure data was performed before unblinding. Hardcoding was present but the form was different than that in study 301. The company had identified duplicate seizures, multiple seizures, and cluster seizures in review of the data. The statistical reviewer conducted a sensitivity analysis removing the hardcodes. The results were not sensitive to hardcoding.

502 subjects were screened, 395 were randomized, and 327 completed the double-blind phase.

The demographics of the ITT population were similar. The mean age was about 37- 38 years in each group (± 11 to 12.6 years). Gender distribution varied from 41% of subjects being male in the ESL 400 mg group to 54% being male in the ESL 1200 mg group. Most subjects were Caucasian (82% to 91% of ESL and 87% of the placebo group).

The mean duration of epilepsy ranged from about 23 years to about 25 years (± 11.5 to 13 years). The most common etiology was "other" (42% to 49% in the placebo and ESL groups). The seizure frequency per 4 week period ranged from 13.3 ± 14 in the placebo group to 15.9 ± 16.3 in the ESL 1200 mg group. Most subjects were taking 2 other concomitant antiepileptic drugs (69 to 76%). The most common concomitant antiepileptic was carbamazepine (58 to 61% of subjects) followed by valproic acid and lamotrigine. Clobazam, a product not marketed in the US, was used by 16% of the placebo subjects, 20% of the ESL 400 mg subjects, 21 % of the ESL 800 mg subjects, and 12% of the ESL 1200 mg subjects.

The statistical reviewer's analysis of the primary endpoint was performed using completers (with a maintenance assessment), with the ITT population and conservative imputation, and with the ITT population and non-conservative imputation. In all three analyses, the 400 mg group was not statistically different from the placebo group (p values=0.8, 0.7, and 0.5). The 1200 mg group was not statistically significant in 2 of three analyses (0.25 and 0.11 for the ITT analyses and 0.035 for the completers analysis). The 800 mg group was statistically positive (p values of 0.006, 0.03, and 0.007 for completers with maintenance assessment, ITT -conservative imputation, and ITT non-conservative, respectively)

Given the problems at site 395, the site was dropped from analyses. The results remained similar.

The statistical reviewer analyzed the percent responder data by two methods. The results of the analysis of this endpoint by both methods supported the primary endpoint but analyses were sensitive to how drop-outs were handled for the 1200 mg group (p value 0.0109 to 0.0548).

The statistical reviewer also conducted an analysis of the % change from baseline using a similar manner as that of the primary endpoint analysis. This analysis indicated that no group showed statistically different reductions from baseline compared to the placebo group in standardized seizure frequency although ESL groups did show greater reductions than the placebo group. The biggest reduction was seen in the 800 mg group (-18%, LS mean, p-value 0.05). For the 400 mg and 1200 mg groups, the results % LS mean differences were -11% (400 mg, p=0.28) and -5.3 % (1200 mg, p=0.66).

Study 303: This study was submitted as supportive of efficacy but not determinative.

303 subjects were screened, 253 randomized, and 195 completed part 1. The pooled regions were Europe (Spain and Portugal) and Mexico.

75% of placebo subjects, 82% of the ESL 800 mg subjects, and 74% of the ESL 1200 mg subjects completed the study.

Demographically, subjects were about 35 to 38 years old (± 11 to 12 years). Male gender ranged from 42% of subjects in the 800 mg group and 50% of the placebo subjects. Overall, 62% of subjects were classified as "other" for race and 38% as Caucasian. This was related to reporting differences with subjects in Mexico of Hispanic ethnicity reporting as "other" while Hispanic subjects in Portugal and Spain reported as Caucasian.

The average duration of epilepsy was 22 to 24 years in the groups (std dev of 12 to 13 years). The most common etiology of epilepsy was classified as "idiopathic" in 38 to 42% and as "Other/unknown" in 23 to 33%. The mean seizure frequency at visit 2, standardized to 4 weeks, was about 12-13 (std dev of 12 to 18). (The statistical reviewer notes that at baseline, 16%, 16%, and 17% of subjects in placebo, ESL 400 mg, and 800 mg groups, respectively had a baseline seizure frequency of <4 per 4 weeks. ) Most subjects were taking two concomitant antiepileptic drugs (76% of placebo, 69% of ESL 800 mg, and 79% of ESL 1200 mg). The most used concomitant was carbamazepine in 69% of placebo subjects, 50% of ESL 800 mg subjects, and 47% of ESL 1200 mg subjects. Valproic acid was the second most common with use in 30% of the placebo subjects, 27% of the ESL 800 mg subjects, and 35% of the ESL 1200 mg subjects.

In the FDA reviewer's analysis of the primary endpoint, the 800 mg group did not separate from the placebo group statistically in analysis of completers (with maintenance assessment), ITT population (conservative imputation), or ITT population (non-conservative imputation) with p-values of 0.88, 0.59, and 0.89 respectively. The 1200 mg group was statistically different from the placebo group (p values of 0.03, 0.04, and 0.03 for the respective analysis). The results of the secondary endpoint of percent responder were similar to the primary analysis (not significant for the 800 mg group and significant for the 1200 mg group). The statistical reviewer's analysis of percent change from baseline indicated that the difference between the ESL groups and placebo were not statistically significant (p values of 0.32 for the 800 mg group and 0.34 for the 1200 mg group).

*Clinical reviewer's preliminary comments on the efficacy results:*

*The way the diaries were filled out is problematic. It seems in seizure trials there is a usual type problem of having subjects who experience events that include loss of consciousness responsible to record these events (diaries could be filled out by subject or caregiver). The errors made secondary to this are statistically thought to be random due to randomization and so the "noise", in theory, should be evenly distributed across*

*groups. This is not perfect but it is difficult to think of a way that seizure information could be reliably and realistically recorded in outpatient clinical trials that last more than a few days. In this study, there is an additional source of misinformation as subjects were advised to only fill out the diary in the event of a seizure. Review of case report forms indicates that it is unclear when a diary has either no entries or some entries whether the blanks are true zeros. The statistical reviewer discusses this and describes sensitivity analyses.*

*The statistical reviewer overall recommends that the data "seem" to support the efficacy of ESL as adjunctive therapy with refractory simple or complex partial seizures. Her review indicates that she has some question of the data quality as there was much hardcoding of the data. She indicates that the 800 mg group showed statistically significantly lower standardized seizure frequency over a 12-week maintenance period when compared to placebo and that the 1200 mg group was only better than placebo in one of the two pivotal studies and was marginally significant in the supportive phase 3 study (303). The 400 mg dose was not significant in either pivotal study.*

*In addition, there is a sponsor analysis of relative change in standardized seizure frequency during the 12-week maintenance period for the pooled phase 3 studies 301 and 302 by seizure type. The sponsor used an ANCOVA model with and without the interaction term. Subjects who did not have a specific seizure type during the baseline period were excluded from the analysis of that seizure type. However, if a subject had only one partial evolving to secondarily generalized seizure during the baseline period and none in the maintenance period, the subject would be included in the analysis as having a 100% reduction in seizures.*

*Based on the sponsor's table 3.4.2.1-5 (see efficacy section) from the March 2009 clinical summary of efficacy, (which of note, does not allow one to see if there was new onset myoclonic or absence seizure), the 800 mg and 1200 mg groups separated statistically from placebo for simple and complex partial seizures. No ESL dose group separated statistically from placebo for secondary generalized seizures (p=0.26, 0.7, and >0.9999 for the ESL groups respectively) and unclassified seizure events (p=0.434, 0.87, and 0.87 for the ESL groups respectively.*

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable at this time.

## 1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable at this time.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

Eslicarbazepine acetate (SEP-0002093, BIA 2-093, ESL) is a single-enantiomer member of the family of anti-epileptic drugs that share a dibenzazepine nucleus bearing the 5-carboxamide substituent. Carbamazepine and oxcarbazepine are first and second generation members of this family. The three compounds differ at the 10, 11-positions.

ESL is a prodrug that is hydrolyzed in first-pass metabolism to the active moiety [BIA 2-194 or (S)-licarbazepine] in animals and humans (95% of total systemic exposure after oral dosing). The sponsor lists minor metabolites as (R)-licarbazepine (BIA 2-195) (4%) and oxcarbazepine (1%). ESL and its metabolites block voltage-gated sodium channels. Whether this is the mechanism of its anticonvulsant properties is not established.

Oxcarbazepine metabolizes to both eslicarbazepine [(S)-licarbazepine] and (R)-licarbazepine. The submission states that unlike carbamazepine, SEP-0002093 is not metabolized to carbamazepine-10, 11-epoxide and is not susceptible to auto-induction of its own metabolism.

Eslicarbazepine is responsible for the pharmacological effects of SEP-0002093. Glucuronic acid conjugates of SEP-0002093, eslicarbazepine, (R)-licarbazepine, and oxcarbazepine are inactive metabolites.

SEP-0002093 has been developed for the adjunctive treatment of partial-onset seizures in adults with epilepsy (specifically, pivotal trials were conducted in refractory patients).

Following oral administration, plasma levels of SEP-0002093 usually remained below the level of quantification. Eslicarbazepine $t_{max}$ is attained 1-4 hours post-dose and steady-state is attained after 4-5 days of once daily dosing (p.23/53 of abuse-potential.pdf). The apparent half-life of eslicarbazepine is 10-20 hrs in healthy subjects and 13-20 hrs in epileptic patients. Eslicarbazepine elimination is primarily renal, in the unchanged and glucuronide conjugated forms. The amount of metabolite recovered in the urine is >90% of a dose of SEP-0002093 (2/3 is unchanged and 1/3 as glucuronide conjugate). Eslicarbazepine binding to plasma proteins is stated to be <40% and independent of concentration. Eslicarbazepine appears to be extensively distributed to tissues.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple marketed anti-epileptics for adjunctive use in patients > 17 years of age with partial onset seizures. These include, but are not limited to, lacosamide, carbamazepine, oxcarbazepine, levetiracetam, zonisamide, pregabalin, and topiramate.

## 2.3 Availability of Proposed Active Ingredient in the United States

ESL, carbamazepine, and oxcarbazepine are structurally similar (p.19/53 of abuse-potential.pdf). SEP-0002093 and oxcabazepine share common active metabolites. As noted above, oxcarbazepine metabolizes to both (S)-licarbazepine and (R)-licarbazepine. Information from OCB (email dated 1-21-10) indicates that the proportion of S-licarbazepine and R-licarbazepine following oral administration of eslicarbazepine acetate is 21:1. When oxcarbazepine is administered orally, the ratio of S to R-licarbazepine is 4:1.

Oxcarbazepine is available in the US as Trileptal ®. Carbamazepine is available as the innovator product (Tegretol®) and in generic forms.

## 2.4 Important Safety Issues With Consideration to Related Drugs

SEP-0002093 is a sodium channel blocker. Sodium channel blockers are used widely as anticonvulsants (for example, carbamazepine and oxcarbazepine) and their toxicities are considered fairly well characterized. CNS toxicities include dizziness, drowsiness, and ataxia. As with CNS toxicity, the degree or prevalence of other adverse events varies with different drugs in the class (such as cardiac rhythm and conduction abnormalities seen with lacosamide). Other adverse effects of this class of drug are multiorgan hypersensitivity (DRESS), serious dermatologic reactions (SJS and TENS), hepatotoxicity, hyponatremia, and blood dyscrasias (aplastic anemia and agranulocytosis). All antiepileptic drugs, regardless of class, are thought at this time to be associated with an increase in suicidal behavior and ideation.

Oxcarbazepine (brand Trileptal) can inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on the plasma concentrations of other drugs. Also, Trileptal prescribing information indicates that several AEDs that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Eslicarbazepine acetate was developed by Bial-Portela & Ca.S.A. Sepracor is the U.S. sponsor of eslicarbazepine and the sponsor of this NDA.

At the time of submission of the initial NDA, all clinical studies had been conducted outside of the U.S. with the exception of 2 phase 2 studies conducted under IND 67466. Bial and Sepracor entered an agreement in December, 2007 which allows Sepracor to develop and market the referenced product in the U.S. and Canada. Ownership of the IND 67466 transferred from Bial to Sepracor as of April 10, 2008.

The first-in-human study was study 2093-101. This study began in July of 2000 in London, UK. IND 67466 was opened in November 2006. As per information in the clinical summary of safety submitted with the 120-day safety update, the clinical

development program consisted of 33 trials: 25 phase 1 trials in healthy subjects or special populations, five phase 2 studies (2 epilepsy and 3 bipolar), and three phase 3 studies (in patients with epilepsy). As per a 2-4-10 submission, there are 10 trials or extensions either ongoing or clinically completed but not reported. Those clinically completed but not reported include one trial each for the indications diabetic neuropathy and post-herpetic neuralgia.

There were meetings with a corporate sponsor (either (b) (4) Bial or Sepracor) during the development of this product.

1) July 21, 2006- pre-IND meeting-Based on meeting minutes, clinical issues discussed included the number of EKGs in study BIA-2093-118
2) January 23, 2008-pre-NDA
3) November 13, 2008-pre-NDA between FDA and representatives from Bial and from Sepracor

As noted, there were two pre-NDA meetings before the final submission of the NDA. One was with Bial on January 23, 2008 and the second was with Sepracor on November 13, 2008. Issues discussed that are particularly relevant to the review of this NDA include:

1) audit program- There was discussion regarding whether FDA would be performing GCP audits and of irregularities in Mexico in study 303. Sepracor noted there were “minor irregularities” at non-Mexican sites in study 303 that were not viewed as having significant compliance issues.
2) Applicability of foreign data-FDA noted this would be a review issue and noted an additionally efficacy study with a significant portion of the patient population from the US would be desirable to confirm the foreign data. The company noted a plan to conduct an efficacy study in North America (US and Canada) for a monotherapy indication. FDA noted the trial submitted as a special protocol assessment was a historical control study of eslicarbazepine as monotherapy in subjects with partial epilepsy unresponsive to current antiepileptic drugs. The Division of Neurology Products expressed a preference for a placebo-controlled study. The sponsor indicated they planned to do a pediatric study in the US, however the data would not be available at the time of NDA filing.
3) Efficacy data was defined as phase 2 and 3 adult epilepsy data without post-hoc analyses.
4) Issues of abuse potential were discussed. FDA noted in a post-meeting note included in the meeting minutes (signed 1-12-09) that all data related to abuse potential of eslicarbazepine acetate and metabolites should be included in the NDA at the time of submission of the NDA.

In addition to these meeting, a protocol for use in monotherapy in subjects with partial epilepsy unresponsive to current antiepileptic drugs (protocol 093-045) was submitted

for review as a Special Protocol Assessment (SPA) on November 11, 2008. A letter of agreement was sent to the company on 2-4-09.

### 2.6 Other Relevant Background Information

As per the Sponsor in the initial submission, this product is not marketed in any country. In February, 2009, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for BIAL-Portela & Ca.S.A. This opinion recommended granting a marketing authorization in the EU under the trade name Zebinix intended for adjunctive therapy in adults with partial-onset seizures with or without secondary generalization. As of the March, 2010, (based on Google search findings), it appears the product has been launched in the UK.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

Submission quality was not optimal. Data integrity appears questionable. Pre-NDA, there were sponsor-identified, significant GCP issues in one of the three studies (study 303) submitted to support the safety database. FDA inspected four sites (two each in studies 301 and 302). The final inspection review indicates that site 112 in study 301 and site 395 in study 302 are considered as having significant deviations from regulations (OAI classification). Data from the other two inspected sites appear to be acceptable.

The review process revealed a number of issues with data presentations. At the individual level, some or maybe all of these issues, may or may not in the end reflect negatively on the product's profile (specifically, the safety profile, but also the efficacy profile). However, several significant corrections or additions to the NDA data seemingly only were found because the Sponsor was responding to an FDA request or in the process of preparing the next FDA submission. This does not promote confidence that the submission has undergone proper quality control checks. To state it bluntly, at this point in the review, I would not be surprised if an additional request to the Sponsor resulted in new adverse events or a correction to previous data.

Examples of data quality issues are described below.

1. 59 part 1 adverse events (includes the controlled phase) from 48 subjects were not reported as part one events in the initial integrated summary of safety. These apparently were reported as part 2 events (open-label events). In the 120-day safety update, the sponsor reported these events as "Delayed-Reported Part 1 TEAEs" (SU p.27/290) and describes that "during evaluation of the Part 2 adverse event data, it was discovered that there were a number of adverse events reported

on Book 3 of the case report form (CRF) (Part 2) that had an onset date occurring during the Part 1 double-blind phase of the study."

As per the Clinical Safety of Summary submitted 8-28-09 (page 31), these 59 events resulted in one event no longer showing a dose response (insomnia) and the addition of an adverse event (alopecia) to the adverse events (seen in Table 2.3-1 of the Clinical Summary of Safety). The sponsor notes that "in many cases the nature of these events (alopecia, increased weight) were such that the event may not have been recognized until a cumulative effect was seen in part 2, but upon reflection, onset was recognized to have occurred in Part 1." (p. 29/80).

The potential impact of this is not necessarily in the proportion of the data considered delayed or whether the individual events change the outcome. The issue is whether this is this an isolated mistake in the presentation of safety data?

2. <u>The 120 day safety update is missing 31 serious adverse events from one trial.</u> The 120 day safety update reported adverse event information from 15 studies considered by the sponsor as ongoing or clinically completed but not reported (Table 9.2-1). This listing (Table 9.2-1) was hard to read, therefore a request for clarification was sent to the sponsor (1-4-10). The difficulty reading the table was not the only problem with the presentation of adverse events from these trials. The presentation also did not include information about discontinuations secondary to an adverse event and only reported data between the cut-off of the initial integrated summary of safety (2-28-08) and the 120-day safety update data (3-30-09). The latter issue left the possibility for events that preceded the initial integrated summary of safety cut-off dates to not be reported.

The Sponsor's 1-25-10 response to the query for clarification of Table 9.2-1 indicated that 31 SAEs had been inadvertently omitted from the referenced table. These events were from study 206, a study in patients with diabetic neuropathy. Study 206 clinically completed on 11-18-08. In the 1-25-10 submission, the sponsor qualified the updated information by noting that data were "preliminary, unconfirmed, and subject to change in the final CSR." (p.63/523 of 1-25-10 submission). In the completion of FDA's requests (for discontinuations from the ongoing trials and for events that occurred before the cut-off date of the initial integrated summary of safety), the 2-4-10 response noted additional corrections to the previous submission.

These additional corrections were that some of the study statuses changed from either ongoing to planning (2 studies) or were no longer considered ongoing as no subjects had been enrolled at the time of the cut-off for the 120-day safety update (4 studies). The sponsor explained that the latter studies had been considered ongoing because a protocol had been submitted to a Competent Authority or Ethics Committee. The reason this apparently small change has meaning is that previously, in Table 9.2-1, the SAE information for these six studies had been described as "No SAEs reported for this study". In the context of studies still in planning or without patients, this information is

interpreted differently than when considering there are at least some patients in the study.

3. The sponsor's 2-4-10 submission reports a death from study 206 that was not in the 120-day safety update's section describing events of death for this trial (section 9.1). A narrative for "the new report of death" (p.5/35, 2-4-10 submission) was included for the subject in the referenced submission. (Of note this death is in a listing in the 1-25-10 response.)

4. There are two adverse events that appear to be serious adverse events that do not have narratives in the ISS and in one case, does not appear to have been categorized at all as an SAE.

   - Subject 119-004 has a narrative in the discontinuation section of the ISS narratives. The heading of the narrative indicates the treatment group is eslicarbazepine acetate with another drug (lamotrigine). As I read the listing 6.3, (listing of discontinuations in attachment 5 of 9-29-09 submission), the subject appears to have been on 1200 mg eslicarbazepine acetate. The ISS discontinuation narrative event is "hypersensitivity". The narrative lacks a detailed clinical description of the event. The CRF indicates this subject was hospitalized (hospitalization makes this event an SAE by definition). Also, based on CRF entries and notes, the subject's reaction course appears to have included an ulcer in the mucosa of the lower lip, perhaps an increased temperature, peeling skin, and liver enzyme elevations. Therefore, even though the subject reportedly was on a product associated with Steven's Johnson/serious skin reactions (lamotrigine), the event should have been captured as an SAE.
   - Subject 117-005 apparently had a purulent tonsillitis considered an SAE. There is no narrative or CRF. This was noted in a table describing CPK elevations in the ISS and is also seen in Listing 6.2 (attachment 4 of 9-29-09 information amendment). Listing 6.2 was submitted in response to FDA request.

5. Information is presented in ways that does not always highlight the potential importance of the event. This includes two identified subjects with ISS narrative bolded information and/or narrative information that is understated to the point of minimizing events that are potentially medically significant (see descriptions below) and a case called "pancytopenia" in the SU that is mentioned briefly in the text of the SU (subject 303-701-70290, p.160, and likely mislabeled as subject is labeled as study 302 in SU, but site 701 was in study 303) with essentially no clinical description of the case. The event is not considered an SAE and is not reported as leading to discontinuation. The term "pancitopenia" is in the integrated summary of safety dataset ADAE2.xpt submitted with the safety update.

●**Subject 110-11** is from a healthy volunteer study with a crossover design of either ESL 900 mg daily, ESL 450 mg BID, or Trileptal. The narrative heading indicates the

event of "Transaminases Increased" occurred on Trileptal 450 mg BID and the text gives the values (without reference ranges). These are about 2x ULN for AST and ~ 5.4 x ULN for ALT. Bilirubin values are reported as within the normal range. While it is the case that the subject sustained transaminases increases on Trileptal and discontinued from the study because of this instance of elevations, the subject sustained higher increases on ESL (3.6x ULN for AST and ~ 8 x ULN for ALT) and was exposed to this first. It seems he also had decreasing transaminases levels during de-challenge (washout). While the text of the narrative does indicate there were increased transaminases in period 1, and earlier in the paragraph, one can see that period one was ESL dosing, the values are not reported for the ESL elevations. The CRF contains information that perhaps this was Wilson's disease and referred to a high ceruloplasmin or an unspecified hepatitis and the subject was for consultation.

●**Subject 203-337-203058**- (bipolar trial) The narrative bolded header is vomiting and this is the stated reason this subject was discontinued from the study but the text indicates that transaminases were high (values of 1447 U/L and 1154 U/L for AST and ALT respectively, without a reference range provided) and that both direct and total bilirubin were elevated (values are given, but there is no reference range). The subject has a history of chronic pancreatitis. The events of vomiting and increased liver function tests occurred three days after starting ESL. All laboratory abnormalities appear to have resolved about a month after discontinuation of ESL. The narrative did not describe ALP results, did not give a reference range, and does not address why this event should not be considered as potential drug induced hepatotoxicity or cholestatic injury, especially since an ALP measure is not provided in the narrative.

●In the pancytopenia case (303-701-70290), the subject is noted to be on valproic acid, which may confound the case or be contributory, but these types of events are rare and potentially serious and should be highlighted in presentations even if in the end, it seems unlikely the event is related to ESL. This case is somewhat hard to notice in the SU because the tables of TE AEs in the body of the SU are for incidence ≥ 2% and the event is in text of the SU (panctyopenia).

6. <u>Audit forms indicate there were discrepancies between source documents and case report findings with respect to possible adverse event and serious adverse event reporting.</u> Due to the GCP problems mentioned previously and discussed in the quality section of this review, FDA requested audit reports of audits performed previously on sites in the studies. It was noted that at a site in study 301 (195), the inspection report indicated that the case report forms of three subjects were audited using complete source documents and that AEs/SAEs were not properly reported for these sampled subjects. FDA requested that, if not already done, the sponsor examine the audit forms for such discrepancies and cross reference events to the various integrated datasets (for example, adverse events) to see if events were captured.

The submission of 1-25-10 provides the response. This document has not been fully reviewed.

Cursory review indicates the sponsor describes the results of evaluation that included Sepracor's audits of sites in studies 301, 302, 303, and 201, and of Bial's audits of 12 phase 1 sites and study 203.

The audits of clinical sites in study 301 found discrepancies involving AE reporting at 6 of 10 sites, involving 11 of the 88 subjects covered by the audits. There were 20 discrepant AEs for these 11 subjects. Five were resolved through data query, leaving 15 unresolved. For study 302, after the process of data query, there were 31 discrepant events. For study 303, after the process of data query there were 33 discrepant events. For study 201, discrepancies were found at 5 of 5 sites involving 6 of 21 audited subjects with 7 adverse events. After data query, six events were still discrepant.

There were 12 clinical sites audited in phase 1 by BIAL. Discrepancy was noted at 1 of 12 sites. This was not resolved by data query. For study 203, there were no discrepant events.

Some of the events above did not end up in the integrated summary of safety AE datasets. The company notes that audits took place more than 2 years after notations were made and some times it was not possible to determine whether these signs and symptoms were overlooked or were part of a seizure (post-ictal) or were determined to be pre-existing. The sponsor states that the nature of many of the audit findings are consistent with the possibility that they were seizure-associated and would not meet criteria for recording as an adverse event. The sponsor concludes that there were no cases associated with ESL that represented a potential rare or previously unrecognized SAE that should be reflected in labeling.

This reviewer notes that one event not in the AE dataset as per the Table 1-1 in the 1-25-10 submission is "severe partial seizures/hemiparesis". The investigator noted this as an SAE on a data clarification form (subject 303-710-70367). Some events, based only on the event term, do not seem necessarily related to a seizure or post-ictal state (e.g.constipation-patient 302-385-80426 and elevated triclyceride in subject 303-710-70334).

7. <u>SAES occurring within a week of study drug discontinuation are not reflected consistently in summary tables.</u> In response to FDA request for clarification of what seemed to be contradictory information between two tables of serious adverse event information (Table 3 of the 8-28-09 and Table 2.1.3-1, same date submission but different document), the sponsor's response included notation that one table included fatal and fatal events and one did not (Table3 was appropriately labeled as non-fatal SAEs). The sponsor also noted (1-25-10 response to 1-4-10 request) that 16 subjects with 18 events were not included in Table 3 (non-fatal SAES) because events started after the treatment period ended. [The sponsor pointed out this had

been explained in a 9-29-09 submission. In the 9-29-09 submission, there is a comprehensive line listing of all treatment emergent SAEs (listing 6.2). These 18 SAES are included, however, the events are not highlighted so one cannot readily tell which events/subjects they are. ]

In the 1-25-10 response, the sponsor displayed information for these 18 events (16 subjects) in a table (Table 9-4, duplicated in the appendix of this review). Based on the referenced table, nine subjects with SAES had SAE onset within a week of the last dose of study medication and are not reflected in the numbers shown in Table 3. Seven of these nine were ≤ 5 days after the last dose of medication (2 with manic symptoms in bipolar studies, 1 with esophageal stenosis in a bipolar study, and 1 each with exanthema, intoxication, status epilepticus, paresthesia of left arm and leg and right leg, and psychogenic paranoid psychosis in study 301).
A subject from the Table 9-4 is subject 303-601-70156. In study 303, subject 601-70156 experienced hyponatremia reported with an event date of 11-25-06 and last dose date of 11-11-05. I checked the study report and CRF (p. 1417/1431 and p. 172/380, respectively). These sources indicate this subject's last dose of study medication was 9-26-06 and the CRF indicates an event of worsening of hyponatremia with onset in October, 2006 and offset or ongoing still on 11-26-06 (p.210/380).

8. Unclear data: Table 4, "Summary of Discontinuations due to Adverse Events in the Entire Eslicarbazepine Acetate Development Program and by Study within each Development Phase", compared to Table 4.1.4.3-1, "Discontinuation of Study Medication Due TEAEs Reported in ≥ 2% of Subjects in Any Dose Group by Overall Treatment Group for part 1 of the Phase III Studies (2093-301 and 2039-302 Pooled vs. 2093-303 (Safety Population)" seemed to conflict in terms of numbers of placebo and ESL patients. The sponsor was asked to clarify.

The sponsor 's response (1-25-10) noted that Table 4 was populated from the CRF termination page of primary and secondary reasons for discontinuation and Table 4.1.4.3-1 was from the adverse event page in the CRF (which had a item inquiring whether action was taken with respect to study medication with the choices of none, discontinuation, or other, please specify). Three subjects were discontinued from the study (Table 4) but were not captured in the discontinuation from study medication table (Table 4.1.4.3-1). The sponsor provided information, which I summarize below. With preliminary review, the responses do not appear to resolve the issue.

►301-112-90393-The sponsor states that leukopenia (per lab finding) was originally reported as an AE that led to patient withdrawal but that a query resulted in the lab finding being considered NCS (presumably the acronym is not clinically significant) and the AE was removed from the AE page, but the completion page was left as withdrawal due to an AE. *(Reviewer's comment: Of note, as per DSI verbal report, there is a value 2.66, the lowest value seen for the subject. 2.66 is not in the lab dataset of lab data for this subject. As the event was not coded as discontinuation secondary to an AE, FDA does not have the CRF. The event also is not in the integrated safety dataset of adverse events, ADAE2.xpt .)*

►301-192-90259-the sponsor states that the subject reported a stomach ulcer (serious) during part 1 of the study 301. The impact on study treatment was listed as none, therefore the subject was not listed in Table

4.1.4.3-1. The sponsor states that since the termination page indicated termination due to an "unacceptable AE", the subject was counted in Table 4. *(Reviewer's comment, if the patient was discontinued from the study because of an AE, in this case stomach ulcer, then logically the subject should no longer be on study medication.)*

►301-211-90059- The sponsor indicates that this subject experienced ataxia and arterial hypertension that was documented to have an impact on study treatment of "none". A data clarification is reported to have questioned why the termination page states discontinuation secondary to an AE, but no AE is reported. The sponsor reports that on the termination form, there is a hand-written note stating "ataxia and arterial hypertension" which implies these are the events leading to discontinuation. (*Reviewer's comment: Again, It seems that any subject who left the study should be off study medication.)*

The sponsor reports that seven subjects who reported an AE that led to discontinuation of study drug (in Table 4.1.4.3-1) were not included in Table 4 because "unacceptable AE" was not listed as a reason for discontinuation on the termination page of the CRF. The sponsor also notes that "based on the AE data and the fact that these subjects withdrew during part 1 of the Phase III studies, it would be expected that they would have been counted in Table 4" (p. 60/77 of 1-25-10 response document, effic-info-amend.pdf)

*Reviewer's comment: It is not unreasonable to have a discontinuation from the study table (versus discontinuation from study medication) but the main summary discontinuation tables should be reporting discontinuation from study medication, should capture or note in some way all subjects who discontinue from study drug because of an AE regardless of inconsistencies in the CRF documentation, and presentations should be consistent across the submission.*

9. ISS narratives are not well organized and include seven subjects from single –blind placebo labeled as "placebo" (The sponsor's 1-25-10 submission confirmed that the events of seven placebo subjects from the single -blind period were labeled as placebo events).

The narratives are not indexed and there is no tabulated summary or page (or hyperlink) with a list of the subject numbers of subjects for whom there is a narrative The ISS narratives are separated by type (death, SAE, and discontinuation) and then appear to be generally by phase, by study, by site, and then in numerical sequence of the subject number for the site, and then by the next site, and so forth. Within a section of narratives, and probably because of the sequential presentation just described, there is no grouping by dose and headers include "placebo" and pre-treatment events ("not treated" and "onset prior to treatment). Two event terms "Unknown Adverse Event" (303-709-70384) and "Adverse Event Leading to Discontinuation Not Defined" (study 203) are notable.

There was no explanation in the ISS of how a narrative is set up (for example, is the bolded heading event(s) the verbatim term, the preferred term, a diagnosis? And is the bolded treatment group the assigned treatment group or the treatment the subject was on at the time?). The seven subjects referenced above experienced events pre-randomization in study 301 but were randomized to placebo.

One subject in the discontinuation narrative section has a reference noting the narrative may be found in the SAE narrative section. There is no narrative for the subject in the referenced section. The event was a pregnancy so the absence of a narrative is not the issue as this should be seen in a listing of pregnancies.

Additionally, the content of some narratives is not very informative. This ranges from almost no meaningful clinical description to lacking pertinent information such as reference ranges or lab values that would be appropriate. The following are examples of a lack of detailed clinical descriptions.

●subject 302-363-80581, is characterized as "skin lesion". The narrative states the subject had a "single episode of skin lesion of moderate severity" that did not require treatment but the subject was discontinued. There is no description of where the skin lesion was or whether it is rash (patient has history of porphyria). The CRF does note that there was skin lesion on arms and legs, so there is at least some additional information that could have been in the narrative.

● subject 302-372-80363 with orthostatic hypotension. No blood pressure measurements are described in the narrative (or are noted as being absent on the CRF) and there is no description of the event otherwise except that the event was moderate, did not require treatment, and was considered resolved about 7 days after last dose of study medication.
●Subject 301-153-1334 intermittently experienced "dystonia" and vomiting.
●Subject 302-338-80164 is reported to have experienced "severe insulinoma" (narrative notes subject experiencing hypertension and hypoglycemia at study entry).

The process of translating the verbatim to preferred terms that may have been used in narratives is not described (for example, are the terms common enough that standard coding would be sufficient or do they need a medically qualified person to assess each?). This point is made because there are a few verbatim terms in the dataset (ADAE2.xpt) that are unfamiliar to me and that I suspect are not terms commonly used in the US and/or may be used differently between countries in the pivotal studies. There are not that many but I do not see that this was addressed specifically (ISS or SU body). Examples from the dataset include amygdalitis, systremma, epigastralgia, and nutcracker syndrome. An example in the narrative is "esophageal stenosis" (subject 205-543-203144, is this reflux?, the subject was given omeprazole but the event is noted as ongoing).

10. Submissions presentations are sometimes displayed in ways that do not facilitate review. The following are some examples:
    - Due to compliance issues with several sites, in the filing letter, FDA asked for a description of adverse events from study 303, sites 702 and 703 and any other AEs from the study of which FDA was not aware. In a 7-13-09 response, the sponsor provided an attachment with links to audit reports and referred to the section of each audit report (B5) that would describe these

events. This would require opening multiple audit reports, going to section B5, capturing the data in some format, and then dealing with the events themselves. The point of the initial request was to see whether there was a reason to be concerned that adverse events picked up on audits had not been transcribed to datasets. FDA later (January 2010) asked the sponsor (predicated on the question of whether this was previously performed) to go through the audit forms, note discrepancies between source documents and CRFs for adverse events and cross reference to the dataset of adverse events, disposition, and exposure to see if the events were included. The sponsor responded on 1-25-10.

- Treatment emergent AEs in phase 1, single dose studies were not comprehensive. The images below are excerpted from tables in the ISS or SU (p. 124 and 135 ISS, p. 192 SU). As noted in the first image, one cannot tell from this table what the common AE was for the subject in the ESL 400 mg group or the 2nd subject in the ESL 200 mg group. In the second image, it is a similar issue.

**Table 8.3.5-1: Treatment Emergent Adverse Events for the Phase I Single-Dose Healthy Volunteer Studies (2093-101, 2093-10 2093-104, 2093-109, 2093-117, and 2093-122) (Safety Population)**

| Study No. Study Type | Category | Control Group n (%) | <100 mg ESL QD n (%) | 200 mg ESL QD n (%) | 400 mg ESL QD n (%) | 600 mg ESL QD n (%) | 800 mg ESL QD n (%) | 900 mg ESL QD n (%) | 1200 mg ESL QD n (%) |
|---|---|---|---|---|---|---|---|---|---|
| 2093-101 | | Placebo | 20 mg /50 mg /100 mg | | | | | | |
| PK/PD Tolerability | No. of Subjects | 16 | 6 /6 /6 | 6 | 6 | 6 | NA | 6 | 6 |
| | Overall TEAE | 4 (25.0) | 4 (66.7) /2 (33.3) /3 (50.0) | 2 (33.3) | 1 (16.7) | 1 (16.7) | NA | 1 (16.7) | 6 (100) |
| | Common TEAE[a] | | | | | | | | |
| | Headache | 3 (18.8) | 3 (50) /2 (33.3) /2 (33.3) | 0 | 0 | 1 (16.7) | NA | 1(16.7) | 0 |
| | Somnolence | 2 (12.5) | 0 /0 /1 (16.7) | 1 (16.7) | 0 | 0 | NA | 0 | 2 (33.3) |
| | URI | 0 | 0 /0 /0 | 0 | 0 | 0 | NA | 0 | 4 (66.7) |
| | Dizziness | 1 (6.3) | 2 (33.3) /0 /0 | 0 | 0 | 0 | NA | 1 (16.7) | 0 |

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**Table 8.3.5-3: Treatment Emergent Adverse Events for the Phase I Drug-Drug Interaction Studies (2093-106, 2093-107, 2093-108, 2093-114, 2093-119, 2093-120, and 2093-121) (Safety Population)**

| 2093-108 Drug-Drug Interaction (warfarin) | | Warfarin Run-In Phase A | Warfarin Alone Phase C | | Warfarin+1200 mg ESL Phase B |
|---|---|---|---|---|---|
| | No. of Subjects | 15 | 13 | NA | 13 |
| | Overall TEAE | 5 (33.3) | 4 (30.8) | NA | 7 (53.8) |
| | Common TEAE[a] | | | NA | |
| | Vasovagal reaction | 1 (6.7) | 0 | | 2 (15.4) |
| | Adhesive tape allergy | 0 | 0 | NA | 2 (15.4) |

- In the image below, it seems possible to determine the dose group at the time of event onset, but it requires noting the stop-start dates of the event compared to stop-start dates of doses.

**Table 9.2-1: Serious Adverse Events by Study Occurring during the Period between 28 February 2008 and 30 March 2009 (Studies 2093-127, 2093-128, 2093-129, 2093-206, 2093-207, 2093-208, 2093-209, 2093-210, 2093-301 Part 3, 2093-301 Part 4, 2093-302 Part 2, 2093-304, 2093-305 Part 1, 2093-311, and 2093-401)**

| Study No. Subject No. Case No. | Country | Age (years) Sex | Dose Start Dose Stop | ESL Daily Dose | Event Onset Event Stop | Reported Term Outcome | Preferred Term System Organ Class | Serious | Relationship |
|---|---|---|---|---|---|---|---|---|---|
| 2093-127 (Plasma and cerebrospinal fluid PK) | | | | | | | No SAEs reported for this study | | |
| 2093-128 (DDI with combined oral contraceptive) | | | | | | | No SAEs reported for this study | | |
| 2093-129 (DDI with carbamazepine) | | | | | | | No SAEs reported for this study | | |
| 2093-206 (Diabetic neuropathy) | | | | | | | | | |
| 5179 | Austria | 70 | 06MAY2008<br>05AUG2008<br>11AUG2008<br>18AUG2008<br>24OCT2008<br>26FEB2009 | 1200 mg<br>400 mg<br>800 mg<br>1200 mg<br>1600 mg<br>1600 mg | (b) (6) | Obstipation | Constipation | Hospitalization | Unlikely |
| 2093-206-501/0004 | | Male | 04AUG2008<br>10AUG2008<br>17AUG2008<br>23OCT2008<br>19FEB2009<br>ongoing | | (b) (6) | Recovered | Gastrointestinal disorders | | |

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- In the ISS section describing electrolyte findings in phase 2 epilepsy studies, the presentation is very brief (without sodium values). Hyperlinks are in-place, however, the hyperlinks go to listings and require one to look for the data within the listing. Please see the image below showing the summary from the ISS.

Serum electrolyte abnormalities were reported as a TEAE in 1 subject in the ESL QD dosing group (Study 2093-201 CSR Section 17.1 Table S02). Subject 19-015 experienced hyponatremia and hypochloremia reported as a mild imbalance in blood electrolytes (Study 2093-201 CSR Appendix 17.6.25). The subject entered the study with low sodium and chloride values, which dropped further before returning to baseline levels at study follow-up (Study 2093-201 CSR Appendix 17.6.20).

- Mean change and shift summary tables (ISS) for part 1 include a treatment week 18. At treatment week 18 in study 302, subjects are one month into open-label, so these data should not be in the tables. These data apparently are not in the tables but this is not that obvious as the legends do not address it and although the numbers at week 18 are smaller, one might initially assume this is from missing data (for example, tables 11.2.1.1-1, 11.1.1.1-2, 11.2.2.1-2, 11.2.3.1-1, 11.2.3.1-2, and 11.2.4.1-1). This is not a fatal data problem, but again suggests a rather informal approach to data presentation.

- ISS presentation of clinical chemistry and hematology data is divided several ways requiring the use of several places in the ISS in order to compile the data presentations. For example, for chemistry labs, sodium, chloride, and potassium are presented for part 1 phase 3 epilepsy studies, then for part 2, phase 3 epilepsy, then phase 2 adult epilepsy, phase 2 pediatric epilepsy, phase 1 healthy volunteers, and phase 1 populations studies. [Bipolar studies are covered in a different section of the review.] Then blood urea nitrogen and creatinine are presented in the same fashion, then AST, ALT, and glucose. Hematology parameters are similarly parsed.

11. The conclusion of FDA's audits are discrepant with the Company's, for 2 of 4 mutual sites audited, creating a situation in which it is unclear how to interpret the conclusions of other audit reports that were submitted.

- Site 112 in study 301- Sepracor's audit was performed September 30-October 2, 2008, about 3 years after the last subject was enrolled in part 1 at that site. The audit findings indicate that AEs/SAEs were properly reported as the evaluation of this was a 1 (adequate) based on 4/17 subjects audited. Records of drug receipt, storage, & return and records of drug dispensed to & returned by subjects are evaluated as "significant non-compliance" and "minor non-compliance" respectively. Submission documents indicate that while some of the audit findings in study 301 found significant GCP deficiencies, the particular deficiencies do not adversely impact the overall utility of the data (p. 5/31, multi-mod-info-amend.pdf, 7-13-09).

  FDA's DSI summary review indicates data at site #112 in study 301 has a preliminary classification that indicates significant deviations from regulations and that data are unreliable.

- Site 395 in study 302-Sepracor (through (b) (4)) audited this site 7-28-09 through 7-31-09. The audit report for this study was submitted 10-02-09. Sepracor classified only AE/SAE reporting as "significant non-compliance" with the data of three of fifteen subjects reviewed. One of these subjects had six adverse events noted in source documents but not recorded in the CRF and for 5 of these six events, the onset dates were unclear (p.5/6 of multi-mod-info-amend.pdf). Drug accountability records were not considered adequate with a comment that documentation for the return of double-blind study medication could not be located by the auditor. This was graded as a minor non-compliance. Sepracor concluded that observations did not adversely impact data utility and gave the site an overall classification of "minor findings". FDA DSI audited resulted in an a classification indicating that there were significant deviations from regulations and that the data are unreliable.

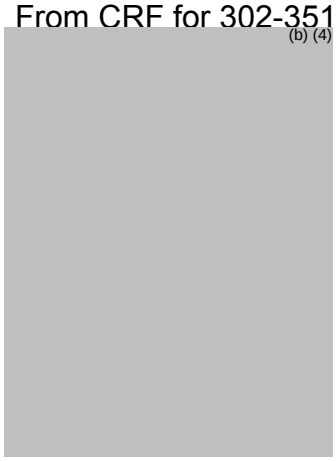
12. There are some CRFs with multiple data clarification forms and/or strikethrough corrections made by study staff and/or auditors making tracking difficult. There are data clarification entries that sometimes appear to obscure an original entry in the text. Sometimes, after significant time expenditure going back and forth from the CRF to data clarification forms, I could tell that what appeared to be obscured text might have been an effort to type the data for readability or might have been because the events were recorded initially in the wrong section of the CRF or for some other reason that seemed acceptable. However, this is not always obvious or the case. Also, there is no hyperlink between the data clarification entry or inquiry and the data clarification form. If there are multiple data clarification forms, it becomes quite time consuming and laborious to track a potential issue.

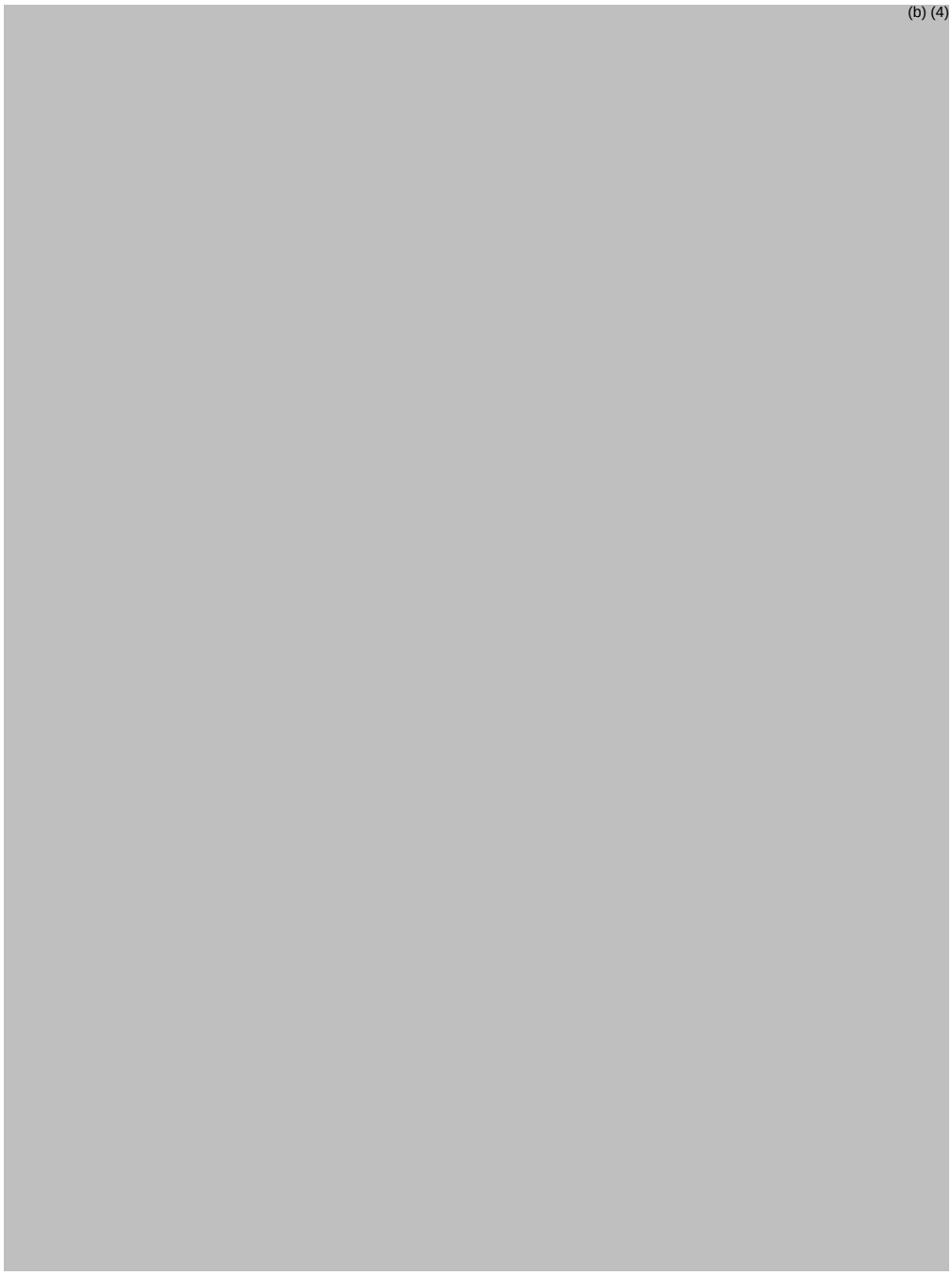
The following table lists a few case report forms that were catalogued during review. It is fair to say these may not represent the totality, but this is part of what was

encountered during the review process. There are a few images of CRF excerpts below to show the reader the way corrections are made.

| Subject number | #DCF | Other CRF |
|---|---|---|
| 303-601-70156 for parts 1&2 of study | > 60 | mark out change to initial SAE entry from yes to no, DCF seems to obscure an original entry, DCFs from page 244-380 of 380 page CRF. Page 63, seems to indicate patient also started topirimate within 2 months after visit 1 and was approved by medical monitor |
| 303-611-70237 for parts 1&2 of study | ~90 | pages 402-528 are DCFs |
| 302-351-80013 part 1 | >30 | see duplicated excerpt of piece of CRF page |
| 303-703-70231 | ~34 + onsite queried | one DCF obscures a column<br>see image below |
| 302-336-80073 | ~45 | handwritten entries marked through in red |
| 302-384-80509 | ~61 | |
| 302-351-80002 parts 1 &2 of study | ~100 | CRF is 432 pages, DCF pages 277-432 |
| 302-301-80670 | >36 | CRF is 198 pages, DCF pages 135-198 |

From CRF for 302-351-80013






13) What appears to be internal inconsistency in AE reporting or coding within NDA. The following are some examples.

- There are different numbers for the incidence of discontinuation secondary to an adverse event. The Sponsor's Table 2-1 compares rates of adverse events for ESL development compared to 5 anti-epileptic drug approvals. This table indicates placebo rates of discontinuation due to an adverse event in ESL trials 301, 302, and 303, as 3.9%, 3%, and 6.9%, respectively. The sponsor's Table 4 of discontinuations secondary to an adverse event shows placebo discontinuations at 2.9%, 3%, and 4.6%

respectively for study 301, 302, and 303. [Discontinuation of study medication is reported in Table 4.1.4.3-1 as 4% for placebo (combined 301 and 302) and 8% for study 303.]

- Subject 301-211-90059- is listed in Listing 6.3 “All Treatment Emergent Adverse Events In Subjects Discontinued Due to Adverse Events” for the safety population. (This listing was submitted 9-29 as response to FDA.) This would seem to indicate the subject discontinued secondary to an adverse event, however, there is no narrative in either the ISS or the SU and there is no CRF. To further cloud the issue, the listing has a column for action taken and one for treatment. Neither of these columns indicates that the subject was discontinued or the medication withdrawn. The listed events are arterial hypertension, dizziness, and diplopia at 400 mg ESL and ataxia at 1200 mg. There are other subjects like this with events listed but no event labeled as leading to withdrawal (for example, subject 110-000-00011, 114-000-00007, 301-181-90013, and 302-313-80265)
- Subject 301-112-90393 is also in listing 6.3 with information of “None reported” in the column that has the verbatim and preferred terms of the adverse event. There is no CRF and no narrative. *(This is the patient identified by DSI as discontinuation 2nd to an AE at site 112.)* Subjects 302-336-80738 and 302-338-80165 also have “none reported” as the adverse event.
- Subject 301-213-90055 is not in listing 6.3 and there is no ISS or SU narrative, yet a CRF was submitted. In the study report, it seems this subject was discontinued because of somnolence (Table 60, p.240/1074, 301a1-table not included in this review) and there is a narrative for discontinuation due to an AE in the study report for the subject (p.257/1074).The study report indicates that the subject received 1200 mg since 12-27-04 and on 4-1-05 experienced somnolence and that study medication was discontinued 4-14-05 although it does say the patient withdrew consent. The CRF adverse event pages indicate somnolence several times (12-30, 3-02, and 4-01) and withdrawal and discontinuation due to this event occurrence on 4-01. However, the CRF termination page has the reason for premature study termination as “withdrawal as consent”. Data clarification (duplicated below) noted the discrepancy. Correction is made such that “other” is chosen as reason for discontinuation with withdrawal of consent as impact on study treatment.


- Subject 302-312-80299- ISS narrative heading for SAE narrative is "Gastroenteritis". ADAE2.xpt has two terms as serious, Gastroenteritis and "Acute on Chronic Renal Failure" with equivalent for the preferred term as "Renal Failure Acute". The text of the narrative includes hospitalization for 2 events ("gastroenteritis and acute chronic renal failure")
- Conflicting information- Examples: 1) Healthy volunteer subject 114-007 experienced a high CPK (>3xULN). The treatment is reported on page 218 as ESL 900 mg. In the ISS Table 8.6.16-5 (table listing subjects in phase 1 with AEs of CPK increased), the subject is listed as treatment of ESL 1200 mg + Microginon. 2) One subject discontinued secondary to elevated transaminases (Subject 11 in study 110). The sponsor states this subject had completed the oxcarbazepine portion of the study 4 days prior to the event. (This subject was first dosed with ESL and experienced increased transaminases. In the next period, the subject was treated with oxcarbazepine and again experienced elevated transaminases, although apparently not as high as with ESL.

Instances of what appeared to be inconsistencies were sent as request to the sponsor on 1-4-10. Response has been received but has not been completely reviewed.

## 3.2 Compliance with Good Clinical Practices

There are three phase 3 studies submitted to support the indication (studies/trials 301, 302, and 303). All were conducted outside of the United States. Bial is the original sponsor of this drug product. Sepracor is the U.S. sponsor of this drug product and the Sponsor of this NDA. Sepracor conducted GCP site audits of 38 clinical sites (34 were reported as per July, 2009 and an additional four as per October, 2009). This includes, but is not limited to, phase 3 epilepsy studies. These audits included an examination of the accuracy of AE reporting. The sponsor concluded that clinical site audits for the phase 3 studies 301 and 302 were conducted in compliance with GCP and that the data are reliable and can support an NDA

Sepracor believes there are sufficient Good Clinical Practice (GCP) issues to consider study 303 only as secondary support for efficacy and supportive of safety, although not to be relied upon formally. Sepracor notes that sites in Mexico in study 303 were "determined to be non-compliant with Good Clinical Practices" (1st clinical overview, p.52/75) with audits of sites in Mexico showing significant GCP deficiencies. These findings were consistent with findings previously seen during audits conducted by BIAL (the original sponsor and owner of the rights in some areas outside of the U.S) (p.64/75 of referenced document).

Sepracor argues, essentially, that within study 303, significant non-compliance problems are limited to one Clinical Research Organization that was responsible for only sites in Mexico. There was, however, evidence of GCP compliance issues at two sites outside of Mexico (Spain and Portugal) in study 303 that Sepracor characterized as of "less overall significance" (p. 64/75 clinical overview document in SDN 000). This was a critical point to confirm. If flagrant GCP issues are contained to one country and one clinical research organization, then the argument that "damage" to data integrity in trial 303 is not an indicator of systemic problems with the other trials is more convincing.

The sponsor believes that safety data from the sites "may be relevant to NDA review" and can be used supportively.

Of interest, the sponsor notes that study 201 (phase 2 epilepsy contributing safety data) was audited by Sepracor (5/19 sites), although not by original sponsor (Bial). There were GCP deficiencies noted at two of the five audited sites (p.64/75 of clinical overview). The sponsor describes these observations as involving informed consent and documentation regarding qualification for enrollment. The sponsor also reports that documentation existed during the study that indicates the subjects did qualify for enrollment and concludes that these deficiencies indicated less than full GCP compliance but do not adversely impact the ability to fully utilize study data.

For study 303, the sponsor summarized the issues at the Mexican sites as including:

1) improper activities relating to study conduct (PI oversight)
2) inappropriate enrollment of randomized subjects
3) data integrity issues (absence of certain source documents to verify/support data entered onto CRFs)
4) failure to "consistently (prospectively) assure subject safety" and control of the investigational product (p. 64/75 clinical overview)

On 6-18-09, the sponsor submitted summary sheets of the audits in Spain (site 611) and Portugal (site 501) (saf-info-amend.pdf). The summary for site 611 (Spain-enrolled 6 subjects in part 1) indicates the records of six subjects were reviewed. Issues include compliance (source documents for 2/6 subjects did not record that they were on a stable dose of AEDs for at least 2 months prior to study, although CRFs indicate the requirement was met), drug accountability logs were not maintained for any subject with

drug accountability data recorded in the worksheets and CRFs, and for 6/6 subjects seizure diaries were not reviewed by staff until "well after " the relevant visit with some reviews a month or more after the visit. The summary notes that diaries "could be correct" and the auditor viewed them as credible. Other findings included that for two of six subjects, a potential AE was noted in the source document but not recorded in the CRF. For one of six subjects, a death was not submitted by the site to the sponsor for 58 days after the investigator completed the SAE form. For this site, good documentation practices were not generally employed with most source document entries not dated and many not signed.

The summary for site 501 (Portugal-enrolled 16 subjects in part 1) indicates that 9 subjects were audited for data review and 16 for consent. Source documents for 2 of 9 did not record eligibility criteria for physical/neurological exam at visit 1, although CRFs indicated these systems were reviewed and the requirement met. Issues of data integrity included that for 4 of 9 subjects reviewed, a potential AE was noted in the source document but not recorded in the CRF. For 6 of 9 subjects, some discrepancies were noted between source document worksheets and CRFs for items such as medical history, BP values, stop dates for AED usage, date of last dose of study drug prior to clinic visit. Confirmation letters for 4 monitoring visits and follow-up letters for 6 monitoring visits were not in the Regulatory Binders and not in other document folders at the site. The audit report indicates that for subject 3149 (=70045), the visit 2 CRF indicated 3 seizures for weeks -8 to -5 and 9 for weeks -4 to -1, however "the CRF was later changed to indicated 6 seizures in each of the 4-week periods". The diary returned indicates 3 and 9 seizures respectively, making the subject not eligible based on exclusion criterion #8. The audit notes that although the diary pages were submitted with the CRF pages, this eligibility issue was not queried by Data Management. This was one of the findings regarding inclusion/exclusion criteria. As a group, inclusion/exclusion criteria were considered an area of significant non-compliance.

Otherwise, in each study report of the epilepsy trials 201, and part 1 of studies 301, 302, and 303, there is a statement that essentially is some adaptation of stating that the trial was conducted according to the study protocol under the consideration of ICH-GCP guidelines (E6 noted for study 302 part 1), the Declaration of Helsinki, and, local laws/other applicable regulations.

FDA:

FDA took several actions to try and evaluate the quality of the phase 3 trial data such as inspections by FDA Division of Scientific Investigations (DSI) and requesting copies of audit forms from sponsor-conducted audits.

A total of four sites were inspected; two from study 301 and two from study 302. FDA's Division of Scientific Investigations (DSI) completed inspections and consider data at two sites (one from each study) as not reliable. In addition, DSI evaluated audit forms submitted by the sponsor to the NDA. DSI reports that audits revealed multiple issues:

"a broad range of violations regarding subject safety, inclusion criteria, poor source documentation, discrepancies between source documents and case report forms in terms of adverse events, use of concomitant medications, and inadequate drug accountability records suggesting a systemic problem across all three studies (301, 302, and 303)."

Audit forms were submitted by the sponsor. I examined them in an exploratory fashion (7-13-09 submission) with formal review by DSI. There are significant limitations in trying to evaluate and reconstruct data from a distance and so long after a trial is completed.

Study 201 (phase 2 epilepsy) audit reports are discussed below as are study 303. The purpose of mentioning study 201 is to highlight that these data are included in the safety dataset and that the audit forms may require further evaluation due to this. The purpose of describing 303 audit summary information is to give an indication as to the nature of findings in this study.

Study 201: Bial audited no sites in the phase 2 epilepsy study (study 201). Sepracor audited 5 sites. All of the audit forms for study 201 document at least one area considered as significant non-compliance. "Major findings" are described as one or more findings considered significant deviations from GCP and/or study requirements but in general do not *de facto* indicate that site data should not be used and that this is evaluated on a case-by-case basis. Sepracor states this rating category likely corresponds to an FDA classification of "VAI". "Minor Findings" are described as one or more findings that are not in full GCP compliance and/or study requirements but if limited in scope, not systemic, and in areas that do not adversely impact subject safety or data utility. Sepracor states this category likely corresponds to an FDA "NAI". The sponsor's summary of audit findings in the referenced submission states that Sepracor audited 5 sits (via (b) (4)) and that 2 were classified as "Major Findings" (sites 5 and 6, both in the Czech Republic) and 3 were classified as "Minor Findings". Sepracor states that in their evaluation, site 5 was generally not compliant but that the scope and nature of deficiencies did not preclude using the data from the site. Sepracor states that the GCP deficiencies observed for the 2 sites with major findings, while problematic, "were not highly systemic and/or did not involve areas of GCP that led to an adverse impact on the utility of the data" (p23/56, 7-13-09 multi-mod-info-amend.pdf).

Study 303 audit findings are summarized by the sponsor as having "highly systemic GCP deficiencies that, in our view, affect the utility of the efficacy data in particular" (p. 24/56, 7-13-09 document). The main finding is described as not maintaining adequate records (patient diaries and other source documents) of baseline seizure frequency. The sponsor describes other "notable" findings as involving "inadequate oversight of study conduct by the principal investigators and serious, systemic deficiencies in study documentation (source documentation versus CRFs and drug accountability)." (p.24/56).

Sponsor summaries of audit findings are provided for seven sites in Mexico, two in Portugal, and one in Spain. Of the seven sites in Mexico, the sponsor states six were found to be "noncompliant" with all of these sites described as having systemic issues that included either drug accountability, poor documentation or both. One of these seven is specifically noted has having systemic deficiencies involving laboratory and EKG testing. The one of seven site audits that is not labeled with the word "noncompliant" sounds very questionable. The audit was of site 707 and covered 3 of 13 enrolled subjects. The summary includes that "the PI reportedly did not ask subjects if they had experienced AES between clinic visits" (p.25/31), records of baseline seizure frequency were missing, and drug accountability was not performed.

For the two sites from Portugal, Sepracor considered one as having "major findings'. One of the listed reasons is the number of AES not recorded in CRFs and the nature of the data entry discrepancies in part 2 data. Sepracor "did not conclude that the data from this site does not have utility" (p. 39/56). For the other site in Portugal, the auditor recommended that the CRO provide closer insight. Source documentation was noted to be incomplete in data entry. The site in Spain was classified as having "major findings" which the sponsor attributes mostly to the absence of timely reviews of subject diaries, late reporting of an SAE, and the number of AES not recorded in CRFs. These were deficiencies were considered to be systemic but Sepracor notes that "We did not conclude that the data from this site does not have utility." (p.40/56).

DSI notes that the audit forms submitted do not assure confidence in the data as the audits do not appear to be sufficient in scope and detail to allow for an adequate assessment to determine data reliability. This reviewer notes that Sepracor and/or Bial audited four of the same four sites that FDA audited. FDA and Sepracor's conclusion are different for two of those four sites. The disparity between Sepracor's conclusions and FDA's may be explainable but does not provide this reviewer with confidence that Sepracor's audits and/or conclusions based on the audits can be assumed dependable.

## 3.3 Financial Disclosures

The compliance document notes that in accordance with 21 CFR 54, all PIs and subinvestigators, except for those noted in Table 2, listed on the signed Forms FDA 1572 for Bial-Portela & C, S.A. for the phase 3 clinical trials 301, 302, and 303, referenced in this NDA, have submitted signed disclosure statements indicating the extent, if any, to which they received compensation in any of the four categories described, as per the submission, below. Also, the investigator agreed to contact Bial-Portela & C, S.A. if any of the above changed during the course of the clinical trial or up to one year after completion. The investigators were to certify whether any of the categories were held, and in what amount, by the spouse or dependent children. The categories are described as per the financial-cert.pdf in the initial NDA submission.

**Category 1:** Financial arrangement in which the value of the compensation could be influenced by the trial outcome. This was to include, as an example, compensation that is explicitly greater for a favorable outcome or in the form of equity interest in the sponsor or compensation tied to the sale of the product.

**Category 2:** Significant payment of other sorts, excluding trial costs. For example, this might be payments made to the investigator or institution to support activities that have a monetary value > $25,000 (i.e., grant for ongoing research, paying for equipment, or retainers for ongoing consultation or honoraria).
**Category 3:** Proprietary or financial interest in the test product, such as patent, trademark, copywriting, or licensing.
**Category 4**: Significant equity interest in the sponsor of the trial. This would include, as examples, any stock options, or other financial interest whose value cannot be easily determined through references to public prices, or any interest publicly traded >$50,0000.

The initial financial disclosure document in the March, 2009 submission included a table that listed the names of 11 investigators for whom financial disclosure information was not available (10 sub-investigators and one principal investigator). Outside of the missing information noted above, Bial-Portela & C, S. A. certified that to the best of the company's knowledge, no investigators or subinvestigators received compensation for Categories 1 and 3 or compensation beyond "the acceptable limits for Categories 2 ($25,000) and 4 ($50, 000). Sepracor noted that, as the sponsor, they made no dispersement to any clinical investigator involved in the Eslicarbazepine acetate clinical development program.

Some investigators were not included in the initially submitted NDA financial disclosure document. This includes, but is not limited to, investigators the sponsor had identified as being unable to obtain disclosure information and some (7) that I identified by comparing the lists of investigators in the document tabular-listing.pdf with the investigator names in the document financial-cert.pdf. An inquiry requesting additional information was sent as part of the filing letter.

The sponsor responded on 7-31-09. Financial disclosure information remains missing for one principal investigator (site 422- Dr. Perju-Dumbrava Lacramioara and also for the site's sub-investigator, (b) (6)), however, the response states this site was closed prior to patient enrollment. Financial disclosure information is still missing for nine other subinvestigators (5 at Dr. O'Brien's site in study 302, 3 at Dr. Ojeda-Chavarria's site in study 303, and one at Dr. Rangel Guerra's site in study 303). As I understand, it is not necessary from a regulatory point-of-view to have sub-investigator financial disclosure information although it is necessary to have principal investigator information. Otherwise, the Sponsor's 7-31 document reports for all of the principal investigators listed in the tabular listing document submitted in March, 2009. Each investigator has a "zero" ($) in each of the categories of disclosure (7-31-09 submission).

Based on information in the 7-31-09 response and the stated understanding of financial disclosure requirements, financial disclosure appears acceptable.

*Reviewer's note: There were a few differences in presentation, such as spelling and reversing the order of names between the investigators in the tabular listing of investigators when compared to the financial certification documents (site numbers are not in the financial certification document, so verification could not be performed using*

*this). For example, the name* (b) (6) *is in one listing but the name is spelled* (b) (6) *in the other document and for one investigator the first name in one document is the last name in the other and one of the names is spelled different* (b) (6)

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Chemistry, Manufacturing, and Controls (CMC) review was performed by Dr. C. Jewell with supervisory signature of Dr. R. Sood. CMC review dated 3-3-10 recommends approval pending resolution of labeling recommendation. (b) (4) CMC recommends that the applicant change the labeling represented on the draft carton and container labels to show the established name eslicarbazepine acetate in parentheses so that the tradename will be linked to this instead of to eslicarbazepine acetate tablets.

## 4.2 Clinical Microbiology

Not applicable

## 4.3 Preclinical Pharmacology/Toxicology

Primary pharmacology-toxicology review was performed by C. Toscano, Ph.D. His review has not been signed off at supervisory levels as of the writing of this section of the review, therefore, the following should be considered preliminary.

Dr. Toscano indicates the major non-clinical issues are carcinogenicity (hepatocellular adenoma and carcinoma) and teratogenicity (cleft palate disorders in mice and rabbit). Dog laboratory values also showed an increase in aPTT.

## 4.4 Clinical Pharmacology

Formal FDA review of the clinical pharmacology data was performed by the Office of Clinical Pharmacology (OCP) review team. The reader is referred to this review for detailed discussion of pharmacokinetic information and recommendations made by clinical pharmacology.

OCP review notes that the extent of systemic exposure is increased by 62%, 116%, and 154% in mild, moderate, and severe renal impairment, respectively as compared to healthy subjects. OCP recommends

- dose reductions in patients with moderate and severe renal impairment. (b) (4) [redacted] The OCP reviewer recommends the following (copied from OCP review), if the clinical impact of QOD dosing will be minimal for the first 2 weeks of treatment. The OCP reviewer notes an alternate consideration would be the development of a 200 mg tablet in the future as a phase 4 requirement.

| Dosing Recommendations | Normal (Clcr >80 ml/min) | Mild (Clcr 50-80 ml/min) | Moderate (Clcr 30-49 ml/min) | Severe (Clcr 15-29 ml/min) |
|---|---|---|---|---|
| Initial | 400 mg QD<br><br>Weekly increments to the next dose | 400 mg QD<br><br>Weekly increments to the next dose | 300 mg QD<br><br>Weekly increments to the next dose | 200 mg QD<br><br>Weekly increments to the next dose |
| Maximum | 1200 mg QD | 1200 mg QD | 600 mg QD | 600 mg QD |

- monitoring of patients on warfarin with dose titration to maintain INR
- additional or alternative non-hormonal birth control
- decrease of phenytoin dose
- no dose adjustment of lamotrigine, topirimate, carbamazepine, valproate, levetiracetam, or gabapentin when used with eslicarbazepine
- the possibility of need for higher eslicarbazepine doses when used with phenytoin, carbamazepine, and phenobarbital. This recommendation was not made with respect to lamotrigine, topirimate, levetiracetam, or gabapentin.

### 4.4.1 Mechanism of Action

Eslicarbazepine acetate (SEP-0002093) is a voltage-gated sodium channel blocker designed as a third generation enantiomer of the family dibenz [b,f/] azepine antiepileptic drugs. A mechanism of action in epilepsy is not known.

### Pharmacodynamics

Information below is taken from the OCP review.

- No dose adjustment was recommended by OCP for the elderly if the patient's creatinine clearance is ≥ 50 ml/min.
- No dose adjustment is recommended based on gender.
- No dosage adjustment is recommended between Caucasian, Black, and Hispanic patients based on race/ethnicity. OCP review states that the PK of

eslicarbazepine was not affected by race based on population analysis. There were too few Asian subjects to make a comparison (n=6).

- Dose recommendations are made for patient with moderate and severe renal impairment. The AUC0-∞ increased by 62% in mild renal impairment, 2-fold in the moderate renal impairment group, and 2.5-fold in the severe renal impairment group following a 800 mg single dose. The relative proportion of active moieties remained "reasonably similar' in the different groups corresponding to about 92-94% of systemic exposure. The reviewer proposed maximum daily doses of 1200 mg in normal and mild renal impairment and 600 in moderate and severe renal impairment. Initial dosing of 400 mg daily for one week for normal and mild renal impairment, 300 mg daily for 1 week for moderate renal impairment, and 200 mg daily for 1 week for severe renal impairment.
- Dosage adjustment not recommended as necessary for subjects with moderate hepatic impairment. Subjects with severe hepatic impairment were not studied.
- Labeling recommendations from an OCP perspective regarding interactions between ESL and other AEDs are made. OCP label recommendations note that co-administered carbamazepine and phenobarbital may need higher dose of ESL. For co-administered phenytoin, may need higher dose of ESL and adjusting of phenytoin dose based on individual response. No dose adjustments are recommended for concomitant valproate, lamotrigine, topirimate, levetiracetam, and gabapentin.
- Labeling recommendations from an OCP perspective regarding interactions between ESL and other drugs are dose adjustment recommendations for warfarin and oral contraception and no dose adjustment for metformin or digoxin.

## Pharmacokinetics

Information from OCB (email dated 1-21-10) indicates that the proportion of S-licarbazepine and R-licarbazepine following oral administration of eslicarbazepine acetate is 21:1. When oxcarbazepine is administered orally, the ratio of S to R-licarbazepine is 4:1.

The OCB review summarizes the pharmacokinetics as follows:

- SEP-0002093 or eslicarbazepine acetate is a prodrug of eslicarbazepine. After oral intake, plasma concentrations of the prodrug usually are not detectable and the major metabolite is formed rapidly [(S)-licarbazepine or eslicarbazepine].
- Cmax is at 1-4 hours after dosing. T1/2 is 10-20 hours for healthy subjects and 13-20 hours for adults with epilepsy.
- PK is linear and dose-proportional in the range of 400 to 1200 mg daily in both healthy subjects and patients with epilepsy.
- Food has no effect on PK.
- Bioavailability is assumed to be high because the amount of active metabolites recovered in urine corresponded to > 90% of the SEP-0002093 dose.
- The binding of eslicarbazepine to plasma proteins is relatively low (<40%).

- Tissue distribution is extensive (high apparent volume of distribution)
- Metabolism of SEP-0002093 is rapid and mainly to eslicarbazepine by first-pass metabolism in the presence of hydrolase. Eslicarbazepine is 91% of the circulating drug entities (using AUC0-24) and 95% of the sum of the active components. (R)-licarbazepine and oxcarbazepine are minor metabolites at 4% and <1% each. There are other metabolites that are pharmacologically inactive.
- SEP-0002093 is eliminated primarily by renal excretion in the unchanged (2/3) and glucuronide conjugate forms (1/3).
- Renal clearance in healthy subjects was about 20 mL/min. This is much lower than the glomerular filtration rate of 80-120 mL/min which suggests renal tubular reabsorption.
- Renal impairment-eslicarbazepine exposure is increased as described above. Tmax was about 1 hour post-dose in mild renal impairment and 3 hours post-dose in moderate and severe renal impairment. The half-life was similar between the normal and mild renal impairment groups (about 11 hours) but significantly increased t o18 and 28 hours in the moderate and severe renal impairment groups respectively. Repeated hemodialysis was effective in removing SEP-0002093 metabolites from the systemic circulation.
- Hepatic impairment-moderate hepatic impairment did not affect the PK of eslicarbazepine. OCP review indicates dosage adjustment is not necessary. PK of eslicarbazepine in subjects with severe hepatic impairment has not been studied.
- Effects of eslicarbazepine on the PK of other drugs: eslicarbazepine is not a substrate of CYP isoenzymes and is not an inducer of oral contraceptives and phase II enzymes for glucuronidation and sulfation. Eslicarbazepine is an inhibitor of CYP2C19. OCP notes that there is a 23% reduction in S-warfarin AUC, 37% and 42% reductions in ethinylestradiol AUC and levonorgestrel AUC respectively, and a 37% increase in phenytoin AUC.
- Phenytoin decreases ESL AUC by 37%. Carbamazepine and phenobarbital increase ESL CL/F by 11-32% and 26% respectively.

# 5 Sources of Clinical Data

As per the ISS Table 5.5-1, there were two phase 1, healthy volunteer studies conducted in the US (Study 116 (QT) and study 118). All other phase 1 healthy volunteer studies reported in the referenced table were conducted either in the United Kingdom, Portugal, Germany, or Canada. All pivotal trial data are foreign. Discussion of this follows the tables of studies/clinical trials below. I chose this section of the review because it seemed the best place in the template to include both the safety and efficacy issues with regard to foreign data comparability versus placing these discussions separately in safety and efficacy sections of the review.

All information reviewed came from the Sponsor in either the initial submission or subsequent submissions (supporting document numbers 0 – 34) and may be found in the FDA electronic document room under NDA 22416.

The sponsor submitted two integrated summaries of safety, one with the initial submission (ISS) and one with the 120-day safety update (SU). The cut-off date for the ISS was about one year before submission of the NDA and was 2-28-08. At that time there were 22 completed phase 1 studies, 5 phase 2 studies, and 3 phase 3 studies in epilepsy. On 8-28-09, the sponsor submitted the 120-day safety update. This document was to provide data for the time period between the ISS and March 30, 2009. The SU included information from 5 recently reported trials (123, 125, 126, parts 2 of 302 and 303). Given the GCP problems in study 303, the SU re-presented safety data from the phase 3 epilepsy trials showing comparison of combined studies 301-302 data to study 303. Additionally, due to an error in the ISS, tables in the SU were updated to include 59 events that occurred in part one of the phase 3 studies but were not included as part one data in the ISS.

Submissions SDN 4, 6, 7, 10, 11, 13, 24, 27, 30, 31, and 33 contain data integral to safety assessment either by evaluation of the data through audits or through content. Several submissions contained information for the clinical reviewer to be aware of (for example, SDN 5, 6, 9, 10) which may be useful to the review but were technically responses to other disciplines. Submissions containing REMS included SDN 18, 22, and 25.

*NOTE: Secondary to review time constraints and data quality issues, multiple submissions have not been reviewed or not been completely reviewed. This lack of review has been discussed with Division management. Please see the review strategy section.*

## 5.1 Tables of Studies/Clinical Trials

As per the 120-day safety update, there were 33 completed studies in the development program. Of these, 25, were phase 1 studies, five were phase 2, and 3 were phase 3. Also as per the SU, there are fifteen ongoing studies. This includes extensions of two of the phase 3 epilepsy studies (301-parts 3 and 4, 302-part 2). Completed phase 2 development was in epilepsy (1 adult and 1 child) and bipolar disorder (3 studies). All completed phase 3 development has been in adults with partial onset seizures.
Data from completed, human studies were reviewed for deaths, non-fatal SAEs, and discontinuations secondary to an adverse event. For efficacy purposes, the review focused on two of the 3 adult epilepsy studies although the efficacy results, as presented by the sponsor, from a third adult study (study 303, a study considered by the sponsor to be not “sufficiently” compliant with GCP) were briefly reviewed as were the phase 2 epilepsy study results (study 201).

As per information in the safety update of 8-28-09, Table 1.2-1 (clinical summary of safety document), there were 2076 unique subject exposures. Table 1.2-1 shows patient enumeration for the patients in the safety database of the initial NDA (SU Clinical Summary of Safety). The highlights reflect changes since the initial NDA submission of March, 2009. The table does not include ongoing studies or studies that were clinically completed but not reported (e.g., studies 206 and 207). These are included a separate table that follows the duplicated sponsor-table, Table 1.2-1.

**Table 1.2-1: Enumeration of Subjects in All Studies (Parts 1 and 2 of 2093-301 to 2093-303; ~~Part 2 of 2093-301,~~ 2093-201 to 2093-205; ~~and~~ 2093-101 to 2093-~~122~~123, 2093-125 and 2093-126) (Safety Population)**

| Study Type<br>Study Number | Placebo<br>N | ESL<br>N | Active Control<br>N | Total<br>N |
|---|---|---|---|---|
| Overall Unique Subjects[a] | ~~501~~527 | ~~1667~~ 1893 | ~~250~~289 | ~~2010~~2076 |
| Phase III Epilepsy Studies | 289 | ~~840~~ 1001 | 0 | 1049 |
| 2093-301 Part 1 | 102 | 300 | 0 | 402 |
| 2093-301 Part 2[b] | 0 | 314 | 0 | 314 |
| 2093-302 Part 1 | 100 | 295 | 0 | 395 |
| 2093-302 Part 2 | 0 | 325 | 0 | 325 |
| 2093-303 Part 1 | 87 | 165 | 0 | 252 |
| 2093-303 Part 2 | 0 | 196 | 0 | 196 |
| Phase II Epilepsy Studies | 47 | 127 | 0 | 174 |
| 2093-201 | 47 | 96 | 0 | 143 |
| 2093-202 | 0 | 31 | 0 | 31 |
| Phase II Bipolar Disorder Studies | 51 | 252 | 0 | 303 |
| 2093-203 | 40 | 121 | 0 | 161 |
| 2093-204 | 11 | 27 | 0 | 38 |
| 2093-205 Part 1[c] | 0 | 104 | 0 | 104 |
| 2093-205 Part 2[c] | 0 | 87 | 0 | 87 |
| Phase I Studies | ~~115~~ 141 | ~~532~~ 597 | ~~255~~ 294 | ~~596~~ 662 |
| 2093-101 | 16 | 48 | 0 | 64 |
| 2093-102 | 8 | 24 | 0 | 32 |
| 2093-103 | 0 | 12 | 0 | 12 |
| 2093-104 | 0 | 12 | 13 | 13 |
| 2093-105 Phase A (Elderly/Young) | 0 | 29 | 0 | 29 |
| 2093-105 Phase B (Elderly/Young) | 0 | 28 | 0 | 28 |
| 2093-106 Phase A | 0 | 4 | 4 | 4 |
| 2093-106 Phase B | 4 | 4 | 4 | 4 |
| 2093-107 | 13 | 13 | 13 | 13 |
| 2093-108 Phase A | 0 | 0 | 15 | 15 |
| 2093-108 Phase B | 0 | 13 | 13 | 13 |
| 2093-108 Phase C | 0 | 0 | 13 | 13 |
| 2093-109 | 0 | 18 | 0 | 18 |
| 2093-110 | 0 | 12 | 11 | 12 |
| 2093-111 (Hepatic) | 0 | 17 | 0 | 17 |
| 2093-112 (Renal) | 0 | 40 | 0 | 40 |
| 2093-113 Phase A | 6 | 12 | 0 | 18 |
| 2093-113 Phase B | 6 | 12 | 0 | 18 |
| 2093-114 | 0 | 19 | 18 | 20 |
| 2093-115 Phase A | 0 | 8 | 24 | 32 |
| 2093-115 Phase B | 0 | 8 | 22 | 30 |
| 2093-116 | 64 | 66 | 62 | 67 |
| 2093-117 | 0 | 18 | 0 | 18 |
| 2093-118 | 4 | 12 | 0 | 16 |
| 2093-119 | 0 | 31 | 32 | 32 |
| 2093-120 | 0 | 32 | 31 | 32 |
| 2093-121 | 0 | 32 | 32 | 32 |
| 2093-122 | 0 | 60 | 0 | 60 |

Table xx

| Completed PHASE 1 | | | | | |
|---|---|---|---|---|---|
| **PK/Toler-ability and Safety** | **BA Food Effect** | **Comparative BA/BE** | **PK/PD** | **Special Populations** | **Drug-drug interactions** |
| 2093-104 | 2093-103 | 2093-109 | 2093-101 SAD (EEG) | 2093-111 (hepatic impairment) | 2093-107-digoxin |
| 2093-110 | 2093-117 | 2093-122 | 2093-102 MAD (EEG) | 2093-112 (renal impairment) | 2093-108-warfarin |
| 2093-115 | | 2093-127 CSF v plasma ESL and OXC | 2093-116 (QT) | | 2093-114-combined contraceptive |
| | | | | | 2093-128 combined contraceptive |
| 2093-113 | | | 2093-123-PD healthy volunteers | | 2093-119-lamotrigine |
| 2093-118 (MTD) | | | | | 2093-120-topiramate |
| 2093-105 (elderly included) | | | | | 2093-106-phenytoin |
| | | | | | 2093-121-phenytoin |
| | | | | | 2093-124 simvastatin |
| | | | | | 2093-125-metformin |
| | | | | | 2093-126-gliclazide |

| Completed PHASE 2 | |
|---|---|
| **Epilepsy** | |
| **Children/adolescents POS** | **Adults POS** |
| 2093-202 (OL-PK and tolerability) **0 placebo and 31 ESL** | 2093-201 (DB, PC) **47 placebo and 96 ESL** |
| **Bipolar** | |
| 2093-203 (acute mania) | |
| 2093-204 (acute mania) | |
| 2093-205- extension of 203 and 204-recurrence of bipolar, 2 part study | |
| **Phase 2 Epilepsy Planning** | |
| **2093-208 – POS** ages 6-16, assess cognitive function | |
| **Phase 2 Other Indications** | |
| 2093-206-**Diabetic Neuropathy**- clinically completed (11-18-08) but not reported as of 3-30-09 | |

| |
|---|
| 2093-207 **Post herpetic Neuralgia**-clinically completed (1-19-09) but not reported as of 3-30-09 |
| 2093-209 **Migraine-** ongoing |
| 2093-210 **Fibromyalgia-** ongoing |
| **Completed PHASE 3 Epilepsy (some ongoing extensions)** |
| 2093-301-parts 1 &2 completed and reported, part 3 "clinically complete" ( 6-27-08) not reported as of 3-30-09, 301-part 4, ongoing |
| 2093-302-parts 1 and 2 completed and reported, part 3 ongoing |
| 2093-303-parts 1 and 2 completed and reported |
| **Phase 3 Ongoing or planning** |
| 2093-304 **Adults, adjunctive use, POS** parts 1 ongoing |
| 2093-305 **Children, adjunctive use**, POS part is 2 ongoing |
| 2093-401 **Elderly, adjunctive use, POS** planning |
| 2093-311-planning |
| |

Table data from tabular listing submitted 1-25-10. POS=partial onset seizures, SAD=single ascending dose, MAD=multiple ascending dose, EEG=electroencephalogram, OL=open label. Study 311 information from xx.

**Foreign Data-Comparability to US data:**

Traditionally, epilepsy trials of AEDs approved in the US contain some US data. This application is all non-US (except some phase 1). In general, this raises issues of the comparability of the population, of the culture and practice of medicine, and of the culture and practice of assessing safety and efficacy. As noted, for this application, the large majority of clinical trials were conducted outside of the IND, which can mean that less discussion of trial design and practice occurred during development. Additionally, Sepracor noted that one of three of the phase 3 trials has significant enough quality issues such that Sepracor believes the trial can be used only in a supportive capacity. Although Sepracor posits that the significant issues in quality were limited to sites in Mexico and to one CRO responsible for sites in Mexico, it is not clear to this reviewer that this is the case. This is discussed elsewhere in this review.

In addition to a lack of US data, only about 25% of the efficacy data in the pivotal trials come from countries grouped by the sponsor as "Western Europe/Rest of the World". Western Europe and the Rest of the World include Australia, Austria, Belgium, Denmark, Germany, Portugal, South Africa, Spain, Sweden, Switzerland, The Netherlands, and the United Kingdom. The other geographic regions are Eastern Europe (Czech Republic, Croatia, Hungary, Lithuania, Poland, Romania, Russia, and the Urkraine), Latin America (Mexico, Argentina, Brazil), and Latin America excluding Mexico.

The pre-NDA meeting minutes from the meeting held on 1-23-08, indicate the applicability of the foreign data to the US population was discussed. FDA indicated that it was unusual for this Division to receive applications in which the phase 3 studies are completely non-domestic. FDA noted that the NDA should address the comparability of the practice of medicine in the countries participating in the studies to US practice

including the possible use of concomitant medications not marketed in the United States. FDA noted that as data quality might vary between different international regions, it was hoped a "sizable" portion of the population is derived from Western European countries. FDA noted that, "An additional efficacy study or studies including a significant portion of the patient population from the US would be desirable to confirm the findings of these non-US studies. The non-IND European pediatric study (BIA-2093-305 in Attachment 5) now in progress and the monotherapy study discussed in Question 6-c could potentially serve this purpose. "

The sponsor addressed data comparability in several places including the ISS-section 19.5.3 2), the clinical summary of efficacy, sections 1.4.5, 3.3.2.5, 3.5.5, and section 6, and the Clinical Overview document of initial submission, section 6.

**Sponsor's assessment of applicability of safety results to US patient population:**

The ISS notes that to demonstrate relevance to US populations, the following three areas of safety were examined:

- GCP audit examining accuracy of adverse event reporting
- Definition of adverse experiences and how they were reported within each protocol
- Comparison of placebo rates for ESL's most common adverse events

Sepracor conducted GCP site audits of the ESL Phase 3 studies (2093-301, 2093-302, and 2093-303) that included an examination of the accuracy of adverse event reporting. The company reports that clinical site audits for the Phase 3 studies 2093-301 and 2093-302 found that the studies were conducted in compliance with GCP and that data are reliable and acceptable to support the NDA submission for review. The audits at clinical sites for study 303 determined the study was not "sufficiently compliant" to be relied upon in a formal manner for conclusions of safety and efficacy. The company views this study as supportive. This is described elsewhere in this review.

AE reporting:
The definition of adverse events and how they were reported within each protocol were examined to confirm the integrity and reliability of e clinical data. The definition of adverse events was identical in the Phase 3 epilepsy studies. The company states that adverse events were defined and reported in accordance with the standards identified in the ICH Good Clinical Practice Guidelines and the mechanism for handling expedited reporting was also in accordance with ICH GCP guidelines. The company concludes that adverse events were collected in a manner that is consistent with the requirements for studies that are conducted in the US. The sponsor did not compare and contrast reporting rates for non-fatal SAEs, discontinuations secondary to AEs, and deaths. This information was requested.

Comparison of placebo rates from ESL's most common AEs with the 5 most recently approved AED products:

The company compared placebo rates of treatment emergent common adverse events from the last five AEDs approved in the US for same indication (adults as adjunctive treatment for partial onset seizures) with ESL.

**Table 19.5.3-1: Placebo Rates for ESL Most Common TEAEs Compared with Placebo Rates for the 5 Most Recently Approved AEDs for Use as Adjunctive Treatment for Partial-Onset Seizures in Adults with Epilepsy**

| TEAE | ESL % of Placebo Subjects | Vimpat % of Placebo Subjects | Lyrica % of Placebo Subjects | Zonegran % of Placebo Subjects | Trileptal % of Placebo Subjects | Keppra % of Placebo Subjects |
|---|---|---|---|---|---|---|
| Dizziness | 7 | 8 | 11 | 7 | 13 | 4 |
| Somnolence | 9 | 5 | 11 | 7 | 12 | 8 |
| Headache | 9 | 9 | NA | 8 | 23 | 13 |
| Nausea | 2 | 4 | NA | 6 | 10 | NA |
| Vomiting | 2 | 3 | NA | NA | 5 | NA |
| Diplopia | 2 | 2 | 4 | 3 | 5 | 1 |

Abbreviations: NA=not applicable; TEAE=treatment emergent adverse event.
Reference: ISS EOT Table 7.4.1 and http://www.drugs@fda.gov.

The company states that when incidence rates of these common AEs were compared by region for the pooled phase 3 studies, the rates observed for Latin America and Western Europe/ROW were comparable to studies conducted in the US with other agents and that data from these regions represent about 2/3 of the overall NDA data. In an analysis with and without Mexico, three additional adverse events (pyrexia, tremor, and fatigue) met the criteria for ≥ 2% and > placebo.

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**Table 19.5.2-1: Treatment Emergent Adverse Events by Geographic Region for the Pooled Phase III Epilepsy Studies (Part 1 of 2093-301, 2093-302, and 2093-303) (Safety Population)**

| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | Placebo (N=289) | | | | Total ESL (N=760) | | | |
|---|---|---|---|---|---|---|---|---|
| | Eastern Europe[b] (N=97) Subjects n (%) | Latin America[c] (N=109) Subjects n (%) | Latin America without Mexico (N=55) Subjects n (%) | Western Europe /ROW[d] (N=83) Subjects n (%) | Eastern Europe[d] (N=284) Subjects n (%) | Latin America[c] (N=264) Subjects n (%) | Latin America without Mexico (N=159) Subjects n (%) | Western Europe /ROW[d] (N=212) Subjects n (%) |
| AT LEAST 1 TEAE | 31 (32.0) | 54 (49.5) | 37 (67.3) | 49 (59.0) | 148 (52.1) | 179 (67.8) | 129 (81.1) | 162 (76.4) |
| Common TEAE | | | | | | | | |
| Diplopia | 0 | 2 (1.8) | 2 (3.6) | 3 (3.6) | 18 (6.3) | 24 (9.1) | 23 (14.5) | 15 (7.1) |
| Dizziness | 2 (2.1) | 13 (11.9) | 7 (12.7) | 6 (7.2) | 30 (10.6) | 87 (33.0) | 63 (39.6) | 49 (23.1) |
| Headache | 6 (6.2) | 12 (11.0) | 7 (12.7) | 7 (8.4) | 25 (8.8) | 36 (13.6) | 29 (18.2) | 23 (10.8) |
| Nausea | 1 (1.0) | 4 (3.7) | 3 (5.5) | 1 (1.2) | 14 (4.9) | 23 (8.7) | 17 (10.7) | 22 (10.4) |
| Somnolence | 2 (2.1) | 19 (17.4) | 14 (25.5) | 6 (7.2) | 28 (9.9) | 45 (17.0) | 30 (18.9) | 27 (12.7) |
| Vomiting | 1 (1.0) | 5 (4.6) | 3 (5.5) | 1 (1.2) | 8 (2.8) | 22 (8.3) | 15 (9.4) | 13 (6.1) |
| AT LEAST 1 POTENTIALLY RELATED TEAE | 15 (15.5) | 43 (39.4) | 30 (54.5) | 41 (49.4) | 104 (36.6) | 166 (62.9) | 124 (78.0) | 147 (69.3) |
| AT LEAST 1 SEVERE TEAE | 3 (3.1) | 7 (6.4) | 5 (9.1) | 3 (3.6) | 10 (3.5) | 36 (13.6) | 29 (18.2) | 29 (13.7) |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; ROW=rest of world (Australia and South Africa; TEAE=treatment emergent adverse event.
a Reported AE terms were coded using the MedDRA version 7.0 dictionary for Study 2093-301 and version 9.0 for Studies 2093-302 and 2093-303.
b Eastern Europe includes Czech Republic, Croatia, Hungary, Lithuania, Poland, Romania, Russia, and Ukraine.
c Latin America includes Mexico, Argentina, and Brazil.
d Western Europe/ROW includes Austria, Belgium, Denmark, Germany, Netherlands, Portugal, Spain, Sweden, Switzerland, and United Kingdom/Australia and South Africa.
Note: The titration, maintenance, and tapering-off periods were combined. Study 2093-302 did not have a tapering-off period. Treatment emergent adverse events are those that occurred on or after the date of first dose, or the date of randomization if the date of the first dose was missing. Adverse events with missing or incomplete onset dates were considered to be treatment emergent unless it could be determined that the event began before the treatment period.
Note: Potentially-related events as those assessed by the Investigator as having a definitely, probably, possibly, unlikely, or unknown/missing relationship to treatment.
Note: Subjects were counted at most once within each system organ class and preferred term.
Reference: ISS EOT Table 7.1.1.5, Table 7.2.1.5, and Table 7.3.1.5

Based on a table (Table 2-3, not shown in this review) in the 1-25-10 information amendment, the company notes it is apparent that placebo rates of the individual common adverse events for a given product are typically lower in non-US studies than US studies. Placebo rates of the individual adverse events for the eslicarbazepine studies are similar to those of non-US studies of approved AEDs. The sponsor argues doses in US studies of other products "frequently" (p. 26/523) included lower maximum doses or dose ranges than those evaluated in US studies. The sponsor uses Lyrica as an example in that study 009 conducted in the US and Canada evaluated only the 600 mg/d dose and tended to have higher placebo-adjusted active AE rates than the European Lyrica study 011 that included doses as low as 150 mg/d but that the rates for study 11 were comparable to those observed for US/Canadian Lyrica study 034 that included the lower doses. The sponsor asserts that while none of the previously approved AEDs relied solely on US, the non-US data were considered sufficiently representative of the US patient population to allow for pooling with data from the US.

*Reviewer's assessment:*

- GCP and audit issues are described elsewhere in this (Data Quality and Integrity Sections). In addition to site issues raised by FDA inspections, there is a discrepancy between the FDA's overall conclusions of the data at site112 in study 301 (Croatia) and site 395 in study 302 (Spain) and Sepracor's conclusions of audits of these sites with Sepracor's audit finding the data from both sites acceptable and FDA audits finding the data as having significant deviations from

regulations. Therefore, other sites considered acceptable from Sponsor audits cannot necessarily be concluded to be acceptable.

- It is unclear AEs were consistently captured and/or classified as such. The written definition of an adverse event includes "Any worsening of a pre-existing condition that occurred during the study was also an adverse event." (ISS p. 386/582). CRF and/or audit reviews indicate that, at least in some cases, this definition was not used. Also, there was suggestion from audit reports that perhaps some AEs were not making it from source documents to CRF (or vice versa) and then into the integrated summary of datasets. Review of the sponsor's response to this concern is not complete therefore, the presentations below are preliminary.

  ● CRF study 303-703-70231-page 216, in data clarification form-query notes that patient noted chest pain in visit 1 diary and to confirm corresponding AE. The reply is "Chest pain was not an adverse event."
  ●CRF center 703-3339 on page 96/523 of 1-25-10 document- Query to the investigator about "depression" noted in patient diary and to confirm the corresponding AE. The reply is "depression was not considered as an adverse event". )
  ● CRF center 710-70367 on page 98/523 of 1-25-10 document-Query to investigator that several adverse events are noted in the comments of the diary, however they are not on the AE pages. The reply is that "I do not consider adverse events the comments"
  ● CRF center 710-70367 on page 100/523-Query to investigator regarding an SAE that was reported to drug safety while it was missing from the AE CRF pages. The SAE was "severe partial seizures/hemiparesis". The investigator's response indicates this was an AE and was an SAE and led to study discontinuation. Information in the document (p.13/523) indicates there is no CRF (and one is not submitted) and that this event is not in the ADAE.xpt dataset for the patient (303-710-70367).
  ● CRF center 703-70349 study 303-audit finding of suicidal ideation, there is no CRF documentation of event and the event is not in the ADAE.xpt dataset.
  ● subject 302-388-80460 -audit finding of migraine without CRF documentation. The attached CRF page on page 87/523 of 1-25-10 document indicates that the subject had a medical history of migraine that was not entered at screening and since 1986, has intermittent migraine, so it seems that if migraine occurred, it was not considered an AE because it was medical history.
  ● 302-336-80711, subject withdrew consent due to increased seizures, CRF termination page indicates this also but the event is not in the ISS dataset as an AE

The sponsor states that many of the findings in the table (1-25-10 submission-summarizes discrepancies between source documents and CRF) are from audits that took place more than 2 years after notations were made and it is not possible to determine whether these signs and symptoms were determined to be pre-existing or were overlooked. The sponsor states that many are typical of symptoms that accompany a post-ictal state and that Investigators were trained to not transcribe individual seizures or their immediate seizure-related sequelae as an adverse event per se. The sponsor says that many of the audit findings are consistent with the possibility that they were in fact seizure-associated and did not meet criteria for recording as an AE.

This may be the case in some instances. It is not possible in the time constraints of this review to request the CRFs or to track the time of these possible events to times of seizures through some other mechanism (datasets).

- Eastern Europe reported the lowest incidence of TEAEs for both the placebo and total ESL compared to all other regions. Eastern Europe contributed 33.6 % of placebo subjects 37% of all ESL subjects. Latin America reported a lower incidence of TEAEs for both the placebo and total ESL compared to Latin America without Mexico. Severe TEAEs (subjects reporting at least 1 severe TEAE) are reported at a considerably lower incidence from Eastern Europe than from Western Europe in ESL groups (3.5% compared to 13.7%). This magnitude of difference is not seen between placebo subjects reporting severe TEAEs (3.1% Eastern Europe compared to 3.6% Western Europe). The sponsor's table from the ISS displays the sponsor's analysis of TEAES by geographic region and is duplicated below.

**Table 19.5.2-1: Treatment Emergent Adverse Events by Geographic Region for the Pooled Phase III Epilepsy Studies (Part 1 of 2093-301, 2093-302, and 2093-303) (Safety Population)**

| | Placebo (N=289) | | | | Total ESL (N=760) | | | |
|---|---|---|---|---|---|---|---|---|
| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | Eastern Europe[b] (N=97) Subjects n (%) | Latin America[c] (N=109) Subjects n (%) | Latin America without Mexico (N=55) Subjects n (%) | Western Europe /ROW[d] (N=83) Subjects n (%) | Eastern Europe[d] (N=284) Subjects n (%) | Latin America[c] (N=264) Subjects n (%) | Latin America without Mexico (N=159) Subjects n (%) | Western Europe /ROW[d] (N=212) Subjects n (%) |
| AT LEAST 1 TEAE | 31 (32.0) | 54 (49.5) | 37 (67.3) | 49 (59.0) | 148 (52.1) | 179 (67.8) | 129 (81.1) | 162 (76.4) |
| Common TEAE | | | | | | | | |
| Diplopia | 0 | 2 (1.8) | 2 (3.6) | 3 (3.6) | 18 (6.3) | 24 (9.1) | 23 (14.5) | 15 (7.1) |
| Dizziness | 2 (2.1) | 13 (11.9) | 7 (12.7) | 6 (7.2) | 30 (10.6) | 87 (33.0) | 63 (39.6) | 49 (23.1) |
| Headache | 6 (6.2) | 12 (11.0) | 7 (12.7) | 7 (8.4) | 25 (8.8) | 36 (13.6) | 29 (18.2) | 23 (10.8) |
| Nausea | 1 (1.0) | 4 (3.7) | 3 (5.5) | 1 (1.2) | 14 (4.9) | 23 (8.7) | 17 (10.7) | 22 (10.4) |
| Somnolence | 2 (2.1) | 19 (17.4) | 14 (25.5) | 6 (7.2) | 28 (9.9) | 45 (17.0) | 30 (18.9) | 27 (12.7) |
| Vomiting | 1 (1.0) | 5 (4.6) | 3 (5.5) | 1 (1.2) | 8 (2.8) | 22 (8.3) | 15 (9.4) | 13 (6.1) |
| AT LEAST 1 POTENTIALLY RELATED TEAE | 15 (15.5) | 43 (39.4) | 30 (54.5) | 41 (49.4) | 104 (36.6) | 166 (62.9) | 124 (78.0) | 147 (69.3) |
| AT LEAST 1 SEVERE TEAE | 3 (3.1) | 7 (6.4) | 5 (9.1) | 3 (3.6) | 10 (3.5) | 36 (13.6) | 29 (18.2) | 29 (13.7) |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; ROW=rest of world (Australia and South Africa; TEAE=treatment emergent adverse event.
a Reported AE terms were coded using the MedDRA version 7.0 dictionary for Study 2093-301 and version 9.0 for Studies 2093-302 and 2093-303.
b Eastern Europe includes Czech Republic, Croatia, Hungary, Lithuania, Poland, Romania, Russia, and Ukraine.
c Latin America includes Mexico, Argentina, and Brazil.
d Western Europe/ROW includes Austria, Belgium, Denmark, Germany, Netherlands, Portugal, Spain, Sweden, Switzerland, and United Kingdom/Australia and South Africa.
Note: The titration, maintenance, and tapering-off periods were combined. Study 2093-302 did not have a tapering-off period. Treatment emergent adverse events are those that occurred on or after the date of first dose, or the date of randomization if the date of the first dose was missing. Adverse events with missing or incomplete onset dates were considered to be treatment emergent unless it could be determined that the event began before the treatment period.
Note: Potentially-related events as those assessed by the Investigator as having a definitely, probably, possibly, unlikely, or unknown/missing relationship to treatment.
Note: Subjects were counted at most once within each system organ class and preferred term.

- Although it is unclear how scientifically valid it is to compare rates of adverse events across trials in differing development programs, I believe this type of evaluation is fairly commonly employed in clinical decision making as physicians choose between similar drug products. Also, it is probably a reasonable exploratory step.

  FDA requested that the Sponsor submit a comparison of SAE and discontinuations secondary to an adverse event. The table sent in response pools ESL studies 301-303 (table duplicated below). Study 303 data generally had lower rates of events than pooled studies 301-302. [Compared to studies 301 and 302, rates of AEs (50% placebo, 66.4% total ESL compared to 41.4 % placebo and 57.6% total ESL) and SAEs ( <1% (0.99) placebo, 4.5% pooled ESL compared to 0% placebo and 0.6% ESL) are lower in study 303. The incidence of discontinuation of study medication secondary to an AE was 4% for placebo subjects and 15.5% for the pooled ESL groups for studies 301 and 302 compared to 8% for the placebo subjects in study 303 and 10.3% for the pooled ESL groups (SU .56/290).]

  When comparing ESL to recent AED approvals, I focus on the placebo group as placebo is expected to have no innate pharmaceutical activity in any development program while the active drug has established efficacy and therefore has some activity. Also, different AEDs, while sharing common features, have different safety profiles.

The non-fatal SAE placebo reporting rate is 0 for 2 of three ESL studies. This is unlike other development programs for US or non-US data. Studies 301 and 302 discontinuation rates are lower than most other products with the exception of Zonegran (one US and one EUR study). Study 303 rate is within the range of other development programs.



**Table 2-1: Summary of Safety Data from Pivotal Studies for Last 5 New AEDs Approved in US Compared with Stedesa (Eslicarbazepine Acetate) Phase III Studies**

| Drug | Study # | Region | Active Doses Studied | Discontinued Due to AEs % Subjects PBO | ACT | ACT-PBO | Deaths % Subjects PBO | ACT | ACT-PBO | SAE % Subjects PBO | ACT | ACT-PBO | AE Overall % Subjects PBO | ACT | ACT-PBO |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vimpat™ (lacosamide) | SP667 | US/EUR | 200, 400, 600 mg/day | 5 | 20 | 15 | -- | -- | -- | 5 | 5.9 | 0.9 | 70 | 84 | 14 |
| | SP754 | US | 400, 600 mg/day | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| | SP755 | EUR/AUS | 200, 400 mg/day | 4.9 | 10.9 | 6.0 | -- | -- | -- | 3.7 | 8.7 | 5.0 | -- | -- | -- |
| Lyrica® (pregabalin) | 009 | US/CAN | 600 mg/day | 7.1 | 22.4 | 15.3 | 0 | 0 | 0 | 3.1 | 3.7 | 0.6 | -- | -- | -- |
| | 011 | EUR | 150, 600 mg/day | 6.2 | 14.1 | 7.9 | 0 | 0 | 0 | -- | -- | -- | 63.5 | 81.1 | 17.6 |
| | 034 | US/CAN | 50, 150, 300, 600 mg/day | 5.0 | 11.6 | 6.6 | 0 | 0 | 0 | -- | -- | -- | 74.0 | 77.9 | 3.9 |
| Zonegran® (zonisamide) | 912-US | US | 400-600 mg/day | 1.4 | 15.4 | 14.0 | -- | -- | -- | 6.8 | 10.3 | 3.5 | -- | -- | |
| | 912-EUR | EUR | 400 mg/day | 1.4 | 6.8 | 5.4 | -- | -- | -- | -- | -- | -- | 31 | 62 | 31 |
| | 922 | US | 400 mg/day | 8.2 | 11.9 | 3.7 | -- | -- | -- | 5.8 | 11.9 | 6.1 | -- | -- | |
| Trileptal® (oxcarbazepine) | OT/PE1 | Ex-US | 600, 1200, 2400 mg/day | 8.7 | 38.5 | 29.8 | 1.2 | 0.77 | -0.43 | 5.2 | 7.5 | 2.3 | 76.3 | 90.8 | 14.5 |
| Keppra® (levetiracetam) | N051 | EUR | 1000, 2000 mg/day | 5.4 | 10.8 | 5.4 | 0 | 0.47 | 0.47 | 2.7 | 4.7 | 2.0 | 73.2 | 73.1 | -0.1 |
| | N132 | US | 1000, 3000 mg/day | 5.2 | 6.5 | 1.3 | 1.05 | 0 | -1.05 | 10.5 | 4.5 | -6.0 | 88.4 | 88.9 | 0.5 |
| Stedesa™ (eslicarbazepine acetate) | 2093-301 | EUR | 400, 800, 1200 mg/day | 3.9 | 11.0 | 7.1 | 0.98 | 0 | -0.98 | 3.9 | 5.0 | 1.1 | 31.4 | 51.7 | 20.3 |
| | 2093-302 | Ex-US | 400, 800, 1200 mg/day | 3.0 | 19.3 | 16.3 | 0 | 0 | 0 | 0 | 4.1 | 4.1 | 68.0 | 80.3 | 12.3 |
| | 2093-303 | Ex-US | 800, 1200 mg/day | 6.9 | 9.7 | 2.8 | 0 | 0 | 0 | 0 | 1.3 | 1.3 | 39.1 | 57.0 | 17.9 |

Abbreviations: ACT=active treatment; AE=adverse event; CAN=Canada; EUR=Europe; PBO=placebo; SAE=serious adverse event; US=United States, "--"=not reported.
Reference: Vimpat: Ben-Menachem, Halász; Lyrica: Beydoun, Arroyo, French; Zonegran: Sackellares, Brodie, Faught (2004), Faught (2001); Trileptal: Barcs; Keppra: Shorvon, Cereghino; Stedesa: CSRs for Studies 2093-301, 2093-302, and 2093-303.

*Reviewer's comments: It is my opinion that it is the events of a more significant nature, captured as SAEs and discontinuations that are most concerning in terms of adequate characterization of the safety profile. If there are fewer non-fatal placebo SAEs reported in general in eslicarbazepine development than for the 5 AED placebo groups, it seems plausible that this under-reporting exists for SAEs for the eslicarbazepine groups. There is no way to model or simulate what may be missing. Also, although similar to oxcarbazepine, this is not identical to oxcarbazepine and II do not believe the safety profile from oxcarbazepine is adequate to address possibly missing SAE information..*

*Common events are not insignificant and under-reporting may offer an apparent marketing advantage as the adverse event tables may "look better" for eslicarbazepine simply due to a lack of US data.*

*The sponsor notes that the non-US data were sufficient to be pooled with US data. Another interpretation is that the US data were of sufficient size to support the non-US data. Also, Lyrica was reviewed for several indications, each with a safety*

*population, therefore, it seems possible that the totality of the experience for safety purposes with Lyrica was broader than the experience in epilepsy.*

*Another issue with respect to foreign data is adverse event terms. There are AE terms in the datasets or narratives that are either diagnoses without other description or are terms I believe are not commonly used in the U.S. For example, in the integrated summary of safety dataset, ADAE2.xpt, the following terms are seen: "nutcracker syndrome", "amydgalitis", "BIA 2093 Related CNS Toxicity Syndrome", "Bradypsyche", "Elbow's Hematoma", "Lumbago", "Systremma", "Toxicodermia", "Trigonitis" "Study Drug Intoxication", "grippe" , "subfebrile state" and "Cerebellar Syndrome". It is unclear how these terms are translated to preferred term equivalents. Although one can make reasonable assumption about some of these terms as to what they mean or constitute and some are older terms (e.g., grippe, lumbago), this should be addressed by the sponsor.*

*Of note, the Sponsor basically raises an issue of clinical patient monitoring or safety in study 303 when noting in study 303 that audit observations included "failure to consistently (prospectively) assure subject safety and control of the investigational product" (p.64/75 of the clinical overview in SDN 000)*.

**Sponsor's position regarding applicability to US data including efficacy point of view:**

The sponsor describes that 5 drugs have been approved for AEDs in the US (as adjunctive in partial-onset seizures); Vimpat (lacosamide) NDA 22253, approved October, 2008, Lyrica (pregabalin) NDA 21724, approved June 2005, Zonegran (zonisamide) NDA 20789, approved March 2000, Trileptal (oxcarbazepine) NDA 21014, approved January 2000, and Keppra (levetiracetam) NDA 21035, approved November, 1999. The medical reviews in the summary basis of approval documents that are published on the FDA website were reviewed and used for the data in the summary, except where indicated otherwise. When information was not available from an SBA, publications were used. The following table is duplicated from the submission and displays the study designs of the studies supporting approval for the last approved AEDs.

The sponsor's discussion covers the following areas:

- Study designs, inclusion criteria, and primary endpoints
- Concomitant medications
- Demographics and baseline characteristics including concomitant medications
- Seizure etiology

Study design: The study designs appear similar. Baseline seizure frequency, as summarized by the sponsor, varied across studies but typically required an average of ≥ 4 seizures per 4 weeks with some studies also including a maximum seizure-free period of 21 to 30 days during the baseline evaluation. As per the sponsor, for almost all of the

approved AEDs, the baseline was observational, although one study each to support Keppra and Zonegran used a single-blind placebo baseline period. Eslicarbazepine studies required at least 4 seizures in each of the 4 weeks of the 8 week baseline and a maximum seizure-free period of 21 days. Study 301's baseline was observational and study 302's was single-blind.

**Table 1.4.5-1: Study Designs of Last Five New AEDs Approved in US Compared with ESL Pivotal Study Designs**

| Drug | Study # | Region | Baseline Period (weeks) | Baseline Type | Titration Period (weeks) | Maintenance Period (weeks) | Number of Concomitant AEDs |
|---|---|---|---|---|---|---|---|
| Vimpat™ (lacosamide) | SP667 | US/EUR | 8 | OBS | 6 | 12 | 1-2 |
| | SP754 | US | 8 | OBS | 6 | 12 | 1-3 |
| | SP755 | EUR/AUS | 8 | OBS | 4 | 12 | 1-3 |
| Lyrica® (pregabalin) | 009 | US/CAN | 8 | OBS | 1 | 11 | 1-3 |
| | 011 | EUR | 8 | OBS | 1 | 11 | 1-3 |
| | 034 | US/CAN | 8 | OBS | 0 | 12 | 1-3 |
| Zonegran® (zonisamide) | 912-US | US | 8-12 | OBS | 4 | 12 | 1-2 |
| | 912-EUR | EUR | 8-12 | OBS | 4 | 12 | 1-2 |
| | 922 | US | 4 | SB PBO | 7 | 5 | 1-2 |
| Trileptal® (oxcarbazepine) | OT/PE1 | Ex-US | 8 | OBS | 2 | 24 | 1-3 |
| Keppra® (levetiracetam) | N051 | EUR | 8 | OBS | 4 | 12 | 1-2 |
| | N132 | US | 12 | SB PBO | 6 | 12 | 1-2 |
| ESL | 2093-301 | EUR | 8 | SB PBO | 2 | 12 | 1-2 |
| | 2093-302 | Ex-US | 8 | OBS | 2 | 12 | 1-3 |

Abbreviations: CAN=Canada; EUR=Europe; OBS=observed; SB PBO=single-blind placebo; US=United States
Reference: NDA SBAs for Vimpat™ (22-253), Lyrica® (21-724), Zonegran® (20-789), Trileptal® (21-014) and Keppra® (21-035)



Inclusion criteria: The sponsor presents a table of key entry criteria for inclusion for the approved AEDs and for ESL (see the appendix of this document, sponsor table 1.4.5-2 duplicated from the summary-clin-efficacy-epilepsy.pdf document). In all studies, subjects were to have a diagnosis of partial-onset seizures including both simple and complex, with or without secondary generalization. The sponsor states that diagnoses were made in accordance with the ICES (developed by the International League Against Epilepsy). The sponsor notes that these criteria have been adopted by the AAN for the diagnosis and classification of seizures. Age criteria ranged from 12-70 years with 5 studies having a minimum age of 18, 4 studies having a minimum age of 16, 1 study with a minimum age of 15, and 2 studies with a minimum age of 12 years. The minimum age for the studies of eslicarbazepine was 18 years. It is noted that ESL studies used a 1981 version of the criteria referenced. The trials were conducted after a newer version of these criteria were released (1989). This alone is probably not a significant issue in terms of impact on conclusions from the data.

Primary endpoint: All studies are reported by the sponsor to have relied on subject or caregiver seizure diaries. ESL studies also used diaries. The primary endpoint in studies supporting Vimpat, Zonegran, and Trileptal studies was percent change in seizure frequency per 28 days. For Lyrica, the primary endpoint was responder

ratio=[(treatment – baseline)/(treatment + baseline)] x 100. For Keppra, the primary endpoint was standardized seizure frequency per 1 week. For eslicarbazepine, the primary endpoint was standardized seizure frequency per 4 weeks over the 12-week maintenance period for study 301 and 302 and 303.

Concomitant medications: In study 302, clobazam was used in 17% of patients as a concomitant medication. Use was most common in Latin America (23.5%) versus 11% in Western Europe and 0.5% in Eastern Europe. In study 301, three subjects used this drug (0.8%). In study 303, clobazam was used in 8.3% of placebo patients, 7.1% of ESL 800 mg patients, and 9.1% of ESL 1200 mg patients (Table 11-4 of the CSR for study 303-not duplicated in this review).

The sponsor's table 3.3.2.5-2 (baseline concomitant use of AEDS) of the CSE indicates that of the 5 newer AED approvals, two NDAs included studies in which patients used clobazam. From this table, in one of the three Lyrica studies, clobazam was used in 17% of patients (there are two other studies) and in one of the two studies for Keppra (the European study), clobazam was used in 8-11% of patients. Although not shown in the sponsor's table 3.3.2.5-2, the corresponding text indicates that in two other studies of Lyrica, 2% and 3% of patients used clobazam and that in one study of Trileptal, 13% used clobazam.

Phenobarbital was used by 11.8% of placebo patients, 7.7% of ESL 400 mg patients, 11.3% of ESL 800 mg patients, and 9.6% of ESL 1200 mg patients based on pooled data of part 1 of studies 301, 302, and 303. (About 1.2% of ESL patients and 2.4% of placebo patients in eslicarbazepine study 303 based on data in the study report). Of the 14 trials listed in the sponsor's table 3.3.2.5-2 of the CSE, none of the trials for Vimpat or Lyrica have phenobarbital in the concomitants listed (top five are listed). For Zonegran, the sponsor's table does not provide percentages (perhaps not available in online documents or literature) but there are two US studies for Zonegran. Trileptal adjunctive trial is displayed as 14-16% of patients using phenobarbital. For Keppra, one study (US) had 7-10% of patients using phenobarbital while phenobarbital is not on the list of 5 concomitants for Ex-US adjunctive study.

In ESL studies, the following concomitant AEDs were used by more than 5% of subjects (302-302); carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, topirimate, and valproic acid. In the US, clobazam is not marketed. The sponsor states that neither clobazam or phenobarbital is approved for use in the US for the treatment of seizures. The sponsor states that for the 4 most common AEDs used in the eslicarbazepine studies, US marketing survey data indicate that of all subjects with partial-onset seizures, 26% to 30% were using carbamazepine, 7-14% lamotrigine, 16-25% valproic acid, and 9-14% levetiracetam. The sponsor concludes that use of concomitant AEDS in the eslicarbazepine studies is consistent with the relative use of these medications in the US population.

**Table 3.3.2.5-2: Baseline Concomitant Use of AEDs for the Last Five New AEDs Approved in US Compared with ESL**

| Drug | Study # (Region) % Subjects using AED | | |
|---|---|---|---|
| Vimpat™ (lacosamide) | Study SP667 (US/EUR)<br>Carbamazepine 21-41%<br>Levetiracetam 26-38%<br>Lamotrigine 23-32%<br>Topiramate 16-26%<br>Oxcarbazepine 15-21% | Study SP754 (US)<br>Levetiracetam 40%<br>Lamotrigine 36%<br>Carbamazepine 25%<br>Oxcarbazepine 21%<br>Phenytoin 19% | Study SP755 (EUR/AUS)<br>Carbamazepine 48%<br>Valproate 33%<br>Lamotrigine 31%<br>Topiramate 28%<br>Levetiracetam 20% |
| Lyrica® (pregabalin) | Study 009 (US/CAN)<br>Carbamazepine 58%<br>Lamotrigine 33%<br>Phenytoin 22%<br>Topiramate 22%<br>Valproate 11% | Study 011 (EUR)<br>Carbamazepine 61%<br>Lamotrigine 33%<br>Topiramate 19%<br>Clobazam 17%<br>Phenytoin 14% | Study 034 (US/CAN)<br>Carbamazepine 52%<br>Phenytoin 29%<br>Lamotrigine 22%<br>Valproate 19%<br>Topiramate 17% |
| Zonegran® (zonisamide) | Study 912-US (US)<br>Carbamazepine<br>Phenytoin<br>Primidone<br>Phenobarbital | Study 912-EUR (EUR)<br>Carbamazepine<br>Phenytoin<br>Primidone<br>Phenobarbital<br>Valproate | Study 922 (US)<br>Carbamazepine<br>Phenytoin<br>Valproate<br>Phenobarbital<br>Primidone |
| Trileptal® (oxcarbazepine) | Study OT/PE1 (Ex-US)[a]<br>Carbamazepine 71-78%<br>Valproic acid 20-29%<br>Phenytoin 18-26%<br>Phenobarbital 14-16%<br>Vigabatrin 12-16% | NA | NA |
| Keppra® (levetiracetam) | Study N051 (EUR)<br>Carbamazepine 71-75%<br>Phenytoin 20-27%<br>Valproic Acid 19-24%<br>Lamotrigine 10-13%<br>Clobazam 8-11% | Study N132 (US)<br>Carbamazepine 53-62%<br>Phenytoin 30-38%<br>Valproic Acid 24-29%<br>Gabapentin 24-36%<br>Phenobarbital 7-10% | NA |
| ESL | Study 301 (EUR)<br>Carbamazepine 58%<br>Lamotrigine 26%<br>Valproic acid 26%<br>Topiramate 14%<br>Levetiracetam 8% | Study 302 (Ex-US)<br>Carbamazepine 60%<br>Valproic acid 22%<br>Lamotrigine 21%<br>Clobazam 17%<br>Levetiracetam 16% | NA |

Abbreviations: AUS=Australia; CAN=Canada; EUR=Europe; ESL=eslicarbazepine acetate; NA=not applicable; US=United States

Reference: NDA SBAs for Vimpat™ (22-253), Lyrica® (21-724), Zonegran® (20-789), Trileptal® (21-014) and Keppra® (21-035) except where noted: [a]Barcs 2000[12].



Demographics and Baseline information: There were minor variations in the entry criteria for age. The mean ages for studies of approved AEDs were similar and ranged from 34 to 39 years. Mean duration of epilepsy for the studies of approved AEDs ranged from about 20 to 28 years. The mean ages and duration of epilepsy for the pivotal eslicarbazepine studies were 37to 39 years and 19-24 years, respectively. Gender split between males and females was similar. Mean subjects weights in the ESL studies was 70 to 71 kg (mean weight in studies outside the US ranged from 66-75 kg). U.S. patients were heavier (73 to 82 kg). The company does not expect the difference to have an impact on data applicability. All studies predominantly enrolled

Caucasian subjects (US 85%, non-US nearly 100%) compared to ESL studies 301-302 with 100% and 88% Caucasian studies.

The sponsor reports that US Center for Disease Control data indicates that based on surveillance from 19 states in 2005 of subjects with a history of epilepsy, 44% were male, half were between ages 35-54, 64% had a BMI between 18.5 and 29.9 kg/m$^2$ , and 74% were white, 8% were black, and 11% were Hispanic. Baseline seizure frequency and the data described above are shown in the sponsor's table 3.3.2.5-1 (CSE p.75/175), which is reproduced below.

**Table 3.3.2.5-1: Demographics and Baseline Characteristics of Last Five New AEDs Approved in US Compared with ESL**

| Drug | Study # | Region | Mean Age (years) | % Male | % Caucasian | Mean Weight (kg) | Duration of Epilepsy (years) | Baseline Seizure Frequency per 4 weeks |
|---|---|---|---|---|---|---|---|---|
| Vimpat™ (lacosamide) | SP667 | US/EUR | ~39 | 45-53 | 91-95 | 75-80 | 24 | 11-13 |
| | SP754 | US | 38 | 49 | 82 | 81 | 25 | 12-17 |
| | SP755 | EUR/AUS | 38 | 52 | 99 | 74 | 22 | 10-12 |
| Lyrica® (pregabalin) | 009 | US/CAN | 39 | 50-51 | 84-89 | NA | 24-28[a] | 10-11 |
| | 011 | EUR | 37 | 48-56 | 93 | 71-75[b] | 24[b] | 9-12 |
| | 034 | US/CAN | 39 | 47-52 | 84-85 | 73-80 | 25[c] | 9.5 |
| Zonegran® (zonisamide) | 912-US | US | 36 | 58-74 | 87 | 73-74 | ~20[d] | 7.5-11.1 |
| | 912-EUR | EUR | ~34 | 59 | 100 | 66-67 | NA | 11-11.3 |
| | 922 | US | 34-36 | 41-62 | 85 | 75-82 | ~22[e] | 11.2-13 |
| Trileptal® (oxcarbazepine) | OT/PE1 | Ex-US | ~34 | 45-56 | NA | 70-73 | NA | 8.6-10.0 |
| Keppra® (levetiracetam) | N051 | EUR | 37 | 48 | 99 | NA | 23 | 5.4-6.9* |
| | N132 | Ex-US | 38 | 60 | 85 | NA | 23 | 5.1-6.9* |
| ESL | 301 | EUR | 39 | 49 | 100 | 71 | 19-23 | 11.7 |
| | 302 | Ex-US | 37 | 49 | 88 | 70 | 24 | 14.8 |

Abbreviations: AUS=Australia; CAN=Canada; EUR=Europe; ESL=eslicarbazepine acetate; NA=not available; US=United States

* frequency per 1-week period

Reference NDA SBAs for Vimpat™ (22-253), Lyrica® (21-724), Zonegran® (20-789), Trileptal® (21-014) and Keppra® (21-035) except where noted: [a]Beydoun 2005[7]; [b]Arroyo 2004[8]; [c]French 2003[9]; [d]Sackellares 2004[10];

Seizure etiology: With respect to seizure etiology, the sponsor states that data were available only for Vimpat, Lyrica, and Keppra and that for all studies, the most common documented etiology was unknown, idiopathic, or other. For Lyrica and Keppra, there was no "idiopathic" category. The percentage of "unknown" etiology was 43-56% when compared to ESL studies (50-64% in study 301 and 61% in study 302).

**Table 3.3.2.5-3: Seizure Etiology for the Recent AEDs Approved in US Compared with ESL**

| Drug | Study # (Region) Etiology of Seizures | | |
|---|---|---|---|
| Vimpat™ (lacosamide) | Study SP667 (US/EUR)<br>Idiopathic 29-34%<br>Other 18-21%<br>Trauma 13-24%<br>Infection 7-12%<br>Congenital 4-14%<br>Birth injury 6-10%<br>Genetic propensity 6-11% | Study SP754 (US)<br>Idiopathic 42%<br>Other 11%<br>Trauma 18%<br>Infection 13%<br>Congenital 9%<br>Genetic propensity 8%<br>Birth injury 6% | Study SP755 (EUR/US)<br>Idiopathic 26%<br>Other 25%<br>Trauma 13%<br>Birth injury 12%<br>Congenital 11%<br>Infection 11% |
| Lyrica® (pregabalin) | Study 009 (US/CAN)[a]<br>Unknown 47-55%<br>Trauma 16-18%<br>Infections 11-16%<br>Other 13%<br>Family history 5-6%<br>Birth injury 4-6% | Study 011 (EUR)[a]<br>Unknown 47-53%<br>Other 18-22%<br>Trauma 8-10%<br>Infections 8-10%<br>Birth injury 7-14% | Study 034 (US/CAN)[a]<br>Unknown 43-48%<br>Trauma 19-21%<br>Other 13-19%<br>Infections 8-13%<br>Family history 8-9%<br>Birth injury 3-7% |
| Keppra® (levetiracetam) | Study N051 (EUR)<br>Unknown 56%<br>Encephalitis 4.6%<br>Birth injury 3.7%<br>Febrile convulsion 2.2%<br>Birth asphyxia 2.2%<br>Congenital 1.9%<br>Meningitis 1.9% | Study N132 (US)<br>Unknown 49%<br>Head injury 16%<br>Encephalitis 4%<br>Fever 4%<br>Febrile convulsion 3%<br>Birth injury 2%<br>Meningitis 2% | NA |
| ESL | Study 301 (EUR)<br>Other 35-39%<br>Head trauma 15-26%<br>Idiopathic 15-25%<br>Infection 6-15%<br>Congenital 6-11%,<br>Cerebrovascular 1-10%<br>Brain tumor 2-5% | Study 302 (Ex-US)<br>Other/unknown 44%<br>Idiopathic 17%<br>Congenital/hereditary 13%<br>Infection 10%<br>Head trauma 9%<br>Brain tumor 3%<br>Cerebrovascular 3% | NA |

Abbreviations: CAN=Canada; EUR=Europe; ESL=eslicarbazepine acetate; US=United States; NA=Not applicable
Reference: NDA SBAs for Vimpat™ (22-253), Lyrica® (21-724), and Keppra® (21-035) except where noted: [a]Gil-Nagel 2008[13].

Best Available Copy

*Reviewer's assessment of the sponsor's arguments above:*

Due to the need to consider the ESL data in terms of comparability to US data, known data integrity issues, and then the data itself, this area of my review represents a preliminary opinion.

Relative to the 5 other products in the sponsor's comparison, the stated designs, entry criteria, and demographics, as presented appear similar enough as to not be significant issues with the possible exception of race (Caucasian in 100% of one trial). The stated baseline seizure frequency per 4 weeks appears to have been on the high end for study 303 (mean 14.8 compared to range of 12-17 in one lacosamide), although acceptable.

A problem with this baseline data may be in how reliable it is if there is poor documentation at other sites as noted by DSI audit of one site.

Several of the comparators are now out about a decade and lacosamide US data may be more representative of current US practice in terms of concomitant medications. Lacosamide US study and US/EUR study used less concomitant carbamazepine (21-25%) than did the ESL studies (58-60%) (data as per Sponsor's table 3.3.2.5-2). Also, as the sponsor notes, clobazam is not marketed in this country.

In terms of the primary endpoint, the issue is less the endpoint itself than the quality of the data. Although most diary collection may be similar, it is not optimal that patients were instructed to fill out diaries only if there was a seizure. When there are pages of a dairy with no entries, it is not clear whether these are blank because there were no seizures or because they were not completed. A line or some notation should be made on the diary. In some cases, seizure diaries may be filled out by a caregiver. Statistical review addresses this issue from a statistical point of view.

It is not possible for this reviewer to tell from the sponsor's application at this time, and possibly not possible to know from a distance, how similar the actual practice of medicine is in non-US sites, specifically Eastern Europe and Latin America.

## 5.2 Review Strategy

Given the known GCP problems with one study, the review strategy was to establish the reliability of the data, consider the fact that there was no US data and review the sponsor's arguments as to the acceptability of this, and then to review the data itself. Evaluating the reliability of the data has consumed large amounts of review time and, directed by findings of the review process, data quality issues became the focus of the review. Essentially, given the number of instances of inconsistencies and corrections to submissions, I felt it was of upmost importance to document these issues so that senior Division staff (the medical Team Leader and the Division Director) could be informed.

I attempted to do go through the exercise of reviewing the NDA submissions, but given the number of issues and the time required to document these issues, I was not able to complete such. It is my opinion, however, that it is premature and not efficient to conclude much from the NDA data at this time.

If the Sponsor can assure data reliability and integrity, in the end, some of the apparent problems (such as narratives that are not detailed or inconsistencies in data presentation as described in the quality section) may in-and-of themselves not be detrimental to the profile of ESL, but this is not clear. For example, in the case of the phase 1 subject with the serious rash (subject 119-004), the subject is not described as a serious adverse event but is described as a discontinuation for hypersensitivity. Because hypersensitivity can be used to cover a range of reactions such as rash and angioedema and the narrative was lacking clinical details but did indicate the use of steroids, I looked at the case report form. In the case report form, there is information indicating hospitalization and clinical events that are consistent with SJS/TENS (mouth ulcer, peeling skin, fever). The subject was on lamictal plus ESL and on lamictal alone

before the combination. Therefore, in the end this case may not reflect poorly on ESL's safety profile (unless there is evidence that ESL potentiates these type reactions), however, as a reviewer, to "find" some of this information in the case report form and not explained in the narrative, undermines my confidence in the data presentations.

Sections of the review are descriptive only.

Efficacy:

The focus of the efficacy review is on the studies submitted as pivotal phase 3 studies, studies 2093-301 and 2093-302. Efficacy data from studies 201 and 303 were evaluated less rigorously. The review of the statistical reviewer is considered the primary efficacy review of the pivotal studies with the sponsor's analyses considered secondary. My efficacy review depended heavily on the FDA statistician's review of the primary endpoints for the trials considered to be pivotal trials. Additionally, the integrated summary of efficacy was used as a reference. Individual study reports were used at times.

Safety:
The focus of the safety review became, primarily, a characterization of data quality followed by an attempt to review the data itself. After discussion with my Team Leader, the Division Director, and the Deputy Office Director, I have decided to limit the presentation of safety data to deaths, non-fatal serious adverse events, and discontinuations secondary to an adverse event. Safety data presented is not completely verified for accuracy and should be considered preliminary. This was discussed with the Team Leader.

## 5.3 Discussion of Individual Studies/Clinical Trials

The focus of this review is on the phase 3 epilepsy trials as the claim sought is for an epileptic population. Five epilepsy trials were completed in adult and pediatric patients with refractory partial epilepsy. All studies were performed outside of the U.S.

Of the five studies, one was in a pediatric population (BIA-2093-202). Of the remaining four studies, one was a phase 2 study (BIA-2093-201) that evaluated once-daily versus twice-daily dosing in adults with refractory partial seizures while the other three were phase 3 studies in adults with refractory partial seizures (BIA-2093-301, 302, and 303). The sponsor considered that due to Good Clinical Practice concerns regarding the conduct of study 2093-303, the efficacy results could be supportive, but not determinative.

# 6 Review of Efficacy

*Efficacy Summary*

## 6.1 Indication

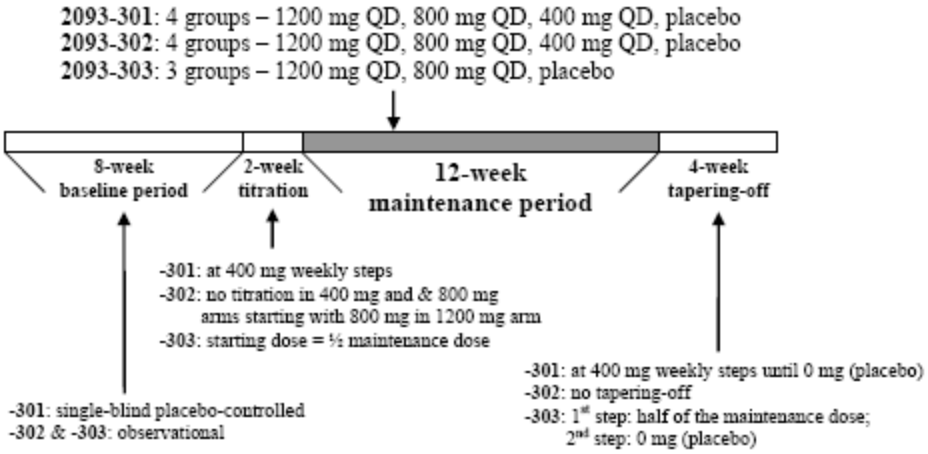
The sponsor is seeking an indication as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.

### 6.1.1 Methods

In general, the phase 3 trials included a 12 week maintenance phase preceded in 2 of 3 studies by a 2 week titration and in all three, an 8 week baseline period. The figure below is duplicated from the sponsor's submission (clinical-overview.pdf submitted with the SU).

Figure XX

**Figure 1.2.2-1: Summary of Part I of the Phase III studies (2093-301, 2093-302, and 2093-303)**




### 6.1.2 Demographics

Subjects in the ITT population for combined studies 301 and 302 can be described generally as mostly Caucasian (100% in study 301 and 82-91% in 302) and about 37 to 39 years old mean age (std deviation of around 11-12 years). Of the total 301-302 population, 3.5% of the placebo group and about 4.1 % of the ESL groups were ≥ 60 years old (2.1% of the 400 mg group, 6.1% of the 800 mg ESL group, and 4.1% of the 1200 mg ESL group). About 50% of the placebo subjects were male and about 46-53

of the ESL groups were male. Baseline disease characteristics are described in section 6.1.3.

Tables xx –duplicated from the Integrated Summary of Clinical Efficacy

**Table 2.1.2-1: Demographic Characteristics (Study 2093-301, ITT Analysis Set)**

| Parameter | Statistic/Class | Placebo (N=102) | Eslicarbazepine Acetate Dose Group | | | Total (N=397) |
|---|---|---|---|---|---|---|
| | | | 400 mg (N=99) | 800 mg (N=98) | 1200 mg (N=98) | |
| Age (years) | N | 102 | 99 | 98 | 98 | 397 |
| | Mean (SD) | 37.0 (11.93) | 37.9 (11.47) | 41.3 (12.04) | 38.3 (11.75) | 38.6 (11.86) |
| | Min, Max | 18.3, 68.6 | 18.0, 71.0 | 18.7, 75.6 | 19.0, 65.2 | 18.0, 75.6 |
| Sex | % Male | 47 | 51 | 55 | 44 | 49 |
| Race | % Caucasian | 100 | 100 | 100 | 100 | 100 |
| BMI ($kg/m^2$) | N | 102 | 99 | 98 | 98 | 397 |
| | Mean (SD) | 24.5 (4.48) | 24.4 (4.45) | 24.5 (4.63) | 24.4 (4.16) | 24.5 (4.42) |
| | Min, Max | 16.0, 39.9 | 15.2, 40.4 | 16.0, 43.4 | 16.6, 38.2 | 15.2, 43.4 |

Abbreviations: SD=standard deviation; BMI=body mass index; Min=minimum; Max=maximum
Reference: CSR 2093-301, Section 15, Table 19.

**Table 2.2.2-1: Demographic Characteristics (Study 2093-302, ITT Analysis Set)**

| Parameter | Statistic/Class | Placebo (N=100) | Eslicarbazepine Acetate Dose Group | | | Total (N=393) |
|---|---|---|---|---|---|---|
| | | | 400 mg (N=96) | 800 mg (N=100) | 1200 mg (N=97) | |
| Age (years) | N | 100 | 96 | 100 | 97 | 393 |
| | Mean (SD) | 36.7 (12.17) | 37.6 (11.19) | 36.6 (12.58) | 36.9 (11.60) | 36.9 (11.87) |
| | Min, Max | 18.0, 68.0 | 18.0, 67.0 | 18.0, 65.0 | 18.0, 69.0 | 18.0, 69.0 |
| Sex | % Male | 52 | 41 | 51 | 54 | 49 |
| Race | % Caucasian | 87 | 91 | 90 | 82 | 88 |
| BMI ($kg/m^2$) | N | 100 | 96 | 100 | 97 | 393 |
| | Mean (SD) | 25.2 (4.68) | 24.8 (5.00) | 24.7 (4.36) | 25.3 (4.54) | 25.0 (4.64) |
| | Min, Max | 16.7, 38.5 | 17.7, 41.1 | 17.0, 39.7 | 18.5, 40.2 | 16.7, 41.1 |

Abbreviations: SD=standard deviation; BMI=body mass index; Min=minimum; Max=maximum
Reference: CSR 2093-302, Section 14, Table 14.1-2.1.4.

**Table 4.2.2-1: Demographic Characteristics, Pooled Pivotal Phase III Studies 2093-301 and 2093-302 (ITT Analysis Set)**

| Characteristic: | Placebo (N=202) | SEP-0002093 Dose Group | | | Total SEP-0002093 (N=588) |
|---|---|---|---|---|---|
| | | 400 mg (N=195) | 800 mg (N=198) | 1200 mg (N=195) | |
| Mean (SD) Age (years) | 36.6 (12.00) | 37.5 (11.29) | 38.6 (12.45) | 37.4 (11.63) | 37.8 (11.80) |
| Age Group, n (%) | | | | | |
| < 60 years | 195 (96.5) | 191 (97.9) | 186 (93.9) | 187 (95.9) | 564 (95.9) |
| ≥ 60 years | 7 (3.5) | 4 (2.1) | 12 (6.1) | 8 (4.1) | 24 (4.1) |
| Number (%) Male | 100 (49.5) | 89 (45.6) | 105 (53.0) | 95 (48.7) | 289 (49.1) |
| Caucasian, n (%) | 189 (93.6) | 186 (95.4) | 188 (94.9) | 178 (91.3) | 552 (93.9) |
| Region, n (%) | 202 | 195 | 198 | 195 | 588 |
| Eastern Europe | 97 (48.0) | 94 (48.2) | 94 (47.5) | 92 (47.2) | 280 (47.6) |
| Latin America | 55 (27.2) | 53 (27.2) | 53 (26.8) | 52 (26.7) | 158 (26.9) |
| Western Europe/ROW | 50 (24.8) | 48 (24.6) | 51 (25.8) | 51 (26.2) | 150 (25.5) |
| Mean (SD) BMI ($kg/m^2$) | 24.9 (4.58) | 24.6 (4.72) | 24.6 (4.48) | 24.9 (4.36) | 24.7 (4.52) |

Abbreviations: SEP-0002093=eslicarbazepine acetate; SD=standard deviation; BMI=body mass index; ROW=rest of world; n= number of subjects with available data

Note: Eastern Europe includes Czech Republic, Croatia, Hungary, Lithuania, Poland, Romania, Russia, Ukraine; Latin America includes Argentina and Brazil; Western Europe/Rest of the World includes Australia, Austria, Belgium, Denmark, Germany, Portugal, South Africa, Spain, Sweden, Switzerland, The Netherlands, United Kingdom

Source: Module 2.7.3 Appendix Table 2.1

### 6.1.3 Baseline Epilepsy Characteristics

The inclusion and exclusion criteria for the studies generally were to select for adult subjects in good general health other than epilepsy and to have met certain lab and EKG criteria (for example, sodium ≥ 130 units and no 2nd or 3rd degree AV block not controlled by pacer). Subjects were to have a documented diagnosis of simple or complex partial seizures with or without secondary generalization and to have at least four partial seizures in each four week period during the eight weeks prior to screening and to be on at least one concomitant medication (not oxcarbazepine or felbamate). Subjects were not to have primary generalized epilepsy or psychogenic seizures and were not to have a history of status or cluster (defined as 3 or more seizures within 30 minutes) within 3 months prior to screening.

At visit 1 (screening):

1) written informed consent
2) aged ≥ 18 years
3) documented diagnosis of simple or complex partial seizures with or without secondary generalization since at least 12 months prior to screening
4) at least 4 partial seizures in each 4 week period during the last 8 weeks prior to screening
5) currently treated with 1 or 2 AEDs (except oxcarbazepine and felbamate), in a single dose regimen during at least 2 months before screening. Patients using vigabatrin should have been on this medication for at least a year with no visual field deficit (confirmed testing within 1 month before study entry). VNS is considered an AED. Study 302-amendment allowed use of 1-3 AEDs (except oxcarbazepine and felbamate). VNS was considered a concomitant AED.
6) Other than epilepsy, patient in general good health based on medical history, physical exam, and laboratory tests
7) Post-menopausal or otherwise incapable of pregnancy by reason of surgery or tubal ligation. In WOCBP, must have serum b-hcG negative and agree to remain abstinent or use reliable

contraception (oral contraception should be combined with a barrier method) beginning at screening and continuing at least
to the post-study visit)

At visit 2 (randomization):

1) At least 4 partial seizures in each 4 weeks during the 8-week baseline period prior to randomization (documented in a diary) and no seizure-free interval > 21 consecutive days
2) For WOCBP, a negative urine b-hcg test
3) Satisfactory diaries completed by the patient or caregiver
4) Satisfactorily complied with study requirements during the baseline period

Exclusion criteria for study 301 and 302:

At visit 1 (screening), patients must not have or be:

1) Only simple partial seizures with no motor symptomatology (classified as A2-4 as per 1981 International Classification of Epileptic Seizures) that are non video-EEG documented
2) Primary generalized epilepsy
3) Known rapid progressive neurological disorder
4) History of status epilepticus or cluster seizures (3 or more seizures within 30 minutes) within 3 months prior to screening
5) Psychogenic seizures. Study 302-within 2 years
6) History of schizophrenia or suicide attempt
7) Currently on or with exposure to felbamate or oxcarbazepine within one month of screening
8) Using benzodiazepines on more than an occasional basis (except as chronic AED)
9) Previous use of BIA2093 or participation in a clinical study of BIA2093
10) Known hypersensitivity to carbamazepine, oxcarbazepine or chemically related substances
11) History of alcohol, drug, or medication abuse within last 2 years
12) Uncontrolled cardiac, renal, hepatic, endocrine, gastrointestinal, metabolic, hematologic, or oncologic disorder
13) Second or third degree AVB not corrected with pacemaker
14) Relevant clinical laboratory abnormalities (for example, Na < 130, ALT or AST > 2xULN, WBC <3000 cells/$mm^3$ )
15) Estimated creatinine clearance < 50 mL/min
16) Pregnancy or nursing
17) Participation in other clinical drug trial within the last 2 months or received an investigational drug within 5 half-lives of this other product, whichever is longer.
18) Not ensured capability to perform the trial
19) Any other condition or circumstance that, in the opinion of the investigator, may compromise the patient's ability to comply with the study protocol

At visit 2 (randomization), patients must not be/have:

1) Inadequate compliance to concomitant AEDs during the 8 week baseline period
2) Inadequate completion of study diary
3) Any other condition or circumstance that, in the investigator's opinion, may compromise the patient's ability to comply with the study protocol

The sponsor's tables indicate that subjects had been diagnosed with epilepsy, on average, 19 to 25 years. The most common "etiology" in all groups including placebo was "other". More subjects in 301 had an "etiology" of "cranial trauma" than did subjects in 302. The average seizure frequency ranged from about 13 (400 mg ESL) to about 14 in the ESL 1200 mg group (this appears to be standardized to 4 weeks based on a different table, not shown, table 2.1.2-2 in the CSE).

Tables xx duplicated from the submission



**Table 4.2.3-1: Characteristics of the Disease, Pooled Pivotal Phase III Studies 2093-301 and 2093-302 (ITT Analysis Set, N=790)**

| Characteristic: | Placebo (N=202) | SEP-0002093 Dose Group | | | Total SEP-0002093 (N=588) |
|---|---|---|---|---|---|
| | | 400 mg (N=195) | 800 mg (N=198) | 1200 mg (N=195) | |
| Mean (SD) Duration of Epilepsy (years) | 22.4 (13.14) | 22.8 (11.73) | 22.8 (12.54) | 21.7 (12.46) | 22.4 (12.24) |
| Mean (SD) Age at Diagnosis (years) | 14.6 (12.24) | 15.1 (12.33) | 16.3 (13.91) | 16.1 (13.12) | 15.9 (13.13) |
| Possible Seizure Etiologies, n (%)[a] | | | | | |
| Idiopathic | 41 (20.3) | 32 (16.4) | 28 (14.1) | 35 (17.9) | 95 (16.2) |
| Cranial Trauma/Injuries | 31 (15.3) | 36 (18.5) | 26 (13.1) | 22 (11.3) | 84 (14.3) |
| Congenital/Hereditary | 15 (7.4) | 20 (10.3) | 21 (10.6) | 24 (12.3) | 65 (11.1) |
| Infectious Diseases | 15 (7.4) | 27 (13.8) | 20 (10.1) | 22 (11.3) | 69 (11.7) |
| Cerebrovascular Diseases | 5 (2.5) | 3 (1.5) | 6 (3.0) | 12 (6.2) | 21 (3.6) |
| Brain Tumors | 8 (4.0) | 4 (2.1) | 8 (4.0) | 5 (2.6) | 17 (2.9) |
| Systemic/Toxic/Metabolic | 2 (1.0) | 3 (1.5) | 3 (1.5) | 4 (2.1) | 10 (1.7) |
| Other/Unknown | 85 (42.1) | 75 (38.5) | 87 (43.9) | 75 (38.5) | 237 (40.3) |

Abbreviations: SEP-0002093=eslicarbazepine acetate; SD=standard deviation
a Subjects may be included in more than 1 category
Source: Module 2.7.3 Appendix Table 2.1

**Table 2.1.2-2: Baseline Disease Characteristics (Study 2093-301, ITT Analysis Set)**

| Parameter | Statistic/Class | Placebo (N=102) | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|---|
| | | | 400 mg (N=99) | 800 mg (N=98) | 1200 mg (N=98) |
| Duration of Epilepsy (years) | N | 102 | 99 | 98 | 98 |
| | Mean (SD) | 19.4 (12.57) | 21.0 (11.70) | 23.1 (13.50) | 20.4 (11.85) |
| | Min, Max | 1.0, 54.0 | 1.0, 55.2 | 1.1, 53.0 | 1.1, 45.8 |
| Most Common[a] Etiology of Epilepsy | %Other | 39 | 37 | 39 | 35 |
| | %Cranial trauma | 20 | 26 | 19 | 15 |
| | %Idiopathic | 25 | 15 | 15 | 16 |
| | %Infection | 6 | 15 | 13 | 10 |
| Seizure Frequency at Visit 2[b] | N | 102 | 99 | 98 | 98 |
| | Mean (SD) | 12.4 (17.94) | 11.4 (9.74) | 11.2 (11.21) | 11.6 (15.92) |
| | Median | 6.7 | 7.5 | 7.0 | 7.5 |
| | Min, Max | 2.0, 153.5 | 2.5, 55.5 | 3.0, 70.5 | 3.6, 141.5 |
| Concomitant AED at Baseline | %Taking Any AED | 100 | 100 | 100 | 100 |
| | %Taking 1 AED | 33 | 39 | 32 | 39 |
| | %Taking 2 AEDs | 66 | 60 | 68 | 61 |
| Most Common[a] Types of AED | %Carbamazepine | 62 | 56 | 60 | 56 |
| | %Lamotrigine | 26 | 24 | 27 | 28 |
| | %Valproic acid | 28 | 26 | 22 | 26 |
| | %Topiramate | 16 | 9 | 19 | 11 |

Abbreviations: SD=standard deviation; AED=antiepileptic drug; Min=minimum; Max=maximum
a Reported in ≥10% of the total ITT analysis set
b Standardized to 4 weeks.
Reference: CSR 2093-301, Section 15, Table 25, Table 27, Table 28, and Table 29.

**Table 2.2.2-2: Baseline Disease Characteristics (Study 2093-302, ITT Analysis Set)**

| Parameter | Statistic/Class | Placebo (N=100) | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|---|
| | | | 400 mg (N=96) | 800 mg (N=100) | 1200 mg (N=97) |
| Duration of Epilepsy (years) | N | 100 | 95 | 100 | 97 |
| | Mean (SD) | 25.4 (13.06) | 24.7 (11.52) | 22.6 (11.59) | 23.0 (12.97) |
| | Min, Max | 2.0, 65.5 | 1.4, 59.3 | 1.9, 58.0 | 1.8, 65.7 |
| Most Common[a] Etiology of Epilepsy | %Other/Unknown | 45 | 40 | 49 | 42 |
| | %Idiopathic | 16 | 18 | 13 | 20 |
| | %Congenital/hereditary | 8 | 15 | 15 | 13 |
| | %Infection | 9 | 13 | 7 | 12 |
| | %Cranial Trauma | 11 | 10 | 7 | 7 |
| Seizure Frequency at Visit 2[b] | N | 100 | 96 | 100 | 97 |
| | Mean (SD) | 13.3 (14.03) | 14.4 (18.65) | 15.5 (15.27) | 15.9 (16.31) |
| | Median | 7.4 | 8.2 | 9.1 | 9.3 |
| | Min, Max | 3.2, 79.4 | 3.3, 127.7 | 3.4, 78.7 | 2.0, 87.9 |
| Concomitant AED at Baseline | %Taking Any AED | 100 | 100 | 100 | 100 |
| | %Taking 1 AED | 15 | 23 | 17 | 21 |
| | %Taking 2 AEDs | 76 | 71 | 73 | 69 |
| | %Taking 3 or 4 AEDs | 9 | 6 | 10 | 10 |
| Most Common[a] Types of AED | %Carbamazepine | 58 | 61 | 61 | 59 |
| | %Valproic acid | 26 | 13 | 28 | 21 |
| | %Lamotrigine | 24 | 22 | 17 | 22 |
| | %Clobazam | 16 | 20 | 21 | 12 |
| | %Levetiracetam | 16 | 16 | 13 | 20 |
| | %Phenytoin | 14 | 11 | 15 | 12 |
| | %Phenobarbital | 18 | 11 | 13 | 9 |
| | %Topiramate | 12 | 11 | 11 | 15 |

Abbreviations: SD=standard deviation; AED=antiepileptic drug; Min=minimum; Max=maximum
a Reported in ≥5% of the total ITT analysis set.
b Standardized to 4 weeks.
Reference: CSR 2093-302, Section 14, Table 14.1-2.3.4, Table 14.1-3.3.2, Table 14.1-3.6.2 and Table 14.2-2.1.1.

**Table 3.3.2.3-1: Seizure Frequency and Type of Seizure During the Baseline Period, Pooled Pivotal Phase III Studies 2093-301 and 2093-302 (ITT Analysis Set, N=790)**

| Characteristic: | Placebo (N=202) | Eslicarbazepine Acetate Dose Group | | | Total ESL (N=588) |
|---|---|---|---|---|---|
| | | 400 mg (N=195) | 800 mg (N=198) | 1200 mg (N=195) | |
| Standardized Baseline Seizure Frequency | | | | | |
| Mean (SD) | 13.5 (17.55) | 13.1 (15.05) | 13.6 (13.73) | 13.8 (16.13) | 13.5 (14.97) |
| Median | 7.1 | 8.0 | 7.5 | 8.5 | 8.0 |
| Minimum, Maximum | 2.0, 153.5 | 2.5, 130.0 | 3.0, 80.1 | 2.0, 141.5 | 2.0, 141.5 |
| Worst Seizure Type during Baseline Period | | | | | |
| Simple Partial | 30 (14.9) | 33 (16.9) | 27 (13.6) | 25 (12.8) | 85 (14.5) |
| Complex Partial | 92 (45.5) | 92 (47.2) | 100 (50.5) | 95 (48.7) | 287 (48.8) |
| Partial Evolving | 76 (37.6) | 66 (33.8) | 66 (33.3) | 70 (35.9) | 202 (34.4) |
| Unclassified | 4 (2.0) | 4 (2.1) | 5 (2.5) | 5 (2.6) | 14 (2.4) |

Abbreviations: SD=standard deviation
Reference: ISE EOT Table 2.1

### 6.1.4 Subject Disposition

Based on the tables below, fewer subjects on ESL 1200 mg dosing completed either study 301 or 302 when compared to other groups. In study 302, most of the 1200 mg ESL subjects withdrew during/end of maintenance compared to study 301, where most of the 1200 mg ESL withdrew in titration, followed by maintenance. In study 301, the group with the highest study completion was the 400 mg ESL group. In study 302, the group with the highest study completion was the placebo group.

The most common reasons for study discontinuation were somewhat different between the studies. Adverse events were the most common reason in all ESL groups in study 302 while in study 301, for the 400 mg group, equal percentages of patients withdrew for adverse events as did for withdrawal of consent. Withdrawal of consent was the second most common reason for early termination in the 1200 mg group in study 301 and was higher in study 301 for the 1200 mg group than it was for the 1200 mg group in study 302 (9.8% in 301 and 3.1% in 302). Withdrawal for unacceptable adverse events was dose related in both studies. In study 302, adverse event discontinuation led to the discontinuation of 25% of the subjects in the 1200 mg ESL group.

Tables xx-duplicated from the submission

**Table 2.1.1-1: Subject Disposition (Study 2093-301)**

| Disposition | Placebo | Eslicarbazepine Acetate Dose Group | | | Total |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | |
| Randomized | 102 | 100 | 98 | 102 | 402 |
| Completed the Study | 84 (82.4) | 90 (90.0) | 85 (86.7) | 71 (69.6) | 330 (82.1) |
| Withdrew Prematurely | 18 (17.6)[a] | 10 (10.0) | 13 (13.3) | 31 (30.4)[a] | 72 (17.9)[a] |
| Withdrew during/end of Baseline | 1 (1.0) | 2 (2.0) | 2 (2.0) | 7 (6.9) | 12 (3.0) |
| Withdrew during/end of Titration | 5 (4.9) | 2 (2.0) | 4 (4.1) | 13 (12.7) | 24 (5.9) |
| Withdrew during/end of Maintenance | 10 (9.8) | 6 (6.0) | 7 (7.1) | 10 (9.8) | 33 (8.2) |
| Withdrew during/end of Taper | 0 | 0 | 0 | 0 | 0 |
| Reasons for Withdrawal[b] | | | | | |
| Unacceptable Adverse Event | 3 (2.9) | 4 (4.0) | 8 (8.2) | 18 (17.6) | 33 (8.2) |
| Withdrawal of Consent | 10 (9.8) | 4 (4.0) | 4 (4.1) | 10 (9.8) | 28 (7.0) |
| Subject Non-compliance | 3 (2.9) | 1 (1.0) | 1 (1.0) | 1 (1.0) | 6 (1.5) |
| Lack of Efficacy | 0 | 0 | 0 | 2 (2.0) | 2 (0.5) |
| Investigator Discretion | 0 | 0 | 1 (1.0) | 1 (1.0) | 2 (0.5) |
| Protocol violation | 1 (1.0) | 0 | 0 | 1 (1.0) | 2 (0.5) |
| Pregnancy | 0 | 0 | 1 (1.0) | 0 | 1 (0.2) |
| Other | 4 (3.9) | 2 (2.0) | 1 (1.0) | 3 (2.9) | 10 (2.5) |

a Includes 2 subjects from the placebo group and 1 subject from the ESL 1200 mg group who finished the tapering-off period but who were reported not to have completed Visits 3 through 6 as scheduled; a reason for discontinuation was therefore specified.

b A subject may have more than 1 reason for discontinuation.

Reference: CSR 2093-301 Part 1. in-text Table 2 and Section 15. Table 16.

**Table 2.2.1-1: Subject Disposition (Study 2093-302)**

| Disposition | Placebo | Eslicarbazepine Acetate Dose Group | | | Total |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | |
| Randomized | 100 | 96 | 101 | 98 | 395 |
| Completed the Study | 94 (94.0) | 84 (87.5) | 81 (80.2) | 68 (69.4) | 327 (82.8) |
| Withdrew Prematurely | 6 (6.0) | 12 (12.5) | 20 (19.8) | 30 (30.6) | 68 (17.2) |
| Withdrew end of Baseline | 0 | 0 | 1 (1.0) | 0 | 1 (2.5) |
| Withdrew during Titration | 0 | 0 | 8 (7.9) | 6 (6.1) | 14 (3.5) |
| Withdrew during/end of Maintenance | 6 (6.0) | 12 (12.5) | 11 (10.9) | 24 (24.5) | 53 (13.4) |
| Reasons for Withdrawal[a] | | | | | |
| Unacceptable Adverse Event | 3 (3.0) | 10 (10.4) | 16 (15.8) | 25 (25.5) | 54 (13.7) |
| Withdrawal of Consent | 1 (1.0) | 2 (2.1) | 2 (2.0) | 3 (3.1) | 8 (2.0) |
| Subject Non-compliance | 2 (2.0) | 1 (1.0) | 0 | 4 (4.1) | 7 (1.8) |
| Lack of Efficacy | 1 (1.0) | 2 (2.1) | 0 | 0 | 3 (0.8) |
| Protocol violation | 0 | 1 (1.0) | 1 (1.0) | 1 (1.0) | 3 (0.8) |
| Investigator Discretion | 0 | 0 | 1 (1.0) | 1 (1.0) | 2 (0.5) |
| Other | 0 | 1 (1.0) | 2 (2.0) | 1 (1.0) | 4 (1.0) |

a A subject may have more than 1 reason for discontinuation.

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**Table 3.2-1: Subject Disposition, Pooled Pivotal Phase III Studies 2093-301 and 2093-302**

| Disposition: | Placebo n (%) | Eslicarbazepine Acetate Dose Group | | | Total ESL n (%) |
|---|---|---|---|---|---|
| | | 400 mg n (%) | 800 mg n (%) | 1200 mg n (%) | |
| Randomized | 202 | 196 | 199 | 200 | 595 |
| Entered the Titration Period | 202 | 195 | 198 | 195 | 588 |
| Entered the Maintenance Period | 198 (98.0) | 192 (98.5) | 182 (91.9) | 180 (92.3) | 554 (94.2) |
| Completed the Study | 178 (88.1) | 174 (89.2) | 166 (83.8) | 139 (71.3) | 479 (81.5) |
| Withdrew During Double-blind Period[a] | 24 (11.9) | 21 (10.8) | 32 (16.2) | 56 (28.7) | 109 (18.5)[b] |
| Reason for Withdrawal | | | | | |
| Adverse Event | 3 (1.5) | 12 (6.2) | 20 (10.1) | 38 (19.5) | 70 (11.9) |
| Withdrew Consent | 11 (5.4) | 5 (2.6) | 6 (3.0) | 10 (5.1) | 21 (3.6) |
| Investigator Discretion | 0 | 0 | 2 (1.0) | 1 (0.5) | 3 (0.5) |
| Non-compliance | 4 (2.0) | 0 | 0 | 3 (1.5) | 3 (0.5) |
| Exacerbation of Seizures | 1 (0.5) | 2 (1.0) | 0 | 1 (0.5) | 3 (0.5) |
| Other | 3 (1.5) | 2 (1.0) | 2 (1.0) | 3 (1.5) | 7 (1.2) |

Abbreviations: ESL=eslicarbazepine acetate
Note: All percents based on number of subjects who entered the Titration Period.
a Double-blind period includes titration, maintenance and tapering-off periods; the latter in Study 2093-301 only.
b Includes 5 subjects in Study 2093-301 who withdrew from the study during the tapering-off period; Study 2093-302 did not include a tapering-off period.
Reference: ISE EOT Table 1.1

### 6.1.5 Protocol Violations

**Study 301:**

The study report for study 301 indicates that 54 subjects from the ITT population were excluded when selecting the PP population. 50 were excluded because they discontinued early and therefore were not treated for 12 weeks and four were excluded

secondary to violations considered by the sponsor as major protocol violations. As per table 2 of the study report (table not shown), one patient in the placebo group and one patient in the ESL 1200 mg group discontinued after randomization secondary to a protocol violation.

The following table is duplicated from the study report for 301 and displays the sponsor's summary of protocol deviations.

Table 17: Protocol deviations (safety population)

| | ESL 1200 mg (N=102) | | ESL 800 mg (N=98) | | ESL 400 mg (N=100) | | Placebo (N=102) | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N (%) | PD | N (%) | PD | N (%) | PD | N (%) | PD | N (%) | PD |
| Total | 102 (100.0%) | | 98 (100.0%) | | 100 (100.0%) | | 102 (100.0%) | | 402 (100.0%) | |
| No Deviation | 45 (44.1%) | | 41 (41.8%) | | 42 (42.0%) | | 37 (36.3%) | | 165 (41.0%) | |
| At Least One Deviation | 57 (55.9%) | 105 | 57 (58.2%) | 129 | 58 (58.0%) | 103 | 65 (63.7%) | 116 | 237 (59.0%) | 453 |
| AED regime violation | 25 (24.5%) | 39 | 29 (29.6%) | 61 | 29 (29.0%) | 39 | 29 (28.4%) | 42 | 112 (27.9%) | 181 |
| IMP regime violation | 14 (13.7%) | 20 | 22 (22.4%) | 32 | 19 (19.0%) | 25 | 24 (23.5%) | 34 | 79 (19.7%) | 111 |
| Occurrence of Excl. Crit. No 7 | 1 ( 1.0%) | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 0.2%) | 1 |
| Occurrence of Excl. Crit. No 14 | 0 | 0 | 3 ( 3.1%) | 3 | 0 | 0 | 0 | 0 | 3 ( 0.7%) | 3 |
| Time frame violation | 39 (38.2%) | 43 | 31 (31.6%) | 31 | 33 (33.0%) | 35 | 34 (33.3%) | 34 | 137 (34.1%) | 143 |
| Unreliable diary data | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 1.0%) | 1 | 1 ( 0.2%) | 1 |
| Violation of Incl. Crit. No 4 | 1 ( 1.0%) | 1 | 1 ( 1.0%) | 1 | 1 ( 1.0%) | 1 | 0 | 0 | 3 ( 0.7%) | 3 |
| Violation of Incl. Crit. No 5 | 1 ( 1.0%) | 1 | 0 | 0 | 1 ( 1.0%) | 1 | 2 ( 2.0%) | 2 | 4 ( 1.0%) | 4 |
| Violation of Incl. Crit. No 8 | 0 | 0 | 1 ( 1.0%) | 1 | 2 ( 2.0%) | 2 | 3 ( 2.9%) | 3 | 6 ( 1.5%) | 6 |

Note: PD = number of protocol deviations, N (%) = number and percent of patients in population
Exclusion Criteria: No 7 = Currently on or with exposure to felbamate or oxcarbazepine within one month of screening.
No 14 = Relevant clinical laboratory abnormalities.
Inclusion Criteria: No 4 = At least 4 partial onset seizures in each 4 week period during the last 8 weeks prior to screening.
No 5 = Currently treated with 1 or 2 AEDs in a stable dose regimen during at least 2 months prior to screening
No 8 = At least 4 partial seizures in each 4 weeks during the 8-week baseline period prior to randomisation.

Statistical Report (Section 17.5), Table A5.1

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Compliance with medication use (ITT population):

The CSR for study 301 indicates that treatment compliance was assessed by counting returned unused tablets and interviewing each patient. Taken on-face, the sponsor's Table 31 of the CSR for 301 indicates that generally, in the 12-week maintenance period, about 91% to 97% for the groups were in the 80 to 120% compliance range for study treatment. In the tapering phase, for about 10% to 27% of patients, compliance was not known. Visit 6 occurred in this study at the end of the tapering phase, it is unclear how the relatively large amount of missing data may impact data interpretation of safety

Table xx

| | | placebo | 400 mg | 800 mg | 1200 mg |
|---|---|---|---|---|---|
| **Baseline** | 80-120% | 101/102 | 98/99 | 98/98 | 97/98 |
| **Titration** | 80-120% | 97/102 | 91/99 | 94/98 | 92/98 |
| **12-week maintenance** | 80-120% | 94/102 | 96/99 | 91/98 | 89/98 |
| | Not known | 6/102 | 3/99 | 6/98 | 6/98 |
| **Taper** | 80-120% | 87/102 | 89/99 | 85/98 | 72/98 |

| | | | | | |
|---|---|---|---|---|---|
| | Not known | 15/102 (14.7%) | 10/99 (10.1%) | 13/98 (13/3%) | 26/98 (26.5%) |

**Data excerpted from Table 31 of the CSR for study 301, page 133/1074 of the bia-2093-301a1-legacy.pdf**

Possible quality control issues: As per preliminary feedback from DSI, drug accountability was not reliably able to be tracked at one of the four sites monitored and at another site, records in general were considered insufficient from a quality point of view. Both Bial and Sepracor conducted site audits of the phase 3 epilepsy studies. In study 301, both of the sites FDA audited (site 213 in the Ukraine, investigator Bitensky and site 112 in Croatia, investigatory Hodoba) were also audited by both Bial and Sepracor. DSI classified site 213 as a "voluntary action indicated" and noted that although regulatory violations were noted, these appeared to be isolated and unlikely important to study outcome. DSI considered the data reliable. The DSI inspection of site 112 resulted in a preliminary classification of "Significant deviations from regulations. Data unreliable." Given the discrepancies in the conclusions of DSI inspectors and those of the sponsor, I have included a summary of the audit findings perhaps relevant to compliance from each source (Bial, Sepracor, and FDA) below.

One of the sites audited by both Sepracor and Bial also was audited by FDA inspectors (site 112 in Croatia). For site 112, Bial's audit, Sepracor's audit, and the FDA's audit (as per form 483) are described.

- Bial's audit was contracted to (b) (4). The audit was performed 3-2-2005. I was not able to locate information on this audit form that describes the number of subjects enrolled, randomized, completed, or with AEs. Under the section, "Investigational Product", there is no discussion of the way medications are dispensed and collected. The audit section about protocol adherence has an auditor's comment of "The protocol is well adhered to." The audit concluded that the site was performing the study very well and that from the audit outcome, there seemed to be no issue for the site to include more patients and to do this well.

- Sepracor's audit was contracted to (b) (4). The audit dates were 9-30-2008 to 10-2-2008. This site started enrollment on 9-13-04 and ended enrollment on 10-20-05. At the time of the audit, 17 patients were randomized, 16 had completed, 1 terminated early, and 4 had experienced an SAE in part 1. The audit form includes sections (B6a and B6b) that assess records of receipt, storage, and return (destruction) and records of drug dispensed to and returned by subjects respectively.

  B6a- "Were drug accountability records adequate for sampled subjects?" The auditor indicated 'No". This section was rated as a "3", which is "significant non-compliance". There is a statement, "Destruction of empty boxes and blisters is not documented." Nine subjects are listed as having discrepancies between the

drug accountability log and the certificate of destruction (differences of destroying more than were returned for 3 subjects, destroying less than returned for six subjects with three subjects only discrepant by 1-4 tablets but three discrepant by 14, 20, and 56 tablets). For one subject (1272), the auditor noted that the drug accountability log indicated the subject received 8 blisters at visit 1 (# tablets is not noted). For subject 1269, the log indicates that the subject received, with the sponsor's approval, 2 blisters of placebo from box #90397 of which he returned 12 tablets. The auditor noted that if the documentation for both subjects is correct, it would mean that subject 1272 received 1 blister with 12 tablets which was already dispensed to subject 1269.

B6b-In response to "Were records detailing dispensing and return of drugs by subject adequate for sampled subjects?", the auditor indicated "no". For subjects 1246, 1250, 1252, and 1264, there is a comment indicating that either dispensation or return of IP for visits 1and 2 was not documented in the source notes. In the summary of the audit, section B6b received a rating of 2 (minor non-compliance).

- FDA's audit: FDA form 483 for site 112 notes the following (duplicated from Form 483 below).

"Investigational drug disposition records are not adequate with respect to quantity.

Specifically, drug accountability records are inaccurate to account for the number of tablets destroyed versus the number of tablets returned by subjects. Notes to File prepared by the Site Monitor on12/15/2008 and 12/18/2008 offers clarification; however, there is no documentation to support these clarifications. The Certificate of Destruction, signed and dated 6/13/2007 by the clinical investigator, does not differentiate between the baseline (placebo) and double-blind phase of the study. For example,

| Subject # | Dispensed | Returned by Subject | Destroyed | Unaccounted For |
|---|---|---|---|---|
| 1245 | 434 | 70 | 56 | 14 |
| 1246 | 434 | 70 | 84 | * |
| 1249 | 434 | 74 | 54 | 20 |
| 1250 | 434 | 68 | 12 | 56 |
| 1251 | 434 | 72 | 94 | * |

• Site documented they destroyed more tablets than returned by subject."

I looked at audit forms for several sites in study 301 to see if there was a suggestion that findings at site 112 were either isolated or more wide-spread. The table below describes findings as related to drug accountability/dispensation.

Table xx- audit report findings-generally limited to drug accountability or investigational product comments and findings

| **Site Country** | **B6a** **"Were drug accountability records adequate for sampled subjects?"** | **B6a rating** | **B6b** **"Were records detailing dispensing and return of drugs by subjects adequate for sampled subjects?"** | **B6b rating** | **Bial audit** |
|---|---|---|---|---|---|
| 177-Poland | part 1-no-1/3 | 2 | part 1-no-1/3 | 2 | NA |
| | part 2-yes-2/3 | 1 | part 2-no-2/3 | 2 | |
| 181-Romania | part 1-no-16/16 | 2 | part 1-yes-5/16 | 1 | Comments limited to storage temperature |
| | part 2-no-14/14 | 2 | part 2-yes-3/14 | 1 | |
| 192-Russia | part 1-yes-9/15 | 1 | part 1-no-9/15 | 2 | one patient noted to have dropped out 2-3 weeks before audit account-ability form not fully completed |
| | part 2-yes-6/12 | 1 | part 2-no-6/12 | 2 | |
| 193-Russia | part 1-yes-3/14 | 1 | part 1-no-3/14 | 2 | NA |
| | part2- no- 3/9 | 2 | part 2-no-3/9 | 2 | |
| 194-Russia | part 1-yes-5/11 | 1 | part 1-yes-5/11 | 1 | NA |
| | part 2-yes-5/10 | 1 | part 2-no-5/10 | 2 | |
| 195-Russia | part 1-yes-3/13 | 1 | part 1-yes-3/13 | 1 | NA |
| | part 2-no-6/12 | 2 | part 2-no-6/12 | 2 | |
| 211-Ukraine | part 1-yes-5/22 | 1 | part 1-no-5/22 | 2 | one patient noted to have dropped out 2-3 weeks before audit account-ability form not fully completed |
| | part 2-yes-4/18 | 1 | part 2-no-4/18 | 2 | |
| 212-Ukraine | part 1-yes-5/17 reviewed | 1 | part 1- no-5/17 | 2 | NA |
| | part 2-no-4/16 | 2 | part 2-no-4/16 | 2 | |
| 213-Ukraine | part 1-yes- 27/27 reviewed | 1 | part 1-yes-6/27 reviewed | 1 | Part 1? Observation that more blister packs dispensed/re-turned than received |
| | part 2-yes- 19/19 | 1 | part 2-no-6/19 | 2 | |

Ratings are taken from the summary page of the audit forms. Rating 1=adequate, 2=minor non-compliance, 3=significant non-compliance

**Study 302:**

Major violations, as defined by the sponsor, were protocol deviations considered as capable of impacting the primary efficacy variable. The sponsor reports identifying these before database lack at a blinded review meeting. 13% of the placebo group, 17.7% of the ESL400 mg group, 9% of the ESL 800 mg group, and 18.6% of the ESL 1200 mg group are reported to have had a major protocol violation (see the sponsor's table 10-1, reproduced below from the CSR).

Table xx

**Table 10-1. Major Protocol Violations Affecting > 1 Patient (ITT Population)**

| | Placebo (N=100) n (%) | ESL 400 mg (N=96) n (%) | ESL 800 mg (N=100) n (%) | ESL 1200 mg (N=97) n (%) | Total (N=393) n (%) |
|---|---|---|---|---|---|
| **Any Protocol Violation** | 13 ( 13.0) | 17 ( 17.7) | 9 ( 9.0) | 18 ( 18.6) | 57 ( 14.5) |
| Baseline seizure frequency per 4 weeks is less than 4. | 10 ( 10.0) | 9 ( 9.4) | 6 ( 6.0) | 10 ( 10.3) | 35 ( 8.9) |
| Inadequate completion of the study diary. | 2 ( 2.0) | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.5) |
| Inadequate compliance to concomitant AEDs during the 8-week baseline period. | 0 ( 0.0) | 2 ( 2.1) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 0.5) |
| Patient treated with more than three concomitant AEDs (patient included after Protocol Amendment 2) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 1.0) | 3 ( 3.1) | 4 ( 1.0) |
| Study drug compliance during the double-blind assessment period ≤ 80% or > 120% | 2 ( 2.0) | 2 ( 2.1) | 2 ( 2.0) | 3 ( 3.1) | 9 ( 2.3) |

Cross-reference: Table 14.1-1.6.2



The sponsor's Table 10-2 (reproduced below) displays protocol deviations affecting more than 3 patient s in the ITT population. In my opinion, some of these protocol deviations are potentially problematic, either by the nature of the violation or the differential incidences, such as changing the AED dose regimen during the double-blind period.

**Table 10-2. Protocol Deviations Affecting > 3 Patients (ITT Population)**

| | Placebo (N=100) n (%) | ESL 400 mg (N=96) n (%) | ESL 800 mg (N=100) n (%) | ESL 1200 mg (N=97) n (%) | Total (N=393) n (%) |
|---|---|---|---|---|---|
| **Any Protocol Violation** | 43 ( 43.0) | 40 ( 41.7) | 41 ( 41.0) | 36 ( 37.1) | 160 ( 40.7) |
| Absences reported during the baseline period. | 0 ( 0.0) | 2 ( 2.1) | 2 ( 2.0) | 6 ( 6.2) | 10 ( 2.5) |
| At least one seizure-free interval exceeds 21 consecutive days during the 8-week baseline period. | 14 ( 14.0) | 13 ( 13.5) | 7 ( 7.0) | 9 ( 9.3) | 43 ( 10.9) |
| Change in AED dose regimen during the double-blind assessment period. | 3 ( 3.0) | 3 ( 3.1) | 9 ( 9.0) | 7 ( 7.2) | 22 ( 5.6) |
| Not at least 4 partial seizures in each 4 weeks during the 8-week baseline period prior to randomization or a seizure-free interval exceeding 21 consecutive days. | 20 ( 20.0) | 15 ( 15.6) | 13 ( 13.0) | 13 ( 13.4) | 61 ( 15.5) |
| Not currently treated with 1 or 2 AEDs in a stable dose regimen during at least 2 months prior to screening. | 7 ( 7.0) | 13 ( 13.5) | 11 ( 11.0) | 8 ( 8.2) | 39 ( 9.9) |
| Patient treated with more than two concomitant AEDs (patient included before Protocol Amendment 2). | 9 ( 9.0) | 7 ( 7.3) | 8 ( 8.0) | 11 ( 11.3) | 35 ( 8.9) |

Cross-reference: Table 14.1-1.7.2

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Compliance with medication use ITT population:

As per the clinical study report for study 302, compliance with investigational product use was assessed by interview and with an inventory of returned tablets. Patients were instructed to return all empty packaging and all dispensed but unused investigational product at each visit after randomization. Non-compliance with study drug (major protocol violation) was considered as ≤ 80% or ≥ 120%. The CSR reports this as 9 patients (2.3%) (2 placebo, 2 ESL 400 mg, 2 ESL 800 mg, and 3 ESL 1200 mg).

FDA and both Bial and Sepracor audited site 338 (investigator Baldur, Brazil). FDA DSI review indicates that although regulatory violations were noted, they are "unlikely to importantly impact data integrity" (Clinical Inspection Summary, 4-9-10) and the site data are considered reliable. Both FDA and Sepracor audited site 395.

Given the DSI report of questionable record-keeping at one site in study 302, I looked at the drug accountability/dispensation records for sites audited by BIAL in study 302. The table below displays the sponsor's assessments of drug accountability and records' dispensation. "3" indicates significant non-compliance.

| **Site Country** | **B6a "Were drug accountability records adequate** | **B6a rating** | **B6b "Were records detailing dispensing and** | **B6b rating** | **Bial audit** |
|---|---|---|---|---|---|

| | **for sampled subjects?" #obis/#audited/total # at site** | | **return of drugs by subjects adequate for sampled subjects?"** | | |
|---|---|---|---|---|---|
| 301-Argentina | part 1-no-1/6/27 | 2 | part 1-no-1/6/27 | 2 | |
| 312-Australia | part 1-no-2/4/18 | 2 | part 1-yes-0/4/18 | 1 | |
| 313-Australia | part 1-no-2/3/7 | 2 | part 1-yes-0/3/7 | 1 | |
| 331-Brazil | part 1-yes-0/4/21 | 1 | part 1-no-0/4/21 | 2 | |
| 333-Brazil | part 1-yes-0/5/18 | 1 | part 1-no-4/5/18 | 2 | |
| 336-Brazil | part 1-yes0/2/27 | 1 | part 1-yes0/2/27 | 1 | |
| **338-Brazil** | part 1-no-2/5/26 | 2 | part 1-no-2/5/26 | 2 | |
| 351-Germany | part 1-no-1/3/17 | 2 | part 1- no5/3/17 | 2 | |
| 351-South Africa | part 1-no- 1/4/4 | 3 | part 1-no-2/4/4 | 2 | |
| 332-Brazil | part 1-yes-0/3/17 | | part 1-yes-0/3/17 | | |
| 388-South Africa | part 1-yes-0/5/9 | 1 | part 1-no-3/5/9 | 2 | |
| 395-Spain | part 1-yes-3/15 | 2 | part 1-yes-3/15 | | |

Ratings are taken from the summary page of the audit forms. Rating 1=adequate, 2=minor non-compliance, 3=significant non-compliance

### 6.1.6 Analysis of Primary Endpoint(s)

Diary card data was provided by either the subject or caregiver.

In each study (301and 302), the primary efficacy endpoint was standardized seizure frequency per four weeks over the 12-week maintenance period. The analysis was an ANCOVA that models the logarithm of the standardized seizure frequency as a function of baseline seizure frequency and treatment. In study 301, region was added to the ANCOVA model. Regions were defined as;

- Western region: Austria, Germany, Switzerland
- Central region: Croatia, Czech Republic, Hungary, Poland, Lithuania
- Eastern region: Romania, Russia, Ukraine.

Tables xx

**Table 2.1.3-1: Primary Efficacy Analysis: Standardized Seizure Frequency per 4 weeks over the 12-week Maintenance Period (Study 2093-301, ITT Analysis Set)**

| Standardized Seizure Frequency per 4 weeks | Placebo (N=102) | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | | 400 mg (N=99) | 800 mg (N=98) | 1200 mg (N=98) |
| N | 99 | 97 | 94 | 94 |
| LS Mean (back-transformed) | 7.64 | 6.73 | 5.66 | 5.35 |
| [95% CI on the Mean] | [6.78, 8.58] | [5.93, 7.60] | [4.92, 6.45] | [4.63, 6.12] |
| Log LSMean Difference to Placebo | | -0.0812 | -0.1869 | -0.2196 |
| ANCOVA p-value[a] | | 0.3332 | 0.0028 | 0.0003 |

Abbreviations: LS Mean=least squares mean; CI=confidence interval; ANCOVA=analysis of covariance
Note: Estimated LS Means with 95% CIs from ANCOVA with treatment as factor and log-transformed baseline seizure frequency as covariate. Estimates from ANCOVA were back-transformed using the exponential function.
a p-value from Dunnett's multiple comparison procedure for the comparison of the active treatment means to the placebo mean.
Reference: CSR 2093-301, Section 15, Table 33

**Table 2.2.3-1: Primary Efficacy Analysis: Standardized Seizure Frequency per 4 weeks over the 12-week Maintenance Period (Study 2093-302, ITT Analysis Set)**

| Standardized Seizure Frequency per 4 weeks | Placebo (N=100) | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | | 400 mg (N=96) | 800 mg (N=100) | 1200 mg (N=97) |
| N | 99 | 95 | 88 | 85 |
| LS Mean (back-transformed) | 9.8 | 8.7 | 7.1 | 7.0 |
| [95% CI on the Mean] | [8.7, 11.1] | [7.7, 9.9] | [6.2, 8.2] | [6.0, 8.1] |
| LSMean Difference to Placebo | | -1.1 | -2.7 | -2.8 |
| ANCOVA p-value[a] | | 0.423 | 0.002 | 0.001 |

Abbreviations: LS Mean=least squares mean; CI=confidence interval; ANCOVA=analysis of covariance
Note: Estimated LS Means with 95% CIs from ANCOVA model with treatment as factor and log-transformed baseline seizure frequency as covariate. Model was based on log-transformed seizure frequencies. Estimates from the ANCOVA model were back transformed using the exponential function.
a p-value from Dunnett's multiple comparison procedure for the comparison of the active treatment means to the placebo mean.
Reference: CSR 2093-302, Section 14, Table 14.2-2.2.1

FDA statistical reviewer:
The primary statistical review was performed by Dr. X. Ling. The statistical reviewer's review had not received all signatures necessary to be considered final, although as of the writing of this section of this review (3-12-09), her review has Team Leader level agreement. Therefore, the following comments should be considered preliminary.

Study 301: The statistical reviewer identified several potential issues in the sponsor's analyses. These included extensive hard-coding, unblinded seizure data review, missing seizure data and a change in the primary analysis use of imputed data from titration. Her review discusses each issue and I refer the reader to this review.

The statistical reviewer's analysis of the primary endpoint, employed a model with only baseline frequency and treatment group in the ANCOVA model, calculated a log standardized seizure frequency, and imputed missing seizure frequency during the

maintenance period in two ways, conservatively using the maximum seizure frequency during the baseline or titration period and non-conservatively using the seizure frequency during titration. The reviewer noted this was the primary analysis method used in the NDA for lacosamide.

Her results are excerpted from the draft review below. Also, Dr. Ling dropped site 112 due to the compliance issues and reports the results were similar.

The results showed that the 800 and 1200 mg/day doses had statistically significantly lower seizure frequencies than placebo during assessment period. The results were robust to the handling of dropouts. Based on the analysis using non-conservative imputation on ITT population, the percent reduction over placebo calculated by 100*(1-exp(LSMean difference of the log standardize seizure frequency)) were 9.5%, 21.8% and 27.3% for 400mg, 800mg and 1200mg groups respectively. The dose response appeared to be monotone.

**Table 1. Study 301: FDA Analysis Results for the Primary Endpoint**

| | | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | **Placebo** | **400 mg** | **800 mg** | **1200 mg** |
| **Completers (with maintenance assessment)** | | | | |
| N | 99 | 97 | 93 | 92 |
| LSmean (SE) | 6.8 ( 0.47) | 6.1 ( 0.44) | 5.1 ( 0.38) | 4.6 ( 0.35) |
| 95% CI | 6.0, 7.8 | 5.3, 7.0 | 4.4, 5.9 | 4.0, 5.4 |
| Log Difference in LSMean (SE) | | -0.10 ( 0.086) | -0.25 ( 0.087) | -0.33 ( 0.087) |
| 95% CI for Difference in LSMean | | -0.30, 0.11 | -0.45, -0.04 | -0.54, -0.13 |
| p-value | | 0.5517 | 0.0128 | 0.0004 |
| **ITT population (Conservative Imputation)** | | | | |
| N | 102 | 98 | 98 | 97 |
| LSmean (SE) | 7.0 ( 0.48) | 6.2 ( 0.44) | 5.3 ( 0.38) | 4.8 ( 0.36) |
| 95% CI | 6.1, 8.0 | 5.4, 7.1 | 4.6, 6.1 | 4.2, 5.6 |
| Log Difference in LSMean (SE) | | -0.11 ( 0.086) | -0.23 ( 0.086) | -0.31 ( 0.086) |
| 95% CI for Difference in LSMean | | -0.31, 0.10 | -0.44, -0.03 | -0.51, -0.11 |
| p-value | | 0.4715 | 0.0181 | 0.0010 |
| **ITT population (Non-conservative Imputation)** | | | | |
| N | 102 | 98 | 98 | 97 |
| LSmean (SE) | 6.9 ( 0.48) | 6.2 ( 0.44) | 5.2 ( 0.38) | 4.8 ( 0.36) |
| 95% CI | 6.0, 7.9 | 5.3, 7.1 | 4.5, 6.0 | 4.1, 5.5 |
| Log Difference in LSMean (SE) | | -0.10 ( 0.086) | -0.25 ( 0.086) | -0.32 ( 0.086) |
| 95% CI for Difference in LSMean | | -0.30, 0.10 | -0.45, -0.04 | -0.52, -0.12 |
| p-value | | 0.5136 | 0.0125 | 0.0007 |

Source: FDA

Study 302:

The statistical reviewer noted that similar issues were identified for study 302 as study 301 except that reviews of seizure data were performed before unblinding of the study and the form of hard-codes was different from study 301. Dr. Ling reports that hardcodes were generated by the Sponsor and CRO based on blinded review. One flag variable ('noseiz") was manually populated based on the review by a team as to whether an event was in fact a seizure. Out of a total of 53912 records, 2285 (4.24%) were flagged as "not a seizure". Of those flagged, 417 have a comment. The most common comment was that it was a few seconds during lunch or breakfast. The review also identified duplicate seizures, multiple seizures, cluster seizures, and re-assessed the missing or implausible date and time. Dr. Ling conducted a sensitivity analysis removing the hardcodes. The results were not sensitive to the hardcoding.

The primary endpoint analyses performed by Dr. Ling showed contrast between the 800 mg group and placebo. Both the 400 mg and 1200 mg groups failed to separate statistically from the placebo group. Using the non-conservative imputation on the ITT population, the percent reduction over placebo was 9.5%, 23.6%, and 16.5% for the 400 mg, 800 mg, and 1200 mg groups respectively. The table below is duplicated from the statistical reviewer's draft review.

**Table 2. Study 302: FDA Analysis Results for the Primary Endpoint**

| | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg |
| **Completers (with maintenance assessment)** | | | | |
| N | 99 | 94 | 87 | 81 |
| LSmean (SE) | 9.0 ( 0.59) | 8.3 ( 0.57) | 6.6 ( 0.48) | 7.0 ( 0.52) |
| 95% CI | 7.9, 10.2 | 7.3, 9.5 | 5.7, 7.6 | 6.0, 8.1 |
| Log Difference in LSMean (SE) | | -0.06 ( 0.085) | -0.27 ( 0.087) | -0.22 ( 0.089) |
| 95% CI for Difference in LSMean | | -0.26, 0.14 | -0.48, -0.07 | -0.43, -0.01 |
| p-value | | 0.8031 | 0.0056 | 0.0354 |
| **ITT population (Conservative Imputation)** | | | | |
| N | 100 | 96 | 98 | 94 |
| LSmean (SE) | 9.2 ( 0.62) | 8.5 ( 0.58) | 7.2 ( 0.50) | 7.9 ( 0.55) |
| 95% CI | 8.1, 10.5 | 7.4, 9.7 | 6.3, 8.2 | 6.8, 9.0 |
| Log Difference in LSMean (SE) | | -0.07 ( 0.086) | -0.22 ( 0.086) | -0.14 ( 0.087) |
| 95% CI for Difference in LSMean | | -0.28, 0.13 | -0.42, -0.02 | -0.35, 0.06 |
| p-value | | 0.7185 | 0.0276 | 0.2470 |
| **ITT population (Non-conservative Imputation)** | | | | |
| N | 100 | 96 | 98 | 94 |
| LSmean (SE) | 9.2 ( 0.64) | 8.2 ( 0.59) | 6.8 ( 0.49) | 7.5 ( 0.55) |
| 95% CI | 8.0, 10.5 | 7.2, 9.5 | 5.9, 7.8 | 6.5, 8.7 |
| Log Difference in LSMean (SE) | | -0.10 ( 0.089) | -0.27 ( 0.089) | -0.18 ( 0.090) |
| 95% CI for Difference in LSMean | | -0.31, 0.11 | -0.48, -0.06 | -0.39, 0.03 |
| p-value | | 0.5368 | 0.0072 | 0.1143 |

Source: FDA reviewer

Due to issues found at DSI inspection, Dr. Ling re-analyzed the data excluding site 395. The results are reported as similar.

### 6.1.7 Analysis of Secondary Endpoints(s)

FDA statistical reviewer:

Dr. Ling performed an analysis of the percent of responders. To handle subjects who did not have seizure data during the maintenance period, she treated them in two ways. In one analysis, these subjects were treated as non-responders (per SAP) and in the other analysis, response during titration was used. Her methods are described in her review. The results of the analysis in which these subjects were considered non-responders indicated that 19.6% of the placebo group, 23.5% of the ESL 400 mg group, 33.7% of the ESL 800 mg group, and 42.3% of the ESL 1200 mg group as responders. Using titration phase data, the percentages of responders per group were similar (19.6%, 23.5%, 34.7%, and 43.3% per group respectively).

Dr. Ling also evaluated % change from baseline in seizure frequency. Her results are displayed below, as per her draft review.

**Table 3. Study 301: Percent Change from Baseline in seizure frequency**

| | | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | **Placebo** | **400 mg** | **800 mg** | **1200 mg** |
| N | 102 | 98 | 98 | 97 |
| LSmean (SE) | -7.7 ( 5.87) | -15.9 ( 5.98) | -28.4 ( 5.98) | -29.6 ( 6.01) |
| 95% CI | -19.2, 3.8 | -27.7, -4.2 | -40.2, -16.7 | -41.4, -17.7 |
| Difference in LSMean (SE) | | -8.24 ( 8.382) | -20.74 ( 8.383) | -21.88 ( 8.402) |
| 95% CI for Difference in LSMean | | -28.02, 11.54 | -40.52, -0.95 | -41.71, -2.05 |
| p-value | | 0.6391 | 0.0373 | 0.0262 |

Source: FDA

## Study 302

As per the sponsor's analyses, there was not statistical separation between the 400 mg or 800 mg group and placebo for the proportion of subjects with a ≥ 75% seizure reduction in the maintenance period.

Table xx

**Table 3.4.3.4-1: Proportion of Subjects with Seizure Reductions of ≥75% During the 12-week Maintenance Period for the Pooled Pivotal Phase III Studies 2093-301 and 2093-302 (ITT Analysis Set)**

| Statistic | Placebo | Eslicarbazepine Acetate Dose Group | | | Overall p-value |
|---|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg | |
| n/N (%)[a] | 17/198 (8.6) | 8/191 (4.2) | 25/180 (13.9) | 28/173 (16.2) | |
| CMH p-value[b] | | 0.0752 | 0.1040 | 0.0286 | 0.0008 |

Abbreviations: CMH= Cochran-Mantel-Haenszel
Note: CMH is stratified by study.
a n/N=number of responders/number of subjects with seizure data in the period
b p-value from pairwise test of each active treatment group compared to placebo
Reference: ISE EOT Table 11.1.1

As per the sponsor's analyses, there was statistical separation between all ESL groups and placebo for the proportion of subjects with a ≥ 25% seizure reduction in the maintenance period.

**Table 3.4.3.6-1: Proportion of Subjects with Seizure Exacerbations of ≥25% by Study Period and by 4-Week Interval in the 12-Week Maintenance Period for the Pooled Pivotal Phase III Studies 2093-301 and 2093-302 (ITT Analysis Set)**

| Period | Statistic | Placebo | Eslicarbazepine Acetate Dose Group | | | Overall p-value |
|---|---|---|---|---|---|---|
| | | | 400 mg | 800 mg | 1200 mg | |
| Weeks 1-2 (Titration) | n/N (%)[a] | 63/202 (31.2) | 48/194 (24.7) | 34/196 (17.3) | 43/191 (22.5) | |
| | CMH p-value[b] | | 0.1542 | 0.0013 | 0.0533 | 0.0132 |
| Weeks 3-14 (Maintenance) | n/N (%)[a] | 48/198 (24.2) | 24/191 (12.6) | 20/180 (11.1) | 25/173 (14.5) | |
| | CMH p-value[b] | | 0.0031 | 0.0010 | 0.0205 | 0.0017 |
| Weeks 15-18 (Taper off[c]) | n/N (%)[a] | 14/84 (16.7) | 14/87 (16.1) | 19/84 (22.6) | 12/71 (16.9) | |
| | $\chi^2$ p-value[b] | | >0.9999 | 0.4373 | >0.9999 | 0.6641 |

Abbreviations: CMH= Cochran-Mantel-Haenszel; wks=weeks; $\chi^2$=Chi-square
Note: CMH is stratified by study.
a n/N=number of responders/number of subjects with seizure data in the period
b p-value from pairwise test of each active treatment group compared to placebo
c Only Study 2093-301 included a tapering-off period.
Reference: ISE EOT Table 11.2.1

FDA statistical review: Percent Responder:
Dr. Ling's review indicates that analyses of the percent responder (performed the same two ways as for study 301) indicated that 1200 mg group p-value was sensitive to how drop-outs were handled. Her table is duplicated below.

**Table 4. Study 302: FDA Analyses Results for the Secondary Endpoint**

| Responder | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg |
| **I. Subjects w/o maintenance data as non-responder** | | | | |
| n/N (%)a | 18/100 ( 18.0 ) | 19/ 96 ( 19.8 ) | 31/ 98 ( 31.6 ) | 29/ 94 ( 30.9 ) |
| CMH p-valueb | | 0.7493 | 0.0266 | 0.0373 |
| Chi-square p-valueb | | 0.8904 | 0.0396 | ***0.0548*** |

| Responder | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg |
| Odds Ratio | | 1.12 | 2.11 | 2.03 |
| 95% CI | | 0.55, 2.30 | 1.08, 4.10 | 1.04, 3.98 |
| **II. Impute Using Titration** | | | | |
| n/N (%)[a] | 18/100 ( 18.0 ) | 20/ 96 ( 20.8 ) | 33/ 98 ( 33.7 ) | 32/ 94 ( 34.0 ) |
| CMH p-value[b] | | 0.6169 | 0.0119 | 0.0109 |
| Chi-square p-value[b] | | 0.7483 | 0.0183 | 0.0169 |
| Odds Ratio | | 1.20 | 2.31 | 2.35 |
| 95% CI | | 0.59, 2.44 | 1.20, 4.48 | 1.21, 4.57 |

a. n/N=number of responders/number of subjects with seizure data in the maintenance period.
b. Unadjusted p-value from pairwise test of each active treatment group compared to placebo.
Source: FDA.

FDA review: % change from baseline

The LS mean % change from baseline was 3.6 for placebo, -10.8 for the 400 mg group, -17.9 for the 800 mg group, and -5.3 for the 1200 mg group. P-values for the contrast with placebo were 0.277, 0.052, and 0.657 for the 400 mg, 800 mg, and 1200 mg group respectively.

### 6.1. 8 Other Endpoints

Relative change in standardized seizure frequency during the 12-week maintenance period as per the sponsor

The table below is duplicated from the sponsor's document, summary-clin-efficacy.pdf:2 submitted with the March 2009 submission of the NDA. This table is based on an Ancova model without the interaction term. The sponsor notes also that subjects who did not have a specific seizure type during the baseline period were excluded from the analysis of that seizure type. However, if the subject had only one partial evolving to secondarily generalized during the baseline period and none during the maintenance period, the subject would be included in this analysis as having a 100% reduction in seizures.

Based on the sponsor's table 3.4.2.1-5, ESL 800 and 1200 mg dose groups experienced a reduction in seizure frequency that was statistically significant for simple and complex partial seizures. Secondary generalized and unclassified seizures were not different, statistically, between the any ESL group and placebo. Although this analysis has limitations, the lack of differences in secondarily generalized seizures and unclassified seizures requires further consideration.

**Table 3.4.2.1-5: Analysis of Relative Change in Standardized Seizure Frequency During the 12-Week Maintenance Period for the Pooled Pivotal Phase III Studies 2093-301 and 2093-302 by Seizure Type (Model 1, without Interaction) - ITT Analysis Set**

| Seizure Type | ANCOVA Statistic[a] | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|---|
| | | | 400 mg | 800 mg | 1200 mg |
| Simple Partial | N | 92 | 85 | 86 | 85 |
| | LS Mean (SE) | 39.6 (13.41) | 3.8 (13.86) | -22.2 (13.74) | -20.2 (14.21) |
| | 95% CI | 13.2, 66.0 | -23.5, 31.1 | -49.2, 4.8 | -48.1, 7.7 |
| | Diff in LS Mean (SE) | | -35.8 (16.83) | -61.8 (16.68) | -59.8 (16.73) |
| | 95% CI for Diff in LS Mean | | -75.6, 4.0 | -101.2, -22.4 | -99.3, -20.3 |
| | p-value[a] | | 0.0885 | 0.0007 | 0.0012 |
| Complex Partial | N | 144 | 137 | 131 | 137 |
| | LS Mean (SE) | 1.2 (8.23) | -20.6 (8.45) | -27.0 (8.81) | -23.4 (8.40) |
| | 95% CI | -14.9, 17.4 | -37.2, -4.1 | -44.3, -9.7 | -39.9, -6.8 |
| | Diff in LS Mean (SE) | | -21.9 (9.81) | -28.2 (9.87) | -24.6 (9.78) |
| | 95% CI for Diff in LS Mean | | -45.0, 1.3 | -51.5, -4.9 | -47.7, -1.5 |
| | p-value[a] | | 0.0686 | 0.0124 | 0.0333 |
| Partial Evolving to Secondarily Generalized | N | 75 | 66 | 62 | 64 |
| | LS Mean (SE) | -54.8 (24.08) | -9.2 (24.26) | -29.1 (25.57) | -55.0 (24.53) |
| | 95% CI | -102.2, -7.3 | -57.0, 38.6 | -79.4, 21.3 | -103.3, -6.7 |
| | Diff in LS Mean (SE) | | 45.6 (28.20) | 25.7 (28.62) | -0.2 (28.44) |
| | 95% CI for Diff in LS Mean | | -21.3, 112.4 | -42.1, 93.5 | -67.4, 67.1 |
| | p-value[a] | | 0.2567 | 0.7052 | >0.9999 |
| Unclassified | N | 24 | 19 | 22 | 21 |
| | LS Mean (SE) | -65.2 (15.77) | -38.2 (18.15) | -52.5 (18.00) | -52.4 (17.28) |
| | 95% CI | -96.6, -33.8 | -74.3, -2.1 | -88.3, -16.6 | -86.8, -18.0 |
| | Diff in LS Mean (SE) | | 27.0 (20.89) | 12.7 (20.77) | 12.8 (20.67) |
| | 95% CI for Diff in LS Mean | | -23.1, 77.1 | -37.1, 62.5 | -36.7, 62.4 |
| | p-value[a] | | 0.4338 | 0.8748 | 0.8704 |

Abbreviations: ANCOVA=analysis of covariance; LS=least squares; SE=standard error of the mean; CI=confidence interval; Diff=difference.

a ANCOVA model with fixed effects for treatment, study, baseline standardized seizure frequency, and number of concomitant AEDs at baseline, without the treatment by study interaction.

Note: Dunnett's multiple comparison procedure was used to calculate the p-values and 95% CIs for the differences of LS Means between each of the active treatment groups and placebo.

Note: Relative change cannot be calculated for subjects without that particular seizure type at baseline

Reference: ISE EOT Table 5.3.1

### 6.1.9 Subpopulations

Gender: The statistical reviewer notes that in the pooled studies 301 and 302, about 51% of all patients were female and that overall there was no “compelling” evidence of differential treatment effect by gender (p=0.54). Her review displays these data in section 4.1.1

Race: Over 90% of patients in the pooled studies 301 and 302 were Caucasian. All patients in study 301 were Caucasian. 2.9% of patients were Black and this is the next

largest racial group. Therefore, the data is limited for non-Caucasians. The statistical reviewer indicates that based on this limited data, there was no compelling treatment effect difference between the groups.

Region:
Study 301-Dr. Ling's review indicates that the Eastern Region had the highest response rate and percent reduction in the 1200 mg group with the Central Region the smallest and similar to placebo. In the 800 mg group, the Eastern and Central Regions responded similarly. In the placebo group, the Central Region had a numerically larger response rate. There were not enough subjects in the Western Region. Region and treatment-by-region interactions are reported as non-significant at 0.23 and 0.58 respectively.

Study 302- Dr. Ling reports that the highest response rate was in Australia and South Africa in the 800 mg group and that these regions had higher placebo effect rates. She reports region and treatment-by-region interaction as no significant in terms of effect on seizure frequency (0.15 and 0.72).

Age: There were only 30 patients above 60 in the pooled patient population for studies 301 and 302. This does not allow for reliable subgroup analysis. The statistical reviewer employed a test for differential effect according to age based on the assumption that seizure rates were linear in age and allowing for a separate linear relationship for each group. Dr. Ling reports that this analysis concluded that the slopes were not significantly different.

AED use: Dr. Ling reports there was no carbamazepine use and treatment-by-carbamazepine use interaction on seizure frequency in studies 301 and 302 (0.17 and 0.87).

### 6.1. 10 Analysis of Clinical Information Relevant to Dosing Recommendations

Deferred until final review pending outcome of DSI and quality issues

### 6.1.11 Discussion of Persistence of Efficacy and/or Tolerance Effects

Deferred until final review pending outcome of DSI and quality issues

### 6.1.12 Additional Efficacy Issues/Analyses

**Collection of diary data-**

A potential issue with the diary data, which is likely not limited to this product is that patients were asked to fill in the diary when a seizure occurred. When looking at selected CRFs during the review, it is of note that a dairy card may have only a few entries on it and the rest is blank. These are presumed to be zero seizures but maybe the patient just did not fill out diaries. Perhaps this is not a big concern given randomization, but it may be avoidable by having patients note there were no seizures or cross out the lines, in real time, or confirm there were not seizure events in some way on the diary.

The statistical review notes the following (p.43/49, final copy),

"In this NDA, the trial participants were instructed to update seizure diary only when they experienced a seizure. As a result, "0" seizure was not recorded. Therefore, true zero seizures could not differentiated from missing seizure data (patient did not record a seizure, missed a visit, or did not return diary card, etc.), and "no seizure data" was assumed as no occurrence of seizure events in the analysis. A worst-case-scenario analysis assessed the effect of the part of missing data that were caused by unreturned diary cards. This analysis showed favorable results, although lost significance for the 800 mg/day dose in one of the study."

# 7 Review of Safety

*Safety Summary*

*As noted in the review strategy, not all data has been 100% verified for accuracy in these presentations, however, given larger quality issues, this does not alter the outcome of the action on the application. Conclusions should be considered preliminary if described or implied.*

## 7.1 Methods

### 7.1.1. Studies/Clinical Trials Used to Evaluate Safety

As noted earlier, the ISS cut-off was about a year before filing of the NDA (cut-off 2-2008). In the ISS, safety data from 30 clinical trials were detailed; 1) part one (includes double-blind phase) of 3 phase 3, epilepsy studies conducted in adults and part 2 of one of these 2) one phase 2 epilepsy study in adults, 3) one phase 2 open-label study in pediatric epilepsy patients, 4) two phase 2 controlled studies in bipolar patients, 5) one phase 2 open-label extension of the two phase 2 bipolar studies 6) 19 phase 1 studies in healthy subjects, 7) three phase 1 studies in special populations. Although completed, 1-year open-label data from part 2 of studies 302 and 303 and data from part 3 of study 301 were not included in the ISS. The 120-day safety update (SU) included data from 2-28-08 to 3-29-09.

Included in the SU were 1) part 2 (open-label) of the studies 302 and 303 and 2) 3 phase 1 studies. Part 2 of study 301 was included in the ISS but was pooled with the other part 2 data in the SU. 15 clinical trials/extensions were ongoing. This includes studies clinically completed but not reported prior to the SU cut-off of 3-30-09 and studies reported but that had ongoing subjects (study 303-part 2). Death and SAE information during the period between 2-28-08 and 3-30-09 were include for studies 2093-127, 2093-128, 2093-129, 2093-206, 2093-207, 2093-208, 2093-209, 2093-210, 2093-301 Part 3, 2093-301 Part 4, 2093-302 Part 2, 2093-304, 2093-305 Part 1, 2093-311, and 2093-401. Therefore it seems that all TEAEs in study 301 part 3 are not included.

The NDA contains data from controlled trials for two indications in adults, epilepsy (three phase 3 adjunctive and one phase 2 adjunctive) and bipolar disorder (two phase monotherapy). Open-label extension data from the controlled trials and open-label data from the phase 1 studies and from the pediatric epilepsy study (202) were reviewed for deaths, non-fatal serious adverse events, and discontinuations secondary to adverse events.

The focus of the safety review was on controlled data from these trials with emphasis on the epilepsy.

### 7.1.2 Categorization of Adverse Events

The ISS states that phase 1 studies were conducted over an approximately 7-year period using MedDRA versions 4.0 through 10.0 or the World Health Organization Adverse Reaction Terminology (WHO-ART) dictionary. Adverse events were reported by MedDRA SOC and LLT for studies 2093-103 to 2093-110, 2093-113 to 2093-115, and 2093-117. Adverse events were reported by MedDRA SOC and preferred term for studies 2093-111, 2093-112, 2093-116, and 2093-118 to 2093-122. Adverse events were reported by WHO-ART body system and preferred term for studies 101 and 102.

The ISS indicates that in phase 2 adult BID and QD dosing study 2093-201, AEs were coded using MedDRA version 5.0 and reported by MedDRA SOC and lowest level term (LLT). In the phase 2 pediatric study, 2093-202, AEs were coded using MedDRA version 9.0.

The sponsor presented an analysis of the MedDRA coding differences between study 201 and studies 302 and 303 part 1. The sponsor concludes the differences were not clinically meaningful.

**Table 8.1-2: Impact Analysis of the MedDRA Coding Differences Between Study 2093-201 (version 5.0) and Studies 2093-302 and 2093-303 Part 1 (version 9.0)**

| Verbatim Term | MedDRA Version 5.0 Lowest Level Term | MedDRA Version 9.0 Lowest Level Term | MedDRA Version 5.0 System Organ Class | MedDRA Version 9.0 System Organ Class |
|---|---|---|---|---|
| Cephalea | **Headache** | Cephalgia | Nervous system disorders | Nervous system disorders |
| Exacerbation of seizures | **Complex partial seizures increased** | Seizures | Nervous system disorders | Nervous system disorders |

Note: Bold text indicates the differences in version 5.0.
Reference: Data on file at Sepracor.

The ISS indicates that adverse events were coded using MedDRA version 7.0 for study 2093-301 and version 9.0 for studies 2093-302 and 2093-303. MedDRA version 9 was used for part 2 of study 301.

The sponsor presented their interpretation as to the impact of analysis of the MedDRA coding differences between study 301 part 1 (version 7.0) and part 1 of studies 302 and 303 (version 9.0). The sponsor concludes that these differences were not clinically meaningful.

**Table 8.1-1: Impact Analysis of the MedDRA Coding Differences Between Study 2093-301 Part 1 (version 7.0) and Studies 2093-302 and 2093-303 Part 1 (version 9.0)**

| Verbatim Term | MedDRA Version 7.0 Preferred Term | MedDRA Version 9.0 Preferred Term | MedDRA Version 7.0 System Organ Class | MedDRA Version 9.0 System Organ Class |
|---|---|---|---|---|
| Ataxia | **Ataxia** | Coordination abnormal | Nervous system disorders | Nervous system disorders |
| Gait ataxia | **Ataxia** | Coordination abnormal | Nervous system disorders | Nervous system disorders |
| Exacerbation of seizures | **Complex partial seizures** | Convulsion | Nervous system disorders | Nervous system disorders |
| Increasing seizure frequency | **Complex partial seizures** | Convulsion | Nervous system disorders | Nervous system disorders |
| Irritability | Irritability | Irritability | **Psychiatric disorders** | General disorders & administration site conditions |

Note: Bold text indicates the differences in version 7.0.
Reference: Data on file at Sepracor.

I audited the dataset ADAE2.xpt for consistency of coding verbatim terms to higher level terms, the appropriateness of coding from the verbatim term→ to higher level terms, and for xx. The sponsor's definition files indicate that the variable "AETERM" is the verbatim term for the event. The variable "AEPTN" is the preferred term code in MedDRA version 7 for study 301 part 1, MedDRA version 9 for study 301 part 2 and studies 302 and 303 part 1, and MedDRA version 10 for part 2 of studies 302 and 303. The variable "AEDECOD" is defined as the equivalent to MedDRA PT term text with versions as noted for the variable "AEPTN". The variable "AELLT" was the lower level term coded as per the MedDRA versions noted for the variable "AEPTN". There were also variables for the SOC (in the various coding dictionaries and the equivalent) and higher level terms.

There terms that could be coded to the same LLT (for example, aggressivity is coded to aggressiveness as LLT while aggressive behavior is coded to aggressive behavior as LLT. The PTs were the same. Ataxia (verbatim) is usually coded as "coordination abnormal" but a few times is coded as "ataxia" (PT). The all adverse events table in the SU (Table 4.1.4.4-2) presents the data by SOC, then further subcategorized by preferred term.

| AETERM | AEDECOD | AELLT | AEBODSYS | AEHLT |
|---|---|---|---|---|
| Aggressivity | Aggression | Aggressiveness | | |
| Aggressive behavior | Aggression | Aggressive Behavior | | |
| Agitated Speech | Speech disorder | Speech disorder | NS Disorder | |

A possible issue noted in the dataset of adverse events in terms of coding is the use of adverse event terms that I suspect may be more commonly used outside of the U.S. This is described elsewhere in the review.

In addition to a cursory audit check of verbatim terms to preferred terms (coding), I examined the integrated summary of safety dataset for coding in terms of discontinuations. Specifically, for discontinuations not attributed to an adverse event (for example, discontinuation due to investigator discretion), I looked to see whether there was an adverse event.

The following table shows the primary reason for discontinuation, as per one of the integrated adverse events datasets, for the three phase 3 studies.

| | **rows** | **subjects** | |
|---|---|---|---|
| **ADVERSE EVENT** | **466** | **133** | |
| **EXACERBATION OF SEIZURES** | **31** | **9** | |
| **INVESTIGATOR DISCRETION** | **42** | **13** | 3 placebo, 1 400, 6 800, and 3 1200 mg ESL |
| **NON-COMPLIANCE** | **21** | **11** | |
| **OTHER** | **131** | **48** | 8 placebo, 11 400 mg, 16 800 mg, and 13 1200 mg |
| **PREGNANCY** | **3** | **2** | |
| **PROTOCOL VIOLATION** | **6** | **1** | |
| **WITHDRAWAL OF CONSENT** | **159** | **65** | |

**Dataset ADAE2.xpt-safety population for part 1 of all three studies (excluding pre-dose). Variable used represented primary reason for discontinuation.**

Examination of the categories of "investigator discretion", "other" and "withdrawal of consent" was performed.

- Investigator discretion- The dose group breakdown is shown in the table above. Using the variable AECN (action taken with study treatment) or AECNOTH Other action taken) for discontinuation and withdrawal respectively, one subject on 1200 mg (301-192-90258) in maintenance has discontinuation and withdrawal noted for events apathy, insomnia, irritability, and nervous. There is an ISS narrative in the discontinuation section. Therefore, it seems this should be coded as a discontinuation secondary to an adverse event. In the final dataset used by the sponsor to make disposition datasets, this may be the case. I do not believe this dataset was submitted to FDA (dataset supporting SU EOT table 2.1.1).
- Other – one placebo subject (301-125-90384) has discontinuation and withdrawal for events dyspepsia and paresthesia of lower limbs. The table below displays the reasons listed for these patients.

| **placebo** | **400** | **800** | **1200** |
|---|---|---|---|
| 8<br>●5-lack of efficacy (one with higher seizure intensity)<br>● 2 Lost to follow-up (1 not able to contact patient and not going to visits)<br>●1 AE | 11<br>●10 lack of efficacy or unchanged seizure frequency<br>●1 lost to follow-up | 16<br>●12 related to lack of efficacy (did not improve,or increased seizure freq and intensity)<br>●1 lost to follow-up<br>●death<br>●patient is to followup<br>●she didn't come back | 13<br>●8-lack of efficacy, inefficacy, or maintenance of seizure<br>●4-Lost to follow-up<br>●1-unplanned departure from country |

- For the "withdrawal of consent" group, 30 rows (15 subjects) had AECN as discontinuation and 28 of these also with withdrawal. Nine were subjects in study 301, 4 were in study 302, and 2 were in study 303. The group breakdown was 3 placebo group, 0 400 mg, 5 800 mg, and 7 1200 mg. One of the 1200 mg was exacerbation of seizures (301-193-90148) and one experienced hair loss, dizziness, gait disorders, and hands trembling (301-174-90449). Other events in these 15 subjects include nausea, vomiting, somnolence, dizziness, and vertigo.

| | |
|---|---|
| 301-191-90144 | vesicular rash with desquamation (allergic reaction noted in parentheses) CRF indicates primary reason discontinue was withdrawal of consent with occurrence of an unacceptable AE noted. CRF AE page has some mark-through corrections but seems to indicate subjects discontinued from study treatment on 4-28-05 due to rash but stayed in the study and was treated with clemastine. About 5 days later, the same patient had blepharospasm on the left and was withdrawn from the study on 5-3-05. <u>This event is included in the ISS as discontinuation secondary to AE</u> |
| 301-506- | facial edema and paresthesias in both hands –withdrawn and treated with medications. There are corrections to the CRF. The investigator marked withdrawal of consent as the |

| | |
|---|---|
| 70094 | primary reason for discontinuation. A query correction indicates adverse event should be noted as a reason for discontinuation but that the primary reason is consent withdrawal.<br>This event is included in the ISS as discontinuation secondary to AE |
| 302-385-80427 | depression- handwritten note during the data clarification process indicates the patient withdrew consent as result of weight gain and the AE page clearly indicates discontinuation of both study and study drug as a result of weight gain<br>This event is included in the ISS as discontinuation secondary to AE |
| 301-193-90148 | 1200 mg – exacerbation of seizures-CRF AE page indicates patient had study medication discontinued and withdrew/was withdrawn from the study secondary to an exacerbation of seizures. However, more than two months after the event is noted to have started, there are corrections that may have been made by the investigator and the entire event is crossed out. The CRF completion page indicates the patient had exacerbation of seizures but that primary reason for withdrawal was withdrawal of consent<br>This event is included in the ISS as discontinuation secondary to AE |
| 301-174-90449 | hair loss, dizziness, gait disorders, and hand trembling<br>This event is included in the ISS as discontinuation secondary to AE |

- For other, one subject has action of medication discontinuation and withdrawal, subjects 301-125-90384, placebo (dyspepsia and paresthesia of lower limbs). There is an ISS narrative for this subject.

*Reviewer's comment: If the data are verified as reliable, we should consider asking the sponsor to indicate what the disposition was for the subjects described in text/tables above or ask the sponsor to indicate which of the datasets was used to build disposition tables and check that dataset.*

*With respect to the use of terms less commonly used in the U.S., the sponsor should describe how preferred terms were selected and by whom. Also, the sponsor should put together a listing of these terms and then explain what the closest U.S. medical language is and describe whether there would be any regional differences in the way terms were used. These explanations should be verified at the medical doctor level and with a statement noting this was performed.*

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In the ISS, the sponsor states that the phase 2 and 3 studies were reviewed for similarities with respect to study population, design, and dosing duration. The sponsor states that since part one of all three phase 3 studies had the same principal design, objective, subject population, inclusion and exclusion criteria, endpoints and approach to statistical analysis, these were pooled in the initial ISS. Due to GCP concerns at study 303 at multiple sites in Mexico, the sponsor performed primary safety analysis with and without sites in Mexico. Treatment-emergent adverse events with an incidence of ≥ 2% were presented with and without Mexico (safety tables used to support labeling).

Due to GCP problems in study 303, the Division requested that a separate presentation of data be submitted that compared study 301-302 to study 303. This was submitted in the 8-28-09 120-day safety update.

Safety data for all phase 1 and 2 studies were presented separately in the ISS using the study report module 5.3 as the primary data source.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The method for the exposure tables described below is as follows (described in the SU).

- Duration of exposure was calculated as the number of days from first to last exposure of study drug for each group. During this interval, days with missing drug exposure data were ignored. If the day of first dose of study drug was unknown, then this was set to the randomization day. If the day of last dose was unknown, then this was set to the day of last contact.

- Average daily dose level (mg) was calculated as the total number of doses taken multiplied by the treatment dose level and divided by the duration in days of treatment. The average daily dose level was summarized by assigned treatment dose.

- Duration of exposure and average daily dose were only calculated for subjects with at least 75% of the contributing dosing data available.

The SU indicates that for all studies, a total of 1889 unique, subjects were exposed to ESL. Taken on-face, this table indicates exposure that meets ICH guidelines for 1 year, 6 months, and overall. A major qualifier is that study 303 is known to have significant GCP issues and the table below includes subjects from this study. A second qualifier is whether the data from 301-302 are reliable, as inspections by FDA indicate significant problems at one of two sites. The sponsor's table showing exposure data, including study 303 subjects, is duplicated below.

**Table 3.1-1: Extent of Exposure and Average Daily Dose by Assigned Dose for Unique ESL-Treated Subjects in All Studies (Parts 1 and 2 of 2093-301 to 2093-303; 2093-201 to 2093-205; and 2093-101 to 2093-123, 2093-125, and 2093-126) (Safety Population)**

| Parameter | Category/ Statistic | Assigned Dose | | | | | |
|---|---|---|---|---|---|---|---|
| | | 20-200 mg ESL QD (N=33) | >200-600 mg ESL QD (N=246) | >600-900 mg ESL QD (N=1153) | 1100-1300 mg ESL QD (N=339) | 1500-2400 mg ESL QD (N=106) | ≥3000 mg ESL QD (N=12) |
| Duration of exposure to study medication (days) | N | 30 | 232 | 1124 | 314 | 101 | 12 |
| | Mean (SD) | 2.4 (2.85) | 66.8 (88.98) | 318.3 (224.97) | 31.5 (43.01) | 53.0 (93.33) | 1.8 (0.39) |
| | Min, Max | 1, 8 | 1, 405 | 1, 943 | 1, 207 | 2, 395 | 1, 2 |
| Exposure category n (%) | 1-7 days | 24 (72.7) | 63 (25.6) | 149 (12.9) | 52 (15.3) | 4 (3.8) | 12 (100.0) |
| | >1-2 weeks | 6 (18.2) | 36 (14.6) | 48 (4.2) | 47 (13.9) | 70 (66.0) | 0 |
| | >2-4 weeks | 0 | 29 (11.8) | 39 (3.4) | 158 (46.6) | 2 (1.9) | 0 |
| | >4-8 weeks | 0 | 18 (7.3) | 15 (1.3) | 13 (3.8) | 1 (0.9) | 0 |
| | >8-16 weeks | 0 | 44 (17.9) | 98 (8.5) | 23 (6.8) | 10 (9.4) | 0 |
| | >16-24 weeks | 0 | 6 (2.4) | 20 (1.7) | 7 (2.1) | 3 (2.8) | 0 |
| | >24-28 weeks | 0 | 10 (4.1) | 20 (1.7) | 10 (2.9) | 1 (0.9) | 0 |
| | >28-52 weeks | 0 | 23 (9.3) | 153 (13.3) | 4 (1.2) | 9 (8.5) | 0 |
| | >52 weeks | 0 | 3 (1.2) | 582 (50.5) | 0 | 1 (0.9) | 0 |
| | Unknown[a] | 3 (9.1) | 14 (5.7) | 29 (2.5) | 25 (7.4) | 5 (4.7) | 0 |
| Average daily dose (mg) | N | 30 | 232 | 1124 | 314 | 101 | 12 |
| | Mean (SD) | 149.0 (130.66) | 548.8 (241.23) | 857.7 (411.56) | 1073.4[b] (272.29) | 1756.9 (306.92) | 3300.0 (313.34) |
| | Median | 100.0 | 521.8 | 800.0 | 1136.8[b] | 1800.0 | 3300.0 |
| | 25th, 75th percentile | 50, 200 | 400, 600 | 773, 926 | 993, 1200 | 1753, 1800 | 3000, 3600 |
| | Min, Max | 20, 375 | 28, 1475[c] | 75, 12600[c] | 75, 4200[c] | 718, 2400 | 3000, 3600 |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; min=minimum; max=maximum; QD=once daily; SD=standard deviation.

a Duration of exposure and average daily dose were only calculated for subjects with at least 75% of the contributing dosing data available.

b A subject contributes to the treatment dose to which they were randomized for the longest period of treatment, the mean and median exposures were influenced downwards by the Phase III studies (2093-301, 2093-302, and 2093-303), where the Part 1 titration period and Part 1 tapering period may have called for the subject to take less than the assigned dose for a period of time.

c These values likely represent outliers that are possibly due to subject recording errors.

Note: Subjects who participated in multiple studies were counted only once in the dose group corresponding to their longest duration. If the subject had the same duration for 2 or more dosing groups, then the subject was assigned to the highest dosing group and the subject's entire study exposure data on ESL, regardless of dose level, was summarized under the assigned highest dosing group. For duration, the durations on ESL treatment from each study were added for a total ESL treatment duration. Of the subjects who received both ESL and placebo in Phase III, 4 subjects received placebo for a longer duration than ESL.

Reference: SU EOT Table 15.1

In order to evaluate the impact of exclusion of study 303 subjects from the exposure numbers, SU tables were examined. Other SU tables showing all exposure are based on calculated dosing and count subjects multiple times. The SU Table 4.1.1-1 displays exposure data for the pivotal epilepsy studies by average daily dose for the combined data from part 1 (includes the double-blind phase) of studies 301-302 compared to study 303. This suggests that the all exposure table above contains about 165 ESL subjects from study 303, at doses of 800 mg or 1200 mg ESL. This table is duplicated as per the submission below.

Table xx

Table 4.1.1-1: Extent of Exposure and Average Daily Dose for Unique ESL-Treated Subjects in Part 1 of the Phase III Studies (2093-301 and 2093-302 Pooled vs 2093-303) (Safety Population)

| Parameter[a] | Category/ Statistic | Studies 2093-301 and 2093-302 Pooled Assigned Dose at Randomization | | | Study 2093-303 Assigned Dose at Randomization | |
|---|---|---|---|---|---|---|
| | | 400 mg ESL QD (N=196) | 800 mg ESL QD (N=199) | 1200 mg ESL QD (N=200) | 800 mg ESL QD (N=85) | 1200 mg ESL QD (N=80) |
| Duration of exposure to study medication (days) | N | 192 | 198 | 190 | 82 | 70 |
| | Mean (SD) | 101.3 (18.09) | 94.0 (31.59) | 86.2 (35.77) | 102.8 (32.04) | 102.6 (33.47) |
| | Min, Max | 5, 126 | 1, 126 | 2, 120 | 1, 155 | 4, 148 |
| Exposure category n (%) | 1-7 days | 1 (0.5) | 10 (5.0) | 7 (3.5) | 3 (3.5) | 1 (1.3) |
| | >1-2 weeks | 2 (1.0) | 7 (3.5) | 8 (4.0) | 2 (2.4) | 2 (2.5) |
| | >2-4 weeks | 0 | 3 (1.5) | 16 (8.0) | 3 (3.5) | 3 (3.8) |
| | >4-8 weeks | 6 (3.1) | 5 (2.5) | 8 (4.0) | 1 (1.2) | 2 (2.5) |
| | >8-16 weeks | 161 (82.1) | 131 (65.8) | 127 (63.5) | 34 (40.0) | 22 (27.5) |
| | >16-24 weeks | 22 (11.2) | 42 (21.1) | 24 (12.0) | 39 (45.9) | 40 (50.0) |
| | Unknown[b] | 4 (2.0) | 1 (0.5) | 10 (5.0) | 3 (3.5) | 10 (12.5) |
| Average daily dose (mg) | N | 192 | 198 | 190 | 82 | 70 |
| | Mean (SD) | 398.0 (19.11) | 758.4 (82.41) | 1046.3 (279.26) | 658.0 (105.61) | 939.8 (182.18) |
| | Median | 400.0 | 759.1 | 1053.9 | 690.1 | 1024.0 |
| | $25^{th}$, $75^{th}$ percentile | 396, 400 | 750, 800 | 1036, 1130 | 646, 709 | 865, 1048 |
| | Min, Max | 267, 510 | 150, 1000 | 75, 4200 | 344, 886 | 160, 1131 |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; min=minimum; max=maximum; QD=once daily; SD=standard deviation SU=120-day safety update.
a The titration, maintenance, and tapering-off periods were combined. Study 2093-302 did not have a tapering-off period.
b Duration of exposure and average daily dose were only calculated for subjects with at least 75% of the contributing dosing data available.
Reference: SU EOT Tables 4.1.1 and 4.1.2



Reviewer's analysis of the dataset ADEX.xpt (submitted with the 120-day SU)

1 year: I used the variable EXAVGD (xx) and chose ≥ 800mg and exposure duration of ≥ 365 days (with variable EXDURAVG). With all studies meeting these criteria (203, 205, 301, 302, and 303), by my evaluation there were 398 unique subjects. Dropping study 303, there were 307 unique subject exposures. If you drop subjects from the bipolar studies (203 and 205), there are 301 unique subjects. Using the variable for duration of exposure (EXDUR), there are 347 unique subject exposures including bipolar subjects but without subjects in study 303.

6 months: Using the same variables as above with duration of ≥ 180 days, there are 449 unique subjects including bipolar subjects but excluding study 303 (variable EXDURAVG) and 463 unique exposures (with bipolar, without 303) using the variable EXDUR.

I re-performed this analysis to make sure I had not inadvertently included placebo subjects. In this re-analysis, I did not do both variables for exposure duration. I chose the variable EXDUR. The results were not substantially different. The sponsor can re-submit exposure tables pending resolution of data quality issues.

### 7.2.2 Explorations for Dose Response

Deferred

### 7.2.3 Special Animal and/or In Vitro Testing

Please see the pharmacology-toxicology review.

### 7.2.4 Routine Clinical Testing

For studies 301 and 303, visit 1 was the beginning of baseline. Visit 2 was the end of baseline and the first day of the titration period. Visit 3 was the end of titration and the first day of dosing in the maintenance period. Visit 4 was halfway through maintenance. Visit 5 was the end of maintenance and the first day of tapering. Visit 6 was the end of the tapering period and the first day of open-label dosing. In study 302, there was no tapering-off period, so visit 5 was the first day of dosing in the open-label period.

In the phase 3 epilepsy studies, generally routine labs were to be collected (fasting) at visits 1, 2, 4, and 5 during the controlled period. EKG was to be collected at the beginning and end (visits 1, 2, and 5) and physical exams were to be performed at the beginning and end (visits 1 and 5). Pregnancy testing was to be performed at most visits in the controlled period. Vital signs, concomitant medications, and adverse event information were to be collected at all visits.

Based on information in the protocols of the 3 phase 3 studies (found in the study reports), investigators were to monitor AEs at each visit from visit 1 throughout the study by inquiring, generally, about the patient's well-being since the last visit. Details of any reported adverse events were to be recorded. An adverse event was defined as "any undesirable change in the function, structure or chemistry of the body occurring to a subject during the clinical study whether or not considered related to the investigational product". AEs could be symptoms, signs, or clinically relevant lab abnormalities. Any worsening of a pre-existing condition during the study was also to be considered an adverse event.

The testing for potential thyroid function was inadequate to allow definitive conclusions as there were no measures of TSH.

No EKGs were performed in the following phase 1 studies: 104, 110, 109, 122, 117, 107, 108, 114, 119, 120, 121, 125, 126, or 106 (effic-info-amend.pdf, 10-14-09 submission). There was a thorough QT study.

Missing data: Shift tables for the phase 3 trials 301 and 302 indicate data are missing at visit 5 for about 9 -29% of some chemistry measures for subjects who started with normal values (more missing in the 1200 mg group generally).

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Please the OCP review.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The ISS included a section of "adverse events of special interest": hyponatremia; rash, hypersensitivity reactions; dizziness; diplopia; blurred vision; somnolence; ataxia, abnormal coordination, gait disturbance, gait abnormal and balance disorder; memory impairment; petit mal (Absence Seizures); depression; suicidality, hypothyroidism; nausea and vomiting, complex partial seizures increased; and CPK elevations. These are events that are seen with the use of antiepileptics. The review of this section is not presented.

Cardiac conduction disorders and hepatobiliary disorders are not separate topics in the referenced section of the ISS. If the data are at some time, re-submitted for review, these presentations should be present. Each topic section also should be comprehensive such that all events from development phases 1-3 are considered and described within the section.

## 7.3 Major Safety Results

Information on deaths, non-fatal serious adverse event, and discontinuations secondary to an adverse event are described.

### 7.3.1 Deaths

I was unable to locate a description as to the length of time after study discontinuation that events of death were collected and described. Presumably, this might have been handled the same way non-fatal SAEs were.

16 deaths in the development program are reported through NDA submissions dated 2-4-10. 14 were in patients who had been exposed to ESL and 2 were in placebo patients. There are 15 deaths in the reviewer-made table below for ESL. This is due to a death reported as an IND safety report that occurred after the cut-off date of the NDA submissions. A table listing and describing the deaths may be found after the text discussion below.

Of the deaths reported in phase 3 epilepsy studies, only one is reported from the controlled phase and this is in a subject on placebo. The other placebo death in the development program was from an ischemic stroke in a subject in a bipolar trial.

Of the 14 other deaths, one was in an elderly subject in a healthy volunteer study, one was a subject in a bipolar trial, four others were from trials in either diabetic neuropathy

or post-herpetic neuralgia, and the remainder were from open-label phase 3 epilepsy trials.

Without regard to whether subjects were on ESL at the time of death, of the 14 ESL-exposed deaths reported in the NDA (not including the IND safety report death), five are from various different cancers (4 of 5 in non-epilepsy trials), three, by report, are directly attributable to seizure episodes/status (epilepsy trials), three are from drowning (epilepsy trials), which may represent seizure events, two are reported as cardiac (one in phase one study and one in epilepsy) , and one is reported as a suicide (bipolar trial).

Cancer deaths: Of the five deaths from cancer, the cancers were of different types (gastric, lung, astrocytoma recurrence, lymphoma, and prostate) and exposure times were about a month or 33 days to 56 days.

The 75 year old subject with prostate cancer had about 5- 6 weeks of exposure before his symptom of “lumbalgia”. He died less than 2 months after the first dose. Prostate cancer in not an uncommon cause of cancer death in men and the biggest risk factor is age. The subject with gastric cancer is reported as having 33 days of exposure and the subject with lung cancer is reported as having pulmonary edema after 2 weeks of ESL exposure and of total drug exposure of about 4-5 weeks. The subject with astrocytoma had a history of astrocytoma and was on drug for about 1 month – 5 weeks. The subject with lymphoma (302-395-80794) died 6-7 months after stopping study medication but was on ESL in part 1 on day 56 when she reported a neck mass, which led to her diagnosis.

These exposure seem short to be causally related, but this does not totally rule it out as a possibility. There is one case in the literature in which the authors describe an anaplastic large cell lymphoma in a subject on carbamazepine for three months for diabetic neuropathy. The authors speculate the possibility of carbamazepine inducing anaplastic large cell lymphoma (Dermatology Online J, 2008 Dec 15; 14 (12):5, Kaliyadan F, Ray S, Mathew MK, Pai S, Sasikala L, Pai R)

Seizure deaths: Sudden unexpected death in epilepsy, SUDEP, is defined by some as sudden, unexpected, death of an epileptic patient with or without seizure evidence, witnessed or unwitnessed, non- drowning and non-traumatic, that excludes documented status epilepticus, and in whom autopsy examination does not reveal a structural or toxicological cause for death (Epilepsia 38 (suppl 11) (1997). Pp.S6-8). The incidence of SUDEP varies in the literature and among patient cohorts. Among patients with chronic, often refractory epilepsy, the risks is 1.1- 5.9 per 1000 person-years (Lancet Neurol. 2008 Nov; 7 (11):1021-31, Tomson T, Tashef L, Ryvilin P). Of the three ESL deaths, reported as directly attributed to seizures (2093-301-90486/1244, 2093-303-703/70252, 2093-305-18502/2075), if one is documented status, by definition, this would not be SUDEP. In the child’s death, the case may be confounded by the use of rectal diazepam. However, the sponsor should discuss whether they believe there are suspicious cases and perform a person-year analysis.

Drowning: In the 3 deaths by drowning, one patient was still on ESL (301-177/90425). The case is consistent with a possible seizure related death and may reflect inadequate seizure control (medication failure) or the difficulty of controlling the underlying epilepsy. In the two other deaths by drowning, the subjects are reported to have been off ESL for 3 weeks and 45 days.

Cardiac: Of the two cardiac events, one was in phase 1 development (2093-105-005) and the second was in a phase 3 epilepsy trial (302-313-80267). Both subjects have have risk factors. Subject 105-005 was in a phase 1 study conducted in healthy elderly and healthy young subjects. Autopsy is reported as indicating acute occlusion of a coronary artery and signs of sudden cardiovascular failure. The epilepsy subject (2093-302-313/80267) was young, hypertensive, and overweight. His autopsy indicated severe coronary artery disease, which is a risk factor for sudden cardiac death but this event was unwitnessed and as such, I consider indeterminate.

The remaining death was in a subject in a trial of bipolar patients who committed suicide. Suicide is a known risk in this population and the this may reflect underlying disease and/or management.

Sponsor's Table of Deaths from 9-29-09 information amendment:

**Table 6-1: Fatal Serious Adverse Events Reported in All Clinical Studies of ESL up Until the 30 March 2009 Cut-off Date**

| Study Type | Study Number/ Site | Subject Number | Treatment | SAE description | Narrative link |
|---|---|---|---|---|---|
| Phase I | 2093-105 | 005 | ESL 600 mg | Acute coronary occlusion | ISS Appendix 25.1.1 |
| Phase II | 2093-205/543 | 203154 | ESL 900 mg | Suicide 11 days after last dose | ISS Appendix 25.1.1 |
| Phase III | 2093-301/177 | 90425 | ESL 800 mg | Drowning | 120-SU Appendix 13.1 |
| Phase III | 2093-302/313 | 80267 | ESL 800 mg | Sudden death, severe atherosclerosis | 120-SU Appendix 13.1 |
| Phase III | 2093-303/703 | 70252 | ESL 800 mg | Multiple prolonged seizures | 120-SU Appendix 13.1 |
| Phase III | 2093-303/611 | 70327 | ESL 800 mg | Relapsed Astrocytoma | 120-SU Appendix 13.1 |
| Phase III | 2093-302/385 | 80426 | ESL 1200 mg | Drowning | 120-SU Appendix 13.1 |
| Phase III | 2093-302/388 | 80468 | ESL 1200 mg | Drowning | 120-SU Appendix 13.1 |
| Phase II | 2093-203/341 | 203181 | Placebo | Ischemic stroke | ISS Appendix 25.1.1 |
| Phase III | 2093-301/194 | 90132 | Placebo | Hypothermia | ISS Appendix 25.1.1 |

Abbreviations: ESL=eslicarbazepine acetate; mg=milligram; ISS=Integrated Summary of Safety; 120-SU=120-day safety update

Note: The event for Subject 203154 [Suicide 11 days after last dose (ESL 900 mg)] was not captured in the clinical database and therefore, is not included in the listing provided in Attachment 3, but is noted here for completeness.

The referenced information amendment also included text that noted "In addition, there were a total of 4 deaths in ongoing studies" during the period between the ISS cut-off

and the SU cutoff. These were subjects, 207-222011/7413, 207-206014/7734, 301-90486/1244, and 305-18502/2075.
Table xx

**Placebo Deaths**

| Study where 1st reported | Subject ID | Summary |
|---|---|---|
| 301<br>ISS | 2093-301-194/90132 | 50 year old male was found dead 132 days after receiving the first dose of placebo and 20 days after receiving the last dose of placebo. He was **found dead** (b) (4) the day after leaving home (b) (4) The autopsy is stated to have **"total supercooling of the body"** listed as the cause of death |
| 203<br>ISS | 2093-203-341/203181 | ischemic stroke -42 year old female with bipolar I disorder with an acute manic episode experienced an **ischemic stroke** 21 days after receiving the first dose of placebo. She died two days later. |

Table xx
**Eslicarbazepine Deaths**

| | Study | ID | Drug-Most recent or using | Summary |
|---|---|---|---|---|
| 1 | 105<br>ISS narrative | 2093-105-005 | ESL<br>600 | **Collapse Cardiovascular** -65 year old male with history of heart palpitations, chronic supraventricular arrhythmia with atrial fibrillation, tobacco use, and past history of alcohol abuse died **after** receiving a single dose of 600 mg ESL. [ISS narrative 4 days after single dose but if read closely, it is 4 days after the first single dose and 1 day after the second single dose. CSR SUSAR form indicates the death occurred 24 hours after the first dose (b) (6) of the multiple dose period.] EKG considered abnormal but clinically insignificant with QRS of 112 ms and QTc of 441 ms. Autopsy results reported as indicating an acute **occlusion of the left circumflex coronary artery and signs of sudden cardiovascular failure.** |
| 2 | 205<br>Bipolar<br>ISS | 2093-205-543/203154 | ESL<br>900 | **Suicide**-30 year old female with bipolar I disorder who withdrew her consent from the study, committed **suicide** either 5 days (p.454/582 of the ISS) or 11 days (p.98/582 ISS) after receiving her last dose of ESL. CRF indicates this suicide occurred 5 days after last dose of ESL. {As per the study report, there were no deaths in either part 1 or 2 of the study and I did not see this suicide described. If this is not described in the study report, it raises the question of how long SAE information was collected and/or reported.} |
| 3 | 206<br>DN<br>2-4-10 | 206-763-763013<br>/5575 | ESL 1200 mg | **Prostate cancer**-75 year old male. Entered trial with history of prostatic adenoma for 4 years. Received first dose of study drug 4-1-2008, took ESL 1200 mg daily 4-9-08 to 5-14-08. On (b) (4) he is reported as experiencing severe lumbalgia due to cancer of prostate. He was admitted to a neurology service due to this. He died (b) (6) |
| 4 | 207<br>Ongoing<br>PHN<br>SU | 2093-207-222011<br>/7413 | ESL 800 | **Gastric cancer-**77-year-old white male with history including gastritis, peptic ulcer, and Boerhavve syndrome with esophagus resection and replacement of stomach tube. Admitted to hospital day 33 of ESL dosing due to gastric stenosis. Study medication stopped and gastric dilation performed. 11 days later, readmitted |

| | | | | |
|---|---|---|---|---|
| | | | | 2nd to jaundice, dysphagia, and reflux. The narrative indicates there was dilation of the biliary tract. Upper endoscopies revealed a gastric lesion that biopsied as gastric adenocarcinoma, involved the head of the pancreas, and compressed the ductus choleducus. Died during hospitalization from septic shock due to cholangitis and tracheobronchitis 76 days after receiving the first dose of 800 mg ESL. |
| 5 | 207<br>Ongoing<br>PHN<br>SU | 207-206014<br>/7734 | ESL 800 | **Lung Neoplasm Malignant**-64-year-old white male with history including pulmonary edema,1 month to 5 weeks exposure to ESL 800 mg (b) (6) with event leading to 1st hospitalization (pulmonary edema) at 2 weeks exposure to dose (b) (6) He recovered. Study medication discontinued (b) (6). Unknown date, he was readmitted to hospital and died (b) (6) (2-4-10 information indicates 2 months after last dose ESL). Final diagnosis on autopsy was pulmonary carcinoma. |
| 6 | 301 part 2<br>ISS | 301-<br>177/90425 | ESL 800 | **Drowning-** 56 year old female on 800mg ESL for 314 days died from asphyxiation by **drowning.** Autopsy results included a small superficial head wound, superficial abrasions left collarbone region & right shoulder, and pulmonary distension. Injuries are reported to have had no causal relationship to death. |
| 7 | 301 part 3<br>Ongoing<br>SU | 2093-301-<br>90486/1244 | ESL 800 | **Brain edema following an epileptic seizure-**A 54-year-old white male experienced **brain edema after an epileptic seizure** that resulted in death 947 days after receiving the first dose of 800 mg ESL. The subject was in part 3 of one the phase 3 epilepsy studies. The investigator was informed of the death about 9 weeks after the death. |
| 8 | 302 part 2<br>SU | 2093-302-<br>313/80267 | ESL 800 | **Arteriosclerosis Coronary Artery and Sudden Death**-30 year old white male with history includes hypertension, asthma, 1st degree AVB, hyperlipidemia, and reportedly 11 kg weight gain in previous 3 months was **found dead** in his room on day 259 of the study (b) (6) He was taking 800 mg ESL in part 2 and took 400 mg ESL in part 1. The autopsy reported severe coronary atherosclerosis as the direct cause of sudden death and epilepsy and hypertension as antecedent causes of death. CRF: Medical history included 1st degree AVB, sinus tachycardia, asthma, overweight, hypertension and hyperlipidemia. CRF AEs show two events of "worsening hypertension" during the trial. EKGs considered normal. Handwritten comment on V2 (5-30-05) that PR interval at top of normal limit. |
| 9 | 302 part 2<br>SU | 2093-302-<br>388/80468 | ESL 1200 | **Drowning-** 31 year old black female death is reported as occurring 45 days after receiving last dose of 1200 mg ESL. |
| 10 | 302 part 2<br>SU | 2093-302-<br>385/80426 | ESL 1200 | **Drowning** -31 year old white male death is reported as occurring 22 days after receiving last dose of 1200 mg ESL (drowning on day 21 after last dose, death the next day). |
| 11 | 303 part 2<br>SU | 2093-303-<br>703/70252 | ESL 800 | **Status epilepticus**-32 year old Hispanic female experienced multiple, **prolonged seizures** reportedly resulting in death 3 days after last dose of 800 mg ESL. The death certificate (no autopsy) is stated to list the cause of death as acute respiratory insufficiency and epilepsy grand mal. Listing 6.1 of 9-29-09 submission indicates the patient was 400 mg ESL and died of status epilepticus. |
| 12 | 303 part 2<br>SU | 2093-303-<br>611/70327 | ESL 800 | **Neoplasm Recurence**-54 year old white male with a low grade astrocytoma died from the **astrocytoma** ("tumor relapse") 29 days after receiving his last dose of 800 mg ESL.. Subject took placebo in part 1 and ESL 800 mg from (b) (6) (CRF has about *90 DCFs; pages 403-528 are data clarification forms}*. |
| 13 | 305<br>SU | 2093-305-<br>18502/2075 | ESL 200 | **Cluster seizures and Cardiac Arrest**-7-year-old White female, reported history of about 60 seizures per month before starting the trial, experienced a **cluster of seizures** resulting in death 55 days (b) (6) after receiving the first dose of ESL 200 mg (but on ESL |

| | | | | |
|---|---|---|---|---|
| | | | | 600 mg -30mg/kg/d). She experienced 2 episodes of cluster seizure at home, was given rectal diazepam, and on that day was taken to hospital with reported sudden circulatory arrest asystolia. Autopsy performed but not available at time of narrative. Table 2 in the 2-4-10 submission notes this child experienced status epilepticus from 4-27-08 to 4-30-08 (pre-randomization). |
| 14 | 302 part 2 | 302-395-80794 | ESL 400-1200 | 61 year old female with **follicular lymphoma** diagnosed in part 1 (day 56 of ESL 800 mg dosing), experienced multiple SAEs during the study and died about 6.5 months after stopping study medication from acute respiratory failure. On day 56 in part 1, she noted a neck mass (b) (6) and was diagnosed with a B-cell lymphoma about 2 weeks later. She underwent chemotherapy and experienced severely low white cell counts, leukocytes, neutrophils, lymphocytes, and monocytes. She took her last dose of study medication on (b) (6) and recovered from low lymphoctyes and low monocytes on (b) (6) Her course was complicated by a hospitalization for low platelets two weeks after stopping drug after presenting with purple coloring of her body and upper limbs, oral hemorrhagic lesions, and lower limb hematomas. Biopsy showed aplastic medullar disease. Her course continued to be complicated including infection of the cutaneous nodules and need for transfusions of platelets and erythrocytes. In (b) (6) she developed oliguria and a right pleural infusion and died of respiratory failure. |
| 15 | 207 IND safety report (death after cut-off for NDA) | reported as PHN | ESL 800 (400 bid) | Bilateral pneumonia - 64 year old female with history listed as post-herpetic neuralgia, hypertension, sinus bradycardia, renal disease, admitted with hospital with high temperature. Started ESL on (b) (6) Also on atenolol. Autopsy "**decompensated respiratory insufficiency, bilateral bronchopneumonia, severe temperature - intoxication syndrome, cardiocirculatory insufficiency, consumption coagulopathy and secondary anemia'.** Pathology indicated chronic pulmopathy, chronic bronchitis, pulmonary emphysema, focal apical pneumofibrosis with microcalcinosis. |

Data sources include the ISS and SU narratives, CRFs, and response submitted 9-29-09. For deaths in study 207 (post-herpetic neuralgia) and study 305, I am unsure whether these are in controlled parts of the study and no CRFS were submitted for the deaths in study 207. Sepracor notes the studies are not completed and are sponsored by BIAL-Portela & CS.A. PHN=post-herpetic neuralgia, ongoing=ongoing study. DN=Diabetic Neuropathy, ISS=integrated summary of safety submitted with initial NDA submission, SU=120-day safety update, CRF=case report forms

*Reviewer's comment: Upon re-submission of the data, the sponsor should discuss SUDEP and whether they believe there are suspicious cases and perform a person-year analysis. The data from completed trials such as study 206 (clinically completed 11-18-08) and 207 (clinically completed 1-19-09) and should be verified and final, especially for deaths, non-fatal serious adverse events, and discontinuations secondary to an adverse event.*

### 7.3.2 Nonfatal Serious Adverse Events

Overview:
Based on information in the phase 3 epilepsy protocols or study report, it seems that generally the phase 3 studies defined SAEs the same and consistent with U.S. regulatory definition. The definition was "any untoward adverse event which a subject suffers during the course of a study that: results in death, or, is life-threatening, or requires inpatient hospitalization or prolonged hospitalization, results in persistent or

significant disability/incapacity, is a congenital anomaly/birth defect, or other medically important condition.

SAEs were to be reported within 24 hours to either a CRO representative or the sponsor (Bial). Study protocols for studies 301, 302, and 303 indicate that post-study visits were to occur for patients who did not enter part 2 (open-label), who discontinued early, and for all patients after the end of part 2 (or in study 303, all patients at the end of part 2 who did continue in a further study extension). This visit was to occur within a month of the date of discontinuation and was to include "adverse event monitoring" (p.389/1074 of CSR301a1, p2746/17103 CSR 302, and p.2314/11481 CSR 303). *It is not clear to this reviewer whether events reported at these visits are included as narratives.*

Methods used for treatment group assignment for SAE table: The ISS states that all summaries of TEAEs, with the exception of the titration period, were presented by the randomized group. For AEs during the titration period, the summaries are presented by the starting dose (400 mg, 600 mg, and 800 mg).

Data:
For phase 1-3 studies, the sponsor reports 3/528 (0.6%) placebo subjects with 3 non-fatal SAEs and 88/1977 (4.5%) ESL treated subjects with 125 non-fatal SAEs.

- In all phase 1, as per the sponsor's table below, no placebo subjects experienced a non-fatal SAE and 4 ESL-treated subjects did.
- In phase 2 epilepsy, one placebo subject and 4 ESL subjects (2 in the adult study and 2 in the pediatric study) experienced a non-fatal SAE. In the phase 2 bipolar studies, no placebo subjects and 13 ESL treated subjects (5.2%) experienced a non-fatal SAE.
- In the phase 3 epilepsy studies, two placebo subjects and 67 ESL subjects experienced a non-fatal SAE (67 must include open-label subjects given the dataset information from ADAE2.xpt).

**Table 3: Summary of Any Non-Fatal SAEs in the Entire Eslicarbazepine Acetate Development Program by Study and by Development Phase**

| Study # (Study Type) | Any Non-Fatal SAEs | | | |
|---|---|---|---|---|
| | Placebo | | ESL | |
| | n / N (%) | # SAEs | n / N (%) | # SAEs |
| All Studies | 3 / 528 (0.6%) | 3 | 88 / 1977 (4.5%) | 125 |
| All Phase I Studies | 0 / 141 (0%) | 0 | 4 / 597 (0.7%) | 4 |
| 2093-107 (DDI Digoxin) | 0 / 13 (0%) | 0 | 1 / 13 (7.7%) | 1 |
| 2093-111 (Hepatic) | -- | -- | 1 / 17 (5.9%) | 1 |
| 2093-117 (Food Effect) | -- | -- | 2 / 18 (11.1%) | 2 |
| All Phase II Epilepsy Studies | 1 / 47 (2.1%) | 1 | 4 / 127 (3.1%) | 4 |
| 2093-201 (Adult Epilepsy) | 1 / 47 (2.1%) | 1 | 2 / 96 (2.1%) | 2 |
| 2093-202 (Pediatric Epilepsy) | -- | -- | 2 / 31 (6.5%) | 2 |
| All Phase II Bipolar Studies | 0 / 51 (0%) | 0 | 13 / 252 (5.2%) | 14 |
| 2093-203 (Bipolar) | 0 / 40 (0%) | 0 | 3 / 121 (2.5%) | 4 |
| 2093-205 (Bipolar) | -- | -- | 10 / 104 (9.6%) | 10 |
| All Phase III Studies | 2 / 289 (0.7%) | 2 | 67 / 1001 (6.7%) | 103 |
| 2093-301 (Epilepsy) | 2 / 102 (2.0%) | 2 | 26 / 380 (6.8%) | 34 |
| 2093-302 (Epilepsy) | 0 / 100 (0%) | 0 | 32 / 389 (8.2%) | 59 |
| 2093-303 (Epilepsy) | 0 / 87 (0%) | 0 | 9 / 232 (3.9%) | 10 |

Abbreviations: ESL=eslicarbazepine acetate, SAE=serious adverse event.
Note: Studies not listed reported no SAE.
Note: No placebo arm was included in studies 2093-111, 2093-117, 2093-202 and 2093-205.
Reference: Attachment 1 Tables 2.1, 2.1.1 and 2.1.2



## PHASE 3 EPILEPSY

### Sponsor's analysis of controlled phase data (titration, maintenance, taper):

Table 4.1.4.2-1 of the SU (reproduced in the appendix of this document) is the sponsor's summary table of treatment-emergent serious adverse events (TE SAES) in part 1 (titration, maintenance, taper) of studies 301and 302 compared to 303. This table includes a death in placebo.

As per this table, for studies 301 and 302, the incidence of subjects with non-fatal and fatal SAEs is 2% (4 subjects) in the placebo group and 4.5% (27 subjects) in the total ESL treated groups. Incidence did not show a dose response (2%, 4.6%, 5%, and 4% for placebo, ESL 400 mg, ESL 800 mg, and ESL 1200 mg, respectively) (SU end-of-text table 5.6.1.1-not duplicated this review). If the fatal SAE is subtracted, which occurred in a placebo subject, the incidence of non-fatal SAEs is about 1.5% in the placebo group (compared to 4.5% in the ESL groups). The dose response information is limited in value given the small numbers and the handling of titration period events.

In study 303 controlled trial data, the incidence is reported as 0% and 0.6% for the total ESL group. By dose group, this is 0%, 0%, and 1.3% for placebo, ESL 800 mg, and ESL 1200 mg respectively (SU end-of-text table 5.6.1.2, not duplicated in this review).

Based on the sponsor's table 4.1.4.2-1, in combined studies 301-302, a total of 3 placebo subjects (3 events) and 27 ESL subjects (45 events) are reported as experiencing non-fatal SAES. The three placebo SAEs occurred in three different system organ classes (SOCs), Nervous System, Infections & Infestations, and

Neoplasm. The two most popular SOCs for ESL subjects are the Nervous System and Gastrointestinal (GI) System. 12 of 27 ESL subjects (with 13 SAES) were coded to Nervous System Disorders and 8 of 27 (with 9 SAEs) to GI Disorders.

The only preferred term in the Nervous System SOC in the placebo group is "paresthesia" (one SAE). The most common single preferred term in the Nervous System SOC in the ESL group is "abnormal coordination", which was reported in 4 subjects (5 SAEs). "Convulsion" or "Complex Partial Seizure" or "Grand mal convulsion" was reported in 4 ESL subjects (4 SAEs). Dizziness was reported in 2 ESL subjects (2 SAEs). Cerebral vasculitis and ataxia were each reported in one subject (1 SAE each).

In the GI SOC, 0 placebo subjects reported an SAE and 8 ESL subjects reported an SAE. The most common preferred term in this SOC was "vomiting" in 4 ESL subjects (5 SAEs). One serious event each of constipation, gastric disorder, gastric ulcer, and nausea was reported.

By preferred terms, overall, the most common SAES across the ESL-treated subjects were abnormal coordination (0.7% of subjects), vomiting (0.7% of subjects), "drug toxicity" (0.5% of subjects), vertigo (0.5% of subjects) and diplopia (0.5% of subjects).

If similar terms are combined, such as vertigo and dizziness, the incidence is 0.8%. Combining ataxia and abnormal coordination, incidence is 0.8%. The preferred term "Drug Toxicity" is reported as an SAE for 3 ESL treated subjects (3 SAES) in combined studies 301 and 302. Other terms such as dizziness, ataxia, vertigo, diplopia, abnormal coordination may be features of drug toxicity and are seen with the use of anti-epileptic drugs. Cerebellar syndrome is the term used in study 303 and seems likely to be a drug toxicity syndrome.

Singular serious events of rash (term-exanthem), hyponatremia, angina, acute renal failure, hypertensive crisis, and constipation were reported. These events are discussed later in this section.

Given the relatively small number of subjects and events, a table showing a listing of subjects and events made from the integrated safety dataset ADAE2.xpt is shown below. This table allows one to see all of the events for a subject although without dates. For the table below, events from titration, maintenance, and taper phases were selected. Pre-dose events are discussed only as background. The sponsor's define file indicates the variable "AETERM" is the verbatim name of the event and is used in the presentations below. The variable "TRTA" was used for the treatment group. This appears to be the randomized group. The define file label calls it the actual treatment group. (Other narratives not reproduced in the text may be found in the appendix of this document.)

**Reviewer's analysis:**

PRE-DOSE EVENTS: 20 subjects with 23 events. Eight events were related to seizures (AETERMS included seizure term). Six events were accidents or injuries. Two were attributed by the sponsor or investigator to carbamazepine (intoxication with and overdose of). Three events in one subject (301-181-90003) are interesting as the events indicate angioneurotic edema (acute urticaria, quincke's edema, and toxicodermia) and the subject may have been on placebo or no treatment. The subject's CRF indicates the subject was dispensed study drug on 9-23 at visit 1. This would have been the beginning of placebo in this study. Events began 10-08. The CRF notes she was not study treatment. The subject discontinued due to withdrawal of consent and occurrence of an unacceptable AE.

Table xx

| TRTA | AETERM (verbatim) |
|---|---|
| **PLACEBO** | |
| 2093301-112-90322 | FIBROADENOMA OF THE BREAST |
| 2093301-141-90169 | ATYPICAL BRONCHO-PNEUMONIA |
| 2093301-182-90023 | PARAESTHESIA OF LEFT ARM AND LEG AND RIGHT LEG |
| **ESL 400 mg** | |
| 2093301-113-90398 | BRAIN CONTUSION AND NASAL BONES FRACTURE 2x narrative bolded term is "Traumatic Brain Injury"-subject fell during seizure |
| 2093301-141-90171 | INTOXICATION WITH AED'S |
| 2093301-146-90192 | ATAXIA, VERTIGO |
| 2093302-334-80097 | ATAXIA, DIPLOPIA, VOMITING, WORSENING DEPRESSION |
| 2093301-153-90505 | CLUSTER SEIZURES (126 days after 1st dose 400mg) |
| 2093301-174-90414 | INCREASED NUMBER OF SEIZURES (144 days after randomized to 400 mg) |
| 2093302-312-80287 | GENERALISED TONIC CLONIC SEIZURE (HOSPITALISED) (22 days after randomized to 400 mg) |
| 2093302-351-80013 | SUSPECTED CEREBRAL VASCULOSIS |
| 2093302-382-80440 | "SHAKY FEELINGS, DIZZINESS, DOUBLE VISION, PSYCHOSIS |
| **ESL 800 mg** | |
| 2093301-113-90333 | VERTIGO |
| 2093301-145-90194 | ANGINA PECTORIS |
| 2093301-172-90407 | CLUSTER SEIZURES (5 days after randomized to 800) |
| 2093301-192-90259 | STOMACH ULCER |
| 2093302-301-80670 | ATAXIA, VOMITING |
| 2093302-306-80614 | ATAXIA, HYPONATREMIA, VOMITING |
| 2093302-312-80299 | ACUTE ON CHRONIC RENAL FAILURE, GASTRO-ENTERITIES |
| 2093302-336-80710 | ENDOMETROSIS |
| 2093302-395-80794 | FOLLICULAR LYMPHOMA LEVEL, LYMPHOMA LEVEL 2 ** |
| 2093302-421-80778 | CARBAMAZEPINE TOXICITY |
| **ESL 1200 mg** | |

| | |
|---|---|
| 2093301-111-90341 | EXANTHEMA |
| 2093301-122-90387 | VERTIGO* (see discussion below) |
| 2093302-401-80348 | DIZZY |
| 2093301-124-90485 | ARTERIAL HYPERTENSIVE CRISIS- history of hypertension- narrative symptoms chest pressure, dyspnea, intermittent blood pressure elevations, then diplopia, nausea, seated and standing vertigo, and inability to stand. BP 210/110, pulse 70. |
| | DIPLOPIA, NAUSEA |
| 2093301-142-90178 | INTOXICATION WITH CARBAMAZEPINE |
| 2093301-201-90094 | OBSTIPATION -hospitalized 2nd to this |
| 2093301-212-90032 | GASTRIC FUNCTION DISORDER – |
| 2093302-334-80094 | ATAXIA (2x), VOMITING (2x) |
| 2093303-703-70374 | CEREBELLAR SYNDROME- the only SAE for study 303 |

**ADAE2.xpt, **-this patient died about 6.5 months after stopping study medication with lymphoma diagnosed while in part 1 of the study. There is a description for this subject in the death section.**

## Narratives

The narrative for the rash seen in subject 301-111-90341 indicates this may have been a more extensive hypersensitivity reaction with LFT elevations, a fever, and thrombocytopenia. The sponsor asserts that the rash, laboratory findings, and course of the event make it most probably viral in etiology. This is not clear.

**301-111-90341 -"exanthem" 1200 mg ESL** –The narrative indicates this may have been a more extensive hypersensitivity reaction. On (b) (6) thirteen days after being randomized to this drug group, the subject was hospitalized after presenting with a generalized macular rash and a fever of 103.6° F. Laboratory results indicated an elevated CRP, leukopenia (2.8 x $10^9$/L), anemia (119g/L), thrombocytopenia (97 x $10^9$/L), and increased LDH, AST, and GGT. No reference ranges are given in the narrative. ALP and bilirubin are reported as within normal and hepatitis B and C testing as negative. The narrative states that the last dose of ESL 1200 mg was received on (b) (6) and that the subject was discontinued because of the event. During hospitalization, the subject was afebrile and the clinical events gradually resolved. The patient was discharged from the hospital on (b) (6) with events reportedly resolved. The sponsor asserts that the rash, laboratory findings, and course are most probably viral etiology. The subject was on concomitant carbamazepine. (CRF page 27/131 indicates carbamazepine started in1986.)

CRF review indicates fever (severe) on (b) (6) with offset (b) (6), exanthema on (b) (6) considered severe and patient withdrawn and study treatment discontinued, exanthema on (b) (6) considered serious and patient withdrawn. The visit 3 date is (b) (6). Visit 3 in study 301 is right after 2 week titration (400 mg daily in the first week and 800 daily in week 2 of titration). It seems the patient probably was not up to 1200 mg just based on the date of the first rash and the date of the study visit. This may be incorrect as the 1-25 information amendment (p.49/523) says that the "treatment header of the narrative identifies the treatment at the time of the SAE (ie, links the SAE with the most recent dose), not the randomized treatment".

The subject with hyponatremia (narrative below) had a sodium of 123 mEq/L and was vomiting and ataxic. This series of events seem likely related to study medication and responded to dechallenge.

**302-306/80614 Vomiting, Coordination Abnormal, Hyponatremia** -**ESL 800 mg.** This 47 year old female, with a history of epilepsy and AED intoxication (September 2004) was randomized to the ESL 800 mg treatment group. She received the first dose of ESL 800 mg (b) (6) On (b) (6), 7 days after receiving the first dose of ESL 800 mg, the subject was hospitalized with vomiting (began (b) (6), coordination abnormal, and hyponatremia. All laboratory parameters were normal except for **sodium (123 mEq/L [baseline sodium level 137 mEq/L]).** The subject was given metoclopramide (10 mg QD) to treat the event of vomiting, and received heparin (5000 UI BID) and ranitidine (150 mg BID) at the time of the event as prophylaxis for thrombosis and gastritis. Concomitant medications included carbamazepine, "clonacepan"' and clonazepam. The subject was **discontinued** from the study because of the events. The last dose of study drug was (b) (6) The event of vomiting was reported as resolving on (b) (6). The event of coordination abnormal resolved on (b) (6) The subject was discharged from the hospital on (b) (6) with sodium of 130 mEq/L. Asymptomatic hyponatremia (while the sodium was 130 mEq/L) is reported to have resolved on (b) (6).

**Subject 301-122-90387's** SAE in the dataset and the narrative bolded heading is "vertigo", however the subject also experienced "insecurity in space", loss of memory, intermittent loss of vision, headache, and loss of appetite as per the narrative text, beginning 17 days after randomization to ESL 1200 mg. The narrative reports improvement of her condition after study drug discontinuation. The narrative lacks significant details and there are no specific, other descriptions of the, "insecurity in space", memory loss, or vision loss. The CRF indicates the nausea and diplopia were SAEs and led to discontinuation of study drug and study.

The subject with cerebral vasculitis (narrative below) has a reported history of previous MRI findings making it seem unlikely related to ESL, although perhaps ESL could contribute to inflammation. In any event, it is a singular case.

**302-351-80013- Vasculitis Cerebral** -ESL 400 mg- 38 year old male with one-year history of epilepsy and medical history of MRI findings of high intensity foci in white matter and lab findings of increased antinuclear antibodies (seen also in CRF as medical history). 78 days after receiving his first dose of ESL, the subject presented with worsening headache and was hospitalized. Reportedly, MRI and CSF "confirmed" cerebral vasculitis and maxillary sinusitis on the right. Treatment included prednisolone. The subject was discontinued from the study due to the event. CRF visit 1 neurological exam notes no abnormal findings including the neurologic exam (p. 6/223). EDV exam performed 6-7-05 (age 98/223) indicates that subject had sensory exam findings of hypesthesia, hypalgesia, paresthesia, left distal sensory exam "neg", and Romberg. CRF onset of "suspected cerebral vasculitis" was 5-30-05 and study stopped on 6-7-05 secondary to this (p. 122/223). CRF appears to have a number of corrections (at least 30 data clarification forms). The original entry for some items is obscured by a typed entry that references a data clarification form. An example from this CRF is shown:

(b) (4)

**Psychiatric SAES:**

Two subjects experienced SAEs that included psychiatric symptoms. One subject, with no reported history (in the narrative) of psychiatric issues experienced two sets of events requiring hospitalization.

- **302-382-80440**- Two events with SAES- **Nervousness, dizziness, diplopia, psychotic disorder**- ELS 400 mg- 40 year old male with 23-year history of epilepsy and history of skull fracture in 1982, received first dose of ESL 400 mg on 7-4-2005. On (b) (6) the subject was hospitalized with nervousness, dizziness, and diplopia. No medications were given as treatment. Carbamazepine and valproic acid levels are reported as within therapeutic. These events are reported resolved on (b) (6). On 9-4-2005, the subject became aggressive, accusative, and paranoid. Symptoms continued until (b) (4), (b) (6) at which time he was hospitalized. He is reported to have been fully oriented and clinically normal except "his thought disorder was interfering in his social interactions". Carbamazepine levels within normal. No treatment medication was reported. The subject was discontinued from the study with the last dose of study medication on (b) (6). The event of **psychotic disorder** is reported to have resolved as of (b) (6) and the subject was discharged from the hospital. The CRF is 232 pages long but I did not see any details in the CRF about the symptoms or course of the psychosis. CRF medical history does not include a psychiatric term. Patient's only listed history is "head injury fractured skull".

- **302-334/80097 Coordination Abnormal, Diplopia, Vomiting, Depression- ESL 400 mg.** 29-year-old female with a history of epilepsy and depression randomized to 400 mg ESL group. She received the first dose of study drug on (b) (6). On (b) (6), 90 days after receiving the first dose of ESL, the subject was hospitalized with coordination abnormal and diplopia. Treatment medication included metoclopramide. Concomitant medication included carbamazepine, and clobazam. The subject's investigational product was lost during hospitalization and study medication was discontinued on (b) (6). The subject reported asymptomatic on (b) (6) and discharged from the hospital on (b) (6) On (b) (6) 10 days after receiving the last dose of study drug, she was hospitalized with vomiting and depression. The subject was given sertraline for depression. Concomitant medication included carbamazepine and clobazam. The dose of carbamazepine was reduced on (b) (6). The events of vomiting and depression were reported as having resolved (b) (6) and the subject discharged from the hospital that same day.

  I looked at the CRF mostly to verify the history of depression. The CRF seems messy with one whole AE page is in as data clarification entries [looks like the AEs were entered on another AE page in the CRF that apparently was not the right location.] AEs of vomiting and ataxia are recorded on 3-2-05 and ending on 3-

9-05, which precede the start of study drug. A handwritten comment on page 129/187 indicates the patient discontinued dosage of 400 mg of carbamazepine due to side effects and that carbamazepine dose was resumed on 3-7 as five divided doses. As I read the study report, the dose of concomitant AEDS were to be stable throughout the study and it looks like this patient had a dose adjustments of carbamazepine between visits 1 and 2.

Several of the subjects with symptoms consistent with toxicity were quite impaired- two could not walk or stand (301-141-90171 and 302-301-80670), although one of these is reported to have taken concomitant medications twice that day (90171).

●**2093301-141-90171**-"INTOXICATION WITH AED'S" 400 mg in the dataset- **drug toxicity per narrative** – non-significant medical history-56 days after being randomized to 400 mg ESL, hospitalized due to drug toxicity. On (b) (6) about 30 minutes after receiving drug, the subject developed ataxia, "insecure walking" and double vision. Within 10-15 minutes, he could not stand or walk without support. About 20-25 minutes later, the subject fell asleep. He was very somnolent and difficult to awake. Blood pressure was 85/60 but visit one was 90/60 and the subject appeared pale. The investigator hospitalized the subject after 2 more hours without improvement. The narrative states that basically the subject had taken concomitant medications twice that day (at 3 that morning and then at the study visit) because the subject had missed concomitant medications for two previous days. He was on concomitant lamotrigine, gabapentin, and clobazam. Based on the lab reference range supplied with the narrative, lamotrigine was above normal range (7.9 with range of 0.5 to 4.5) although intoxication symptoms appear to have been improving. Study medication was "interrupted" and the subject's condition is reported as improved several hours later. Also, the study medication was discontinued with the last dose on (b) (6) The event of toxicity was reported resolved two days after the visit. CRF indicates events of hypotonia, somnolence, drowsiness, double vision, circulation problems [these are crossed out and written above is "intoxication with AED's"] on (b) (6) leading to discontinuation of study treatment and withdrawal of the study.

●**302-301-80670 Vomiting. Coordination Abnormal -800 mg ESL-** 44-year-old white female with medical history of neurosurgery for hypothalamic tumor, received the first dose of ESL 800 mg on 1-26-05. On 1-28-05, the subject experienced mild ataxia. Her condition worsened progressively and on (b) (6), she began vomiting. On (b) (6), she could not walk or stand up and was hospitalized. Sodium was 132 mEq/L (normal reference range not provided). CT and MRI were performed and showed no new lesions. No treatment medications were reported. Concomitant medication included carbamazepine (1000 mg TID). The subject was discontinued with the last dose of study drug on (b) (6) Vomiting was reported as having resolved on (b) (6) Coordination abnormal resolved on (b) (6). CRF sodium at visit 1 was 143 and 141 at visit 2.

●**3303-703-70374** – 43 year female with 33 year epilepsy history who experienced **"cerebellar syndrome**" 7 days after receiving the first dose of 1200 mg ESL but 22 days after first dose of ESL 800 mg. Mild vertigo was reported 1 hour after starting study medication and increased to severe at 3 hours post dose. At 4.5 hours post-dose, the subject was alert, speech was dysarthric, no nystagmus, dysmetria and dysdiadochokinesia mainly on the left, and ataxic with lateropulsation. No treatment was reported. Concomitant medication included carbamazepine. The subject was discontinued secondary to the event. Symptoms resolved and the subject was discharged from the hospital the next day. CRF AE page states only "cerebellar syndrome" as event without further description.

**Seizure events**: **1)** 301-153-90505- **convulsion**-400 mg – 47 year old male with simple or complex partial seizures, 126 days after first dose of 400 mg ESL, hospitalized on (b) (6) with confusion and uncontrolled restlessness, had experienced a total of 12 seizures on June 5 and June 6, none reported on June 7 or 8. **2)** 301-172-90407-**convulsion**-800 mg-43 year old male with a history of

complex partial seizure was hospitalized 5 days after randomization to the 800 mg group for convulsion. The subject experienced a complex partial seizure and 3 seizures with secondary generalization, which repeated twice during hospitalization. EEG is reported as showing "insignificant pathological changes". No treatment was reported and study medication was not changed. The event was considered resolved at hospital discharge, about 9-10 days after event(s) *(Note: these events occurred 5 days after randomization, given the study design, the patient may have been only at 400 mg ESL)* . **3**) 301-174-90414- **Complex Partial Seizures**-400 mg-45 year old male with 6-year history of partial seizures and seizures with secondary generalization following surgery for left hemisphere hemangioma. He experienced an increase in the number of partial seizures 122 days after being randomized to ESL 400 mg and was hospitalized. EEG reported as single sharp theta waves. Valproic acid, clonazepam, mannitol, and other medications were used for treatment. Study medication was not changed. There were no further seizures during hospitalization. The subject was discharged 5 days after hospitalization. **4**) 302-312-80287- **Grand mal convulsion**-43 year old female with history of simple or complex partial seizures and callosal dysgenesis, randomized to ESL 400 mg group with first dose on 12-7-2005. On (b) (6) the subject was hospitalized with grand mal convulsion. Treatment included midazolam. Event is reported as resolved on (b) (6). **5**) **Traumatic Brain Injury**-(subject 301-113-90398-ESL 400 mg)-This subject fell during a seizure. CT reported as showing left frontal hemorrhagic brain contusion zones with edema. Study medication was unchanged and the subject reportedly finished the study. (Note-This subject went into part 2, experienced a seizure 287 days into part 2 and sustained a skull fracture. He had a progressive deterioration of consciousness and developed a left hemiparesis. He was found to have a subdural hematoma. He was discontinued from the study and the outcome of the skull fracture is unknown.) Although this subject has three narratives in the ISS including two for part 2 events, the ISS narrative for part 1 does not even reference the part 2 events. CRF reviewed. Reviewer found it difficult to trace event time lines from CRF, some words were unreadable (p. 109/302).

*Reviewer's preliminary conclusions:*

*Although this could be within a viral presentation, a relationship to drug cannot be ruled out for the serious rash in subject 301-111-90341. The event of hyponatremia was symptomatic and responded, as presented, to dechallenge. There seem to have been some serious drug toxicity syndromes. The event of psychotic disorder resolved by 5 days after drug discontinuation and the subject has no clearly stated psychiatric history. This is somewhat suspicious but not conclusive. There was a serious case of obstipation (301-201-90094). This may be of interest given the animal findings of delayed GI motility without a NOEL.*

*The narratives are at times not complete and/or hard to read. For example, the subject with acute on chronic renal failure (2093302-312-80299) has two narratives in the ISS narrative section. One is for the SAE of "gastroenteritis" (hospitalized (b) (6) resolved (b) (6)) and the other is for the discontinuation due to "vision blurred" (began 5-11-06, discontinued on 6-6-06 with attribution to the vision blurred AE). The discontinuation narrative includes a history of chronic renal failure, which is not in the SAE narrative, although the SAE narrative notes a history of acute renal failure and lupus. The SAE narrative reports the acute renal failure as secondary to gastroenteritis. The subject was vomiting and dehydrated and hospitalized with this 35 days after starting ESL (hospitalized on (b) (6). Per the CRF, he received a fistula about a week after the acute renal failure (on (b) (6) It seems less likely that the study medication contributed to this subject's vomiting and dehydration and renal failure if he continued on study medication and did not continue to vomit, but the SAE narrative does not specifically address this and the subject discontinued*

*Another example is the "drug toxicity" of subject 302-421-80778. The narrative notes that the subject was hospitalized with "carbamazepine toxicity". No symptoms are described, no levels are given, no explanation as to why this would be carbamazepine and not ESL. As the narrative reads, both carbamazepine and study drug eventually were stopped.*

**Part 2 (open-label) of studies 301, 302, and 303:**

As per the SU Table 5.5.2-1 (duplicated in the appendix of this review), there were 47 subjects (7.4%) with 63 treatment emergent serious adverse events in part 2 of studies 301 and 302 and 11 subjects (5.6%) with 13 treatment emergent serious adverse events in part 2 of study 303. If all of three studies are pooled, the incidence of TE SAES was 6.9%, which is higher than the part 1 rate for ESL-treated subjects. As the sponsor indicates, a higher incidence in part 2 compared to part 1 would not be unexpected given the longer follow-up in part 2. My analysis of the dataset ADAE2.xpt is consistent with the SU in terms of number of SAEs and subjects experiencing SAEs in part 2. There were 58 subjects with 76 SAEs in part 2 of the studies. 22 events were in study 301, 41 were in study 302, and 13 were in study 303.

| **AEBODY SYS**<br>**AETERM** (as written in dataset unless otherwise indicated) | **# events** | **# subj** |
|---|---|---|
| BLOOD AND LYMPHATIC SYSTEM DISORDERS (acute lymphadenitis) | 1 | 1 |
| EAR AND LABYRINTH DISORDERS (vertigo) | 1 | 1 |
| HEPATOBILIARY DISORDERS (suspected hepatitis) | 1 | 1 |
| METABOLISM AND NUTRITION DISORDERS (Hyponatremia) | 1 | 1 |
| PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS | 1 | 1 |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 1 | 1 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS<br>Aspiration pneumonia | 1 | 1 |

| | | |
|---|---|---|
| CARDIAC DISORDERS<br>Auricular flutter, Severe coronary atherosclerosis | 2 | 2 |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS<br>"Decreased mobility requiring inpatient rehabilitation", "Rheumatoid Nodules" | 2 | 2 |
| GASTROINTESTINAL DISORDERS<br>Nutcracker Syndrome<br>Fibrosed Appendiceal Tip, Nausea | 3 | 3 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)<br>Colorectal tumor, insulinome, astrocytoma refers to tumoral relapse | 3 | 3 |
| INFECTIONS AND INFESTATIONS<br>Acute Right Suppurative Otitis Media, Pyelonophritis, pneumonia, infection urinary | 4 | 4 |
| INVESTIGATIONS<br>Low leukocytes, low lymphoctyes, low monocytes, low neutrophils | 4 | 1 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS<br>3 are drowning, one is sudden unobserved death, and one asthenia | 5 | 5 |
| PSYCHIATRIC DISORDERS (see below for listing of AETERMS) | 8 | 7 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS<br>Three AETERMs include word "intoxication", One is "(Laceration) Liver Rupture", several terms are for fractures, head trauma, or burns | 16 | 15 |
| NERVOUS SYSTEM DISORDERS<br>See below for listing of AETERMS | 22 | 21 |

**ADAE2.xpt ( part 2 events noted to be SAEs)**

Review of the narrative and/or CRF for the cases of suspected hepatitis, hyponatremia, auricular flutter, nutcracker syndrome, and the liver rupture case were conducted as well as for the drownings and sudden death. The 4 deaths (drowning and sudden death are described in the Death section of this review for patients 301-177-90425, 302-385-80426, 302-388-80468, and 302-313-80267). The bolded headings are as per the narrative.

Subject 302-401-80732- **Hepatic Rupture**-The case of hepatic rupture in the table above is in a subject who reportedly fell during a seizure hitting her right side (subject 2093-302-401-80732-800mg ESL). As per the narrative, the fall caused severe liver laceration. She was hospitalized in a trauma ward. Apparently, the subject received CT of the thorax, body, brain, heart, and lung, but results were not reported. The subject experienced elevations of C-reactive protein, neutrophils, and ALP which were considered (as per the narrative) secondary to liver injury and are reported to have "normalized during recovery". She took her last dose of study medication on (b) (6) is stated to have recovered from the event of hepatic rupture on (b) (6). The subject was considered recovered from the event about 7-8 weeks later.

Subject 303-503-70008- **hepatitis-**This is a 44 year old male who received placebo in part 1. He began part 2 treatment on 8-23-05. On (b) (6) at a dose of 1200 mg ESL, the subject was hospitalized with fever, upper abdominal discomfort, dizziness, asthenia. "Moderate suspected hepatitis was reported." Laboratory tests "indicated" leukocytosis" with predominant lymphocytes and low levels of neutrophils, low platelets, increased creatinine, cholestasis, high transaminases and ALP, high IgE, and normal albumin, coagulation parameters, IGG, IGM, IGA, thyroid, and ferritin. Reportedly, the subject gradually recovered and was discharged from the hospital "asymptomatic" on (b) (6) The narrative notes he remained on study medication and completed visit 11 but it seems from the dates that study drug

treatment is noted as ending on 8-15-06. CRF review: 8-23-05 labs-AST, ALT, ALP,CPK, Albumin, creatinine, and total bilirubin WNL- CRF: visit 2, AST and ALT a little above normal at 46 u/l and 67 u/l respectively with ULN of 39 and 45 respectively. Total bilirubin was a little low (3.4 with RR 3.8-21.9 umol/L) and ALP was within the reference range at 86 u/L (35-123). These parameters are within reference ranges at visit 1 and at all subsequent visits (including visit 11 on 8-16-06).

Subject 303-601-70156- **Urinary tract infection and Hyponatremia** -53 year old female on ESL 800 mg in part 1. Part 2 dosing was from 11-11-05 to 9-26-06. History of hyponatremia in 1999. Hyponatremia is reported as non-serious from October ("exact date unknown" to November 25, 2006 but resulted in study medication discontinuation on (b) (6). On (b) (6) she was hospitalized with severe UTI and hyponatremia (sodium 125 mmol/L). Chloride was low at 92mmol/L and the absolute eosinophil count is reported as high (0.6 x $10^9$/L). Narrative is poorly written and seems contradictory in timing of event to last study medication use (60 days after last dose of 800 mg in line 6 of the 2nd paragraph or 2 days later from dates in the 3rd line of paragraph 2 or about 60 days based on the dates in the 2nd sentence of the first paragraph). The narrative reports symptoms of instability, dizziness, and urinary disturbance in the weeks prior to hospitalization. CRF has hyponatremia as a data clarification (DCF) entry. On one DCF (175765512) there is a handwritten note that states the sodium "is low since before the inclusion in the trial, so not to consider as an AE, as it is ongoing disease". Onsite Query on page 338/380 of the CRF has handwritten note asking that hyponatremia be added to the ongoing disease page 4 of book 1 since patient had since 1999. The author of the note indicated this was probably due to carbamazepine. There are at least 60 data clarifications for this CRF.

Subject 302-301-80674- **Atrial Flutter-**61 y.o. male with history of hypertension and back pain. Placebo in part 1. Started part 2 on 6-24-05. "moderate atrial flutter" beginning on (b) (6) reported as serious, as per the narrative, because intervention was required. The dose of study medication was titrated down to 400 mg/day starting on the date of onset. At visit 6 procedures, the EKG showed "auricular flutter". The subject was asymptomatic and previous study EKGs are reported as normal. Started atenolol and acenocoumarol and discharged from the hospital with flutter ongoing. Subject completed visits 6-10 with the last dose of study medication taken on 6-20-06.

Subject 302-336-80710**-Dyskinesia Esophageal in narrative (Nutcracker Syndrome in dataset)-** I am not familiar with "nutcracker syndrome". In Stat ref in a pediatric text book there was reference to a "nutcracker esophagus" that is an esophageal motility disorder. Stedman's medical Dictionary (28th ed) indicates "nutcracker syndrome" is non-glomerular hematuria due to compression of the left renal vein between. This 27 year old female who received ESL 800 mg part 1. Dosing for part 2 on 3-2-06. Concomitant CBZ, phenytoin, and clobazam. Hospitalized on (b) (6) with "severe nutcracker syndrome (dyskinesia esophageal)" on 1200 mg ESL daily. Study medication temporarily interrupted with recovery reported by (b) (6). Last dose of study medication reported as 6-25-07 with subject completing visits 6 and 10. CRF indicates that study medication stopped temporarily (p227/351) and that patient recovered with sequelae (page 227/351). Page 228 of the CRF has an entry under of "nutcracker syndrome" and notes a 4-day discontinuation. This is entry is crossed out. Based on DCF #189374912 (p349/351 of the CRF), the sequelae is mild to moderate epigastric pain. This CRF has about 65 DCFs and an onsite query form. The ADAE2 dataset indicates this patient had 22 adverse events. One of these (fever) led to stopping study medication for a few days in part 1. An episode of chest pain on 1-28-06 (CRF page 125/351) appeared to be missing from the dataset but at the top of the CRF page with this event term, there is a boxed note (like the ones from data clarification) that states "This CRF page will not be entered in the database". There is no explanation for this on the page and no referenced DCF, so it is unclear why this page is stamped with this (see the appendix for a copy of the page).

**PSYCHIATRIC SAES**

| STUDY | Unique Subject ID | AETERM |
|---|---|---|
| 301 | 2093301-172-90436 | DELUSIONS (**narrative Delusion as SAE** and different time, **Grand Mal Convulsion, which is stated to be atonic** seizures for the first time in open-label) |
| 301 | 2093301-214-90041 | PSYCHOGENIC PARANOID PSYCHOSIS-narrative reports medical history non-significant |
| 302 | 2093302-306-80604 | DEPRESSION WITH PSYCHOTIC SYMPTOMS CRF-medical history not indicate previous psychiatric history. CRF has many DCFs. |
| 302 | 2093302-306-80612 | ACUTE PSYCHOSIS- CRF medical history pages are blank |
| 302 | 2093302-312-80286 | INCREASED AGGRESSIVE BEHAVIOUR-CRF not indicate psychiatric history in past |
| 302 | 2093302-312-80286 | AGGRESSIVE BEHAVIOUR |
| 302 | 2093302-332-80188 | WORSENING OF PSYCHOTIC MANIFESTATION |
| 302 | 2093302-362-80552 | PSYCHOSIS (see narrative below) |

302-362-80552- **Drug toxicity, somnolence, and psychotic disorder** -65 year old male with no stated history of mental illness, experienced two SAEs. The subject was on ESL 1200 in part1. Part 2 dosing on (b) (6) Event 1: Day 19 of part 2 on 800 mg day-"did not speak and kept his eyes closed". He was taken to the ER the day after onset and admitted. Drug intoxication was suspected. Lamotrigine level was within the normal range. Medication given and levetiracetam reduced. Recovered on day 20 from drug intoxication and from drowsiness the next day. Event2: Day 74 on 800 mg daily, patient experienced "moderate psychosis" requiring hospitalization. Reportedly, at the end of part 2, the subject's wife noted that the subject had become gradually more agitated and aggressive towards end of part 2 although these traits were present before study entry. He was given "medication" and considered recovered by day 96. Subject completed through day 368 on study medication and completed visit 10. The company notes that safety report lists "psychosis possibly due to levetiracetam". CRF, no psychiatric history reported, shows agitation about 10 weeks earlier, handwritten note (p.201/295 of CRF) indicates patient overdosed "by error" on day of psychosis. CRF indicates subject stayed in study.

## NERVOUS SYSTEM DISORDERS SAES (as per SOC by sponsor)

| STUDY | Unique Subject ID | AETERM |
|---|---|---|
| 303 | 2093303-712-70144 | TRANSITORY ISQUEMIC ATTACK |
| 301 | 2093301-124-90357 | MILD RIGHT-SIDED HEMIPARESIS |
| 301 | 2093301-175-90417 | PSYCHOMOTOR AGITATION |
| 302 | 2093302-336-80067 | ATOXIA |
| 302 | 2093302-336-80073 | BIA 2093 RELATED CNS TOXICITY SYNDROME |
| 303 | 2093303-712-70102 | CEREBELLAR SYNDROME |
| 301 | 2093301-111-90329 | STATUS EPILEPTICUS |
| 301 | 2093301-161-90069 | STATUS EPILEPTICUS |
| 302 | 2093302-332-80196 | EPILEPTIC STATUS |
| 302 | 2093302-336-80076 | STATUS EPILEPTICUS |
| 303 | 2093303-703-70252 | EPILEPTIC STATUS |
| 301 | 2093301-125-90363 | EPILEPTIC SEIZURE (GENERALIZED TONIC-CLONIC SEIZURES) |
| 301 | 2093301-171-90404 | PROLONGED CONFUSION AFTER COMPLEX PARTIAL SEIZURES |
| 301 | 2093301-172-90436 | GENERALIZED SEIZURES |

| | | |
|---|---|---|
| 301 | 2093301-174-90414 | SEIZURE SECONDARILY GENERALIZED |
| 301 | 2093301-178-90461 | EPILEPSY WORSENING |
| 302 | 2093302-312-80286 | GTCS (X3) |
| 302 | 2093302-315-80256 | HOSPITALISATION DUE TO SEIZURES |
| 302 | 2093302-395-80742 | SEIZURES |
| 302 | 2093302-336-80078 | SEIZURES |
| 302 | 2093302-336-80078 | DROWSINESS |
| 302 | 2093302-362-80552 | DROWSINESS |

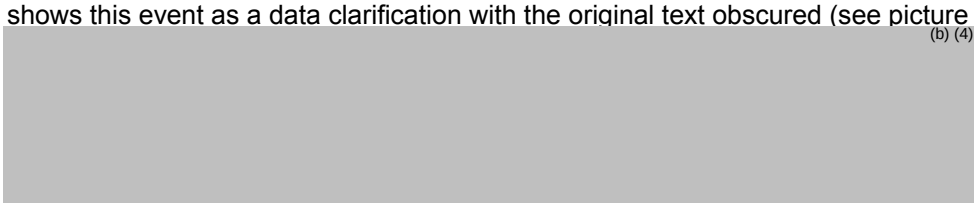
301-712-70144-**Transient Ischemic Attack**-77 year old female who was on placebo in part 1 and 800 mg ESL daily in part 2. On day 3 of part 2, she experienced a TIA and was hospitalized with loss of consciousness and left facial paresis. She is reported to have recovered with sequelae after 4 hours but study medication was discontinued. CRF indicates no history of HTN, DM or smoking, no concomitant medication that is antihypertensive, and blood pressure was 100/60 at visit 1. There seem to be several visit 1 laboratory re-tests. Total cholesterol 6.03 (3.59-5.38) and LDL at upper end of normal. CPK high at 368 on one re-test although not at first test and creatinine high at 100 (50-94) on re-test.

301-124-90357-**Hemparesis; Drug Intoxication-**This is a 41 year old female who was on placebo in part 1 and on ESL 1600 mg in part 2 (she is reported to have mistakenly taken 2-800 mg tablets daily). Event 1: The narrative describes that the subject experienced hemiparesis, vertigo, and walking instability 7 days (b) (6) after receiving the first dose of ESL 1600 mg. CT and MRI are reported as showing small old ischemic lesion in the left parietal region of the brain. The subject apparently had no stated history of stroke. Study medication was not changed. About a week after onset of the event, the subject was discharged with "only minimal asymmetry of reflexes, and paretic signs were not present". Event 2: 28 days (b) (6) after receiving the first dose of ESL 1600 mg, the subject was hospitalized with "drug toxicity" described as slowly progressing bradypsychic response, drowsiness, unsteady standing position, and unsteady gait that had started a week or so before hospitalization. Apparently, she was still on the erroneous dose of 1600 mg daily. All AEDs, including ESL, were stopped on the day she was hospitalized for the drug toxicity. Symptoms are reported as disappearing during the first 2 days. She was started on lamotrigine on (b) (6).

301-175-90417-**Psychomotor Hyperactivity-** 39 year old female with medical history reported as not significant. This subject was randomized to ESL 400 in part 1. 31 days after starting 800 mg in part 2, hospitalized with "psychomotor hyperactivity". Exam reported as "periodical excitement with movement of legs, no paresis, no pathological symptoms" and EEG as fast, low-voltage activity, some slow wave 4-6 Hz discharges in temple lead. No treatment medication is reported. Concomitants included CBZ and levetiracetam. Study medication is reported as not changed. Discharged from hospital (b) (6) with event reported resolved. CRF page 183/245 indicates the patient had an episode of "psychomotor agitation" on 8-24-05, anxiety on 9-15-05, and psychomotor agitation on 10-01-05. The event of anxiety is marked as causing withdrawal from the study. The first event of psychomotor agitation is noted as serious and the CRF page indicates a medication was given. The second psychomotor agitation is noted as moderate.

302-336-80073- **Nervous System Disorder in narrative, dataset is BIA 2093 RELATED CNS TOXICITY SYNDROME-**30 year old female who received placebo in part 1 and started part 2 dosing on (b) (6). On day 3 of 800 mg daily, she is reported as experiencing "severe BIA 2093-related central nervous system toxicity syndrome" and non-serious, moderate dehydration. She was hospitalized. Vertigo, nausea, loss of coordination, ataxia, and speech disturbance had started 8 hours post-study medication and were followed by vomiting, abdominal pain, and headache. Symptoms resolved after 16 hours. Study medication was given the next day and subject became nauseated and vomiting. This was her last dose of study medication (b) (6). Subject recovered (b) (6) and discharged. Creatinine was low during study with BUN within normal.

303-712-70102-**Cerebellar Syndrome**- 62 year old male who received placebo in part 1 and doses of both 800 mg ESL and 1200 mg in part 2. The narrative reports the subject experienced intermittent moderate cerebellar syndrome on day 307 (on 800 mg daily) and was hospitalized. The investigator suspected carbamazepine toxicity, but levels "were not determined" and considered the event probably related to study drug. The subject was discharged from the hospital on day 308 and the event considered resolved on day 314. The subject completed visits 7-11 as scheduled. Narrative states the subject has 62.8 year history of epilepsy. CRF indicates that the investigator decreased the dose of ESL from 800 mg to 400 mg due to the SAE but that the patient may have continued with 800. Patient is reported to have taken 15 more tablets than PI aware and it appears patient had a box of "compassionate use" medication accidentally given by the site (p. 233/336 CRF). CRF page with AE of "cerebellar syndrome" shows this event as a data clarification with the original text obscured (see picture below).




**Phase 2 epilepsy studies:**

Study 201 is a study in adults with epilepsy.
Study 202 is a study in pediatric patients with epilepsy.

Sources of data include:

- Sponsor's Table 3 in the 8-28-09 submission- 1 placebo non-fatal SAE in the combined adult and pediatric epilepsy subjects compared to 4 SAEs in 4 ESL-treated subjects.
- ISS narratives adult epilepsy study 201 in appendix 25.1.2.3 and for the pediatric study, 202, in appendix 25.1.2.4. Narratives for adults -1 placebo and two ESL. Narratives for pediatric subjects: 2 applicable (3 are included but one is for a subject event that is labeled pre-treatment/pre-first dose of study drug- subject 202-106. The pre-treatment event is not described below. The bolded terms are bolded as per the sponsor's narrative.

| | |
|---|---|
| 201-05/145 | **Placebo**-**viral gastroenteritis**-6 days after starting placebo, subject hospitalized with viral gastroenteritis, clinical features are reported as including severe dehydration and subject experienced status epilepticus. The investigator suspected the gastroenteritis to be due to "suspicious" drinking water 24 hours earlier. |
| 201-12/087 | **ESL 400 mg**-**gastrointestinal infection NOS**-32 days after starting drug, the subject hospitalized with gastrointestinal infection "NOS" suspected to be bacterial gastroenteritis that began 18 hours after eating rotten herring. |
| 201-14/079 | **ESL 400 mg**-**ischemic stroke NOS-**46 year old female with reported history of "left venous carotidis thrombosis" (CRF), experienced stroke in the right MCA (presented with left hemiparesis) onset 60 days after starting ESL 400 mg. Patient also on a concomitant oral contraceptive. CRF adverse event of "INR elevation" on 6-3-2002 (2.98 with RR of 0.9 to 1.3) and anemia on 6-3-2002 (Hemoglobin 6.95 with RR 7.45-9.93, hematocrit |

| | |
|---|---|
| | 0.36 with RR 0.35 to 0.47). INR was within normal on 7-1-2002. Hemoglobin and hematocrit were both low. Acenocumarol and antihypertensives started on 7-5-02 for carotid thrombosis. |
| 202-114 | **ESL 30mg/kg/d – Seizures Increased** -2 year old female with focal epilepsy with first dose of ESL of 5mg/kg/d. ESL dose was escalated to 30 mg/kg/d over about 7-8 weeks. The subject was hospitalized 70 days after starting the first dose of ESL with increasing seizure duration and severity and with some events generalizing. EEG the day after hospitalization showed "many pathological features, generalized spikes and spike- waves" (narrative in ISS p. 491). ESL was titrated down and discontinued on (b) (6) Hospital medications included dexamethasone and mannitol and oxcarbazepine was started. Subject is reported as discharged from the hospital on (b) (6) with the adverse event resolved. |
| 202-201 | **ESL 30mg/kg/d – Seizures Increased** -11 year old female with focal epilepsy, first dose of ESL of 5mg/kg/d which escalated to 30 mg/kg/d over about 7 weeks, experienced increasing seizure duration and frequency 67 days after first dose of ESL and about 13 days after starting the 30 mg/kg/d dose. She was hospitalized on (b) (6) with the increased seizures, which had been increased for 5 days. EEG on admit, continuous generalized spikes and spike and waves. ESL dose was reduced and then discontinued by 10-02-05. Medications in hospital included dexamethasone, mannitol, and diazepam. The subject had a follow-up visit on 10-17-05 and the ISS narrative reports the subject's "evaluation was favorable" with the mother reporting a significant reduction in the seizure number. |

**"Ongoing" epilepsy studies:** *[Note:The word "ongoing" is in quotes because study 301 part 3 is reported as clinically completed 6-27-08.]* Events from trials described as ongoing are most recently reported, by trial, by part of the trial, in Table 2 of the 2-4-10 submission (301-parts 3 & 4, 302 part 3, 304 part 1, and 305 parts 1& 2). A cursory review of this table indicates SAEs in ESL groups (either 400 mg, 800 mg, or 1200 mg) are generally similar to those seen in other epilepsy studies (seizure related and vertigo) or are not uncommon events (discopathy-assuming this is a herniated disc or something similar and "exacerbation of chronic bronchitis"). The term "ataxia due to contusion" is listed for one subject on 800 mg ESL.

Study 305 is a phase 3 study of subjects ages 2-16 years with partial seizures, treated with 1-2 AEDs. Events that occurred in the observational period of study 305 include those stating or suggesting seizure worsening, an arm fracture, and events of infection (e.g. pneumonia, acute respiratory infection). One event is "hereditary metabolism disorder".

In study 305, double-blind period, there are blinded reports of ventriculo-peritoneal shunt malfunction, seizures, and one report each of serious rash and vomiting. In the

open-label period of study 305, the serious adverse events are infection (chicken pox and pneumonia) and two of vomiting.

*Reviewer's preliminary conclusions:*

- *Ask sponsor to get background rate and send the reference (if article, send article) for psychiatric events in epilepsy and compare to the open-label rates.*
- *Ask sponsor to describe new onset atonic seizure.*
- *Status/seizure events may request comparison to background*

## NON EPILEPSY

**Phase 1**:

There are several places in the NDA to obtain this information. These include,

- 8-28-09 submission, Table 3. There were 0 placebo group and 4 ESL group non-fatal serious adverse events in all phase 1 studies.
- Narratives in the ISS (appendices 25.1.2.6 and 25.1.2.7 for healthy volunteer studies and special populations respectively). There are narratives for non-fatal events for subjects 107-111, 114-008, and 111-9. No narratives for subjects from study 117 were submitted in the SAE narrative section of the ISS (117-05 and 117-15). Although subject 117-05 has a discontinuation "narrative" that references the reader to the SAE narrative, which is not there. (The event is pregnancy.)
- 1-25-10 submission, Listing 52 (attachment 29), ""Serious Treatment Emergent Adverse Events, Safety Population, Phase 1 Studies Only". This listing has four subjects (107-11, 111-09, 117-05, and 117-15). This listing does not include subject the subject in study 114.

Summary information for the non-fatal SAEs in phase 1:

| | |
|---|---|
| 107-011- | **ESL 1200 mg Hypertension worsened**<br>Narrative-27 year old female, screening blood pressure 165/100. Highest BP was 240/130 mmHg the day after a single dose of digoxin 0.5 mg in period 2. Reportedly, she was referred to a cardiology center and diagnosed with probable secondary hypertension due to renal parenchymatous disease. CRF: BP was 165/100 at screening suggesting a pre-existing condition perhaps worsened by digoxin or within the scope of a pre-existing hypertension. |
| 111-9 | **ESL 800 mg Hepatic Encephalopathy**<br>58 year old female with moderate hepatic impairment and reported history of hepatic encephalopathy received her first dose of ESL 800 mg on (b) (6) and 4 days later was hospitalized. At dosing on the day of hospitalization, she was noted to have difficulty responding to commands, was disoriented and had vomited that morning. Labs: low albumin, high total bilirubin (41 umol/L RR 0-21), high conjugated bilirubin (14 umol/L-RR 0-6), low protein, and high ammonia (140 umol/L RR 19-63). AST, ALT, and ALP, and vital signs were within normal. Ascites was noted on exam. She was diagnosed with hepatic encephalopathy secondary to increased protein intake (meat the night before). She was discontinued from the study and treated. The event resolved and she was discharged on (b) (6) CRF |

| | |
|---|---|
| | indicates "moderate" ascites at screening and history of hepatic encephalopathy, renal impairment and liver disease. The event is in a patient with a reported history of hepatic encephalopathy and, as reported, may be confounded by eating protein the night before. |
| 114-008 | **ESL 1200 mg Neutrophil Count Decreased and WBC Decreased**<br>Narrative-21 year old female received single dose of contraceptive on 3-15-05. From 4-09-05→ 4-23-05, received 1200mg ESL + contraceptive for 15 days. On 4-24-05, neutrophils 0.7 (30%) [RR 2.1-7.6 and 40-80%] and WBC 2.3 [RR 4-11]. Lowest value of neutrophils was on 4-26 at 0.48 and ~14%. WBC count lowest was 2.3. 4-28 neutrophils still low. 5-1 neutrophils and WBC WNL. Anti-Epstein Barr IgG reported +. Subject had headache and hyperthermia and was treated with paracetamol. CRF indicates lower lip paresthesia and "recurrent dizziness" on 4-9, "recurrent somnolence on 4-12", then "Putatite erythema infecaosum-parvovirus, B 19 infection" on 4-19. No event is marked as serious. Possibly drug-related fever and effects on WBC/neutropils or viral infection. |
| 117-005 | **Pregnancy**-also had CPK elevation from 91 to 657 on 5-29-2007, 4 days after dosing with 800 mg ESL (not serious). Pregnancy was noted on (b) (6). The pregnancy was terminated in July (CRF documents abortion as voluntary). Pregnancy was considered the serious AE on CRF. |
| 117-015* | **Tonsillitis (purulent tonsillitis)-** no narrative seen in ISS (initial ISS), no CRF in initial submission- subject also with CPK elevation and in looking at description of the CPK elevation, I noted the word serious for an event, which was tonsillitis. This subject is seen as an SAE in Listing 6.2, a listing of serious treatment emergent adverse events was submitted in response to FDA request (attachment 4 of 9-29-09 information amendment). The event itself may or may not be notable but the inconsistency in reporting is noted. |
| 119-004* | **Hypersensitivity-** reported to be on ESL + Lamotrigine in the ISS narrative of discontinuation (not called an SAE). In the heading of the discontinuation narrative the subject is reported to be on ESL and lamotrigine. In the narrative text, it says the subject was not on concomitant medications at the time of event onset and as I read the listing 6.3, the subject was on ESL 1200 mg (listing of discontinuations in attachment 5 of 9-29-09 submission). The narrative lacks a detailed clinical description of the event. The CRF seems to indicate this subject was hospitalized (by definition, an SAE). Also, it seems from the CRF, that the subject's clinical course included an ulcer in the mucosa of the lower lip, perhaps an increased temperature, peeling skin, and liver enzyme elevations. Therefore, even though the subject reportedly was on a product associated with serious skin reactions (lamotrigine), if the subject was hospitalized, the event should have been captured as an SAE. This event is described in much more detail xx |

**RR = reference range. Units were omitted from some labs. CRF=Case Report Form, * see reviewer's comment below.**

*Reviewer's summary of phase 1 non-fatal SAEs: Subject 117-005's event is pregnancy and was reportedly terminated voluntarily. Subjects 107-011 and 11-9 have reported pre-existing conditions or history of event. Subject 114-008 may have had a drug reaction or may have had virus. Subject 117-005 does not have a narrative in the ISS. Tonsillitis is fairly routine so it would be interesting to see how it came to be classified as an SAE in this phase 1 study. Subject 119-004 is described elsewhere in this review. Based on events seen in the CRF, this subject was hospitalized and therefore is an SAE regardless of possibly be explained/confounded by lamotrigine..*

## Phase 2 Bipolar Studies (203, 204, 205)

In phase 2 bipolar studies, 51 subjects received placebo and 252 received eslicarbazepine (clinical overview in SDN000, module 2). Studies were of monotherapy

use. Studies 203 and 204 were studies to evaluate the efficacy and safety of eslicarbazepine in acute manic episodes associated with bipolar I disorder. Both are described as randomized, double-blind, placebo-controlled studies with 203 comparing 2 dose-titration regimens of eslicarbazepine with placebo and 204 being fixed dose of 3 doses of eslicarbazepine versus placebo. Study 205 was a recurrence prevention study that was an extension of studies 203 and 204. Study 205 had an open-label part and a double-blind, parallel-group part of three ESL doses (no placebo group).

- **Study 203**
  The ISS states there were six TE SAEs reported by 5 subjects. The ISS reports the incidence as 2.5%, 3.1%, and 3.5% for the placebo, 600 -1800 mg ESL daily, and 800 – 2400 mg ESL daily groups respectively.

  Placebo-ischemic stroke in 42 year old female
  ESL 600 mg-1800 mg -leukopenia and hyponatremia* (see narrative below) in 33 year old female (203215/11276), mania aggravated in 20 year old female
  ESL 800 mg- two subjects, worsening mania and a manic episode (66 year old male and 33 year old female).

**Subject 203-301/203215- ESL 1800 mg –Leukopenia, Hyponatremia –**Narrative information: 33 year old female with bipolar 1 disorder and medical history otherwise reported as non-significant, on (b) (6) 11 days after randomized to ESL 600 mg and one day after receiving last dose of ESL 1800 mg, leukocytes and sodium low. Subject discontinued the same day (b) (6) )-leukocytes (2.47 with range 4-10). Sodium was 128 (range 135-145 mmol/L). Subject hospitalized. It is stated she was on concomitant isotretinoin from 9-18 to 9-27, lorazepam, and ferrous sulfate. Hyponatremia was seen on early discontinuation visit (128 with range 135-145). On 9-28-06, WBC was 3.57 (4-10) and by 10-3-06, the result was 4.19. Sodium on 10-24-06 was 139 (135-145). CRF indicates sodium was 138 mmol/L and leukocytes were 4.55 G/l at admission visit on (b) (6). Neutrophils and lymphocytes also low at early discontinuation visit although reference ranges not given. A data clarification form indicates high direct bilirubin at visits 1 and 8, but I do not see this on the actual lab pages for these visits (visit 1 lab page has "ND" (not done) for direct bilirubin and visit 8 page is blank and marked out). {The ISS SAE narrative is lacking clinical details and is difficult to follow.}

- **Study 204 (as per CSR, p.46/1987):** this study only randomized 38 patients (11 to placebo, 8 to ESL 600 mg, 9 to ESL 1200 mg, and 10 to ESL 1800 mg). There were two TEAE SAEs of mania (one placebo with worsening mania and one ESL 1800 mg patient with severe manic episode).

- **Study 205-** The ISS states there were 11 SAEs across the open-label and double-blind periods and that no dose relationship was observed for the double-blind period.

  As per the CSR, (Table 12-9 of the CSR, page 63/5893), there were 35 subjects in the 300 mg group, 26 in the 900 mg group, and 26 in the 1800 mg group. As per this CSR table (Table 12-9), there were 2 subjects with SAEs in the 300 mg group, 4 in the 900 mg group, and 2 in the 1800 mg group. This dose

presentation is for descriptive purposes only as there is no placebo group and the numbers are small.

| Preferred term | BIA 2093 300 mg n=35 | BIA 2093 900 mg n=26 | BIA 2093 1800 mg n=26 | Total n=87 |
|---|---|---|---|---|
| Any AE? | 2 (5.7%) | 4 (15.4%) | 2 (7.7%) | 8 (9.2%) |
| Anemia | 0 | 1 (3.8%) | 0 | 1 (1.1%) |
| Esophageal stenosis | 0 | 1 (3.8%) | 0 | 1 (1.1%) |
| Bronchitis | 0 | 0 | 1 (3.8%) | 1 (1.1%) |
| Pneumonia | 0 | 1 (3.8%) | 0 | 1 (1.1%) |
| Depression | 0 | 1 (3.8%) | 0 | 1 (1.1%) |
| Mania | 2 (5.7%) | 0 | 0 | 2 (2.3%) |
| Disease Progression | 0 | 1 (3.8%) | 1 (3.8%) | 2 (2.3%) |

**Data from CSR table 12-9, "Summary of Serious Adverse Events by Preferred Term: Part II Double-Blind Period (Safety Population)" MedDRA version 9, patients are reported as counted once within a preferred term**

According to the sponsor's Table 3 (summarizing number of all non-fatal SAEs), there were 10 subjects with 10 SAEs compared to the ISS which indicates there were indicates there were 11 SAES across the open-label and double-blind periods. Seven of the 11 SAEs were related to psychiatric events ["Disease Progression" (3), "Depression" (1), or "Mania" (3)]. The non-psychiatric events are summarized below.

Table XX

| | | |
|---|---|---|
| **503-203083** | Bronchitis-serious but narrative states dc 2nd to diarrhea on the same date | ESL 1800 mg |
| **543-203144** | Anemia- discontinued secondary to this (event 8-28) Esophageal stenosis (event 8-29) treated with omeprazole, but CRF and narrative indicate event ongoing- | ESL 900 mg *ESL300mg |
| **544-203159** | Pneumonia | ESL 900 mg *ESL 300mg |
| **651-203196** | Dizziness | ESL 300 mg |

Table dose group are from the CSR Appendix 16.2 Listing 16.3-3. * The ISS narrative headers sometimes had a different dose group. In those cases, the ISS dose group is noted with an *. * also indicates the information is from the narrative in the ISS.

R*eviewer's summary bipolar: The narrative for the patient with leukopenia and hyponatremia lacks clinical details. This patient was on other medications, specifically isotretinoin (Accutane). It is unclear whether this may have confounded the picture and it appears that both ESL and isotretinoin were stopped.*

*When data quality issues are resolved, a request for clarification can be made in the action letter to request a presentation of all events throughout development of AST and/or ALT meeting certain criteria and describe these in one place and with all pertinent other lab values (such as bilirubin and ALP) and to present, in one place, all subjects in the development program with elevated bilirubin and provide relevant medical information..*

*Regarding the subject with anemia and esophageal stenosis, the CRF does not give reference ranges but there is a box for one to check as to whether the values are out of range and one to check if the value is clinically significant. At the early discontinuation visit, erythrocytes, hematocrit, and hemoglobin, are all noted as out of range and clinically significant as are platelets. The CRF AE terms are "anemia" and "inferior esofagian stenosis".*

**Ongoing and clinically completed but not reported studies:**

Review of SAE data up to the cut-off date of the 120-day safety update (3-30-09) from trials classified by the sponsor as either ongoing or clinically completed but not reported is not complete. Recent submissions (2-4-10 and 1-25-10) have updated and/or corrected the original information submitted. Quality issues with the 120-day safety update table that originally reported these events have been described in the Quality section of this review.

Table 2 of the 2-4 submission(not duplicated in this review) displays, in a listing format, reported SAEs terms from the following trials; 127, 128, 206 baseline, double-blind, and open-label, 207 baseline, double-blind, and open-label, 301 parts 3 and 4, 302 part 3, 304 part1, and 305 part 1, baseline and double-blind, and 305 part 2(open-label). Epilepsy serious adverse events were summarized previously in this section. No narratives are available.

The data in the referenced Table 2 are not finalized (sponsor notes the table is "preliminary, unconfirmed, and subject to change in the final Clinical Study Report") and my review of the data is preliminary. The referenced Table 2 does not provide denominator information. Therefore, even if a trial has a placebo group, no dose-response relationships are made or implied.

No SAES are reported in studies 127 (plasma and CSF PK, clinically completed 2-7-09) and 128 (DDI with oral contraceptives, clinically completed 11-14-08).

Study 206 is a trial in diabetics with diabetic neuropathy. This study was clinically completed 11-18-2008. As I understand the design, there was a 12 week maintenance period in which subjects were randomized to either placebo or ESL doses. By my count, the sponsor's Table 2 (2-4-10 submission) indicates that during the double-blind period, no SAES are reported in placebo subjects, 5 SAES in 4 subjects are reported for the 800 mg ESL group, 9 SAES in 5 subjects are reported for the 1200 mg ESL group, and 4 SAES in 4 subjects are reported for the 1600 mg ESL group. (SAES means non-fatal in this text).

- During the double-blind period, based on reported terms, there were a number of cardiac events including, "heart pain", "Angina Pectoris", 3 subjects with myocardial infarction (MI), 1 subject with LBBB and dilated cardiomyopathy (this

is one of the subjects who reported angina pectoris and this subject also with term “heart failure”), one with bradyarrythmia and hypoglycemia, and two other subjects with “cardiac decompensation”.

- During the double-blind period, one subject experienced what is classified as a life-threatening loss of consciousness (5638-2093-206/704/0001 Russia), one experienced “ascites” and two experienced renal events (hydronephrosis lateral dexter and colica renalis in one subject and one with acute pyelonephritis. The subject with acute pyelonephritis also experienced inflammatory polyarthropathy).

- Observational ,baseline, pre-randomization, SAEs include a “recurrent brain ischemic attack”, bradycardia, and acute gastroenteritis. Open label SAEs include an obstipation, chest pain, and duodenal ulcer with bleeding.

Study 207 is a study conducted in patients with post-herpetic neuralgia. This study clinically completed on 1-19-09. By my count, the sponsor’s Table 2 (2-4-10 submission) indicates that during the double blind period, there were no placebo SAES, 6 SAES in 6 subjects in the 800 mg ESL group, 5 SAEs in 5 subjects in the 1200 mg ESL group, and 1 SAE in 1 subject in the 1600 mg ESL group. (SAES are non-fatal in this text.)

- In the double-blind period, based on reported terms and there was one subject who experienced an MI, three infections (Klebsiella pneumonia, biliary tract infection, and intercostal herpes zoster) and singular events of rash, hyponatremia, esophageal stenosis, dizziness, hemoptysis, fracture of C-2, heavy back pain, and reactive arthritis.
- There is one reported SAE in the observational, baseline, pre-randomization period. This was dyspnea. Open-label SAEs include a hyponatremia, “neuroanemic syndrome”, suicide attempt, cholecystolithiasis, and cerebrovascular insufficiency with dehydration.

The sponsor provided the following summary table (Table 3) pooling these 2 trials (one diabetic neuropathy and one post-herpetic neuropathy). Regardless of any possible pooling issues, the table is reproduced below as a way to reflect the events in a way that may be easier to read than text. Denominators are not provided in the table. The table cannot be viewed as comparative data.

There were no treatment emergent SAEs in the placebo group. The most common SAEs in ESL groups were cardiac related (11/of 31 non-fatal SAEs and 3 that are cardiac failure). Although one might expect higher numbers of cardiac events in the diabetic population and in older subjects, no placebo subjects experienced such events, although, without knowing how balanced the groups are, conclusions are not possible. There was an SAE of hyponatremia. Serious rash, esophageal stenosis, and obstipation, and loss of consciousness also were reported. Two events of arthritis are noted (reactive and polyarthritis). Further information is needed for the overall events and presentation.

Table xx

**Table 3: Summary of Treatment Emergent Non-Fatal Serious Adverse Events in Unblinded Placebo-Controlled Ongoing Studies up to 30 March 2009 (Studies 2093-206 Double-Blind Period and 2093-207 Double-Blind Period Pooled)**

| | Studies 2093-206 DB and 2093-207 DB Pooled | | | |
|---|---|---|---|---|
| | Placebo | ESL 800 mg/day | ESL 1200 mg/day | ESL 1600 mg/day |
| Preferred term | Events n | Events n | Events n | Events n |
| Total Number of SAEs | 0 | 11 | 14 | 6 |
| Acute myocardial infarction | 0 | 0 | 2 | 0 |
| Angina pectoris | 0 | 1 | 1 | 1 |
| Arthritis reactive | 0 | 0 | 1 | 0 |
| Ascites | 0 | 0 | 1 | 0 |
| Back pain | 0 | 1 | 0 | 0 |
| Biliary tract infection | 0 | 0 | 1 | 0 |
| Bradyarrhythmia | 0 | 0 | 0 | 1 |
| Bundle branch block left | 0 | 0 | 1 | 0 |
| Cardiac failure | 0 | 0 | 1 | 2 |
| Congestive cardiomyopathy | 0 | 0 | 1 | 0 |
| Dizziness | 0 | 1 | 0 | 0 |
| Dyspepsia | 0 | 1 | 0 | 0 |
| Haemoptysis | 0 | 0 | 1 | 0 |
| Herpes zoster | 0 | 1 | 0 | 0 |
| Hydronephrosis | 0 | 1 | 0 | 0 |
| Hypoglycaemia | 0 | 0 | 0 | 1 |
| Hyponatremia | 0 | 0 | 0 | 1 |
| Loss of consciousness | 0 | 1 | 0 | 0 |
| Myocardial infarction | 0 | 1 | 0 | 0 |
| Oesophageal stenosis | 0 | 1 | 0 | 0 |
| Pneumonia klebsiella | 0 | 1 | 0 | 0 |
| Polyarthritis | 0 | 0 | 1 | 0 |
| Pyelonephritis acute | 0 | 0 | 1 | 0 |
| Rash | 0 | 0 | 1 | 0 |
| Renal colic | 0 | 1 | 0 | 0 |
| Spinal fracture | 0 | 0 | 1 | 0 |

Abbreviations: ESL=eslicarbazepine acetate; DB=double-blind period; SAE=serious adverse event.
Note: The 12-week (Study 2093-206) and 8-week (Study 2093-207) double-blind maintenance periods were combined across studies. Treatment-emergent adverse events are those that occurred on or after the dose start date.
Reference: Data on file at Sepracor



*Reviewer's preliminary conclusions non-fatal SAEs-*

- Events of interest include ataxia, vertigo, diplopia, and vomiting, hyponatremia, possibly GI motility disorders (obstipation, esophageal stenosis).

### 7.3.3 Dropouts and/or Discontinuations

The table below (Table 4) is duplicated from the sponsor (8-28-09 module 1, information amendment) and displays the incidence of discontinuation across the phases of development of ESL. For part one of the phase 3 studies this is based on the termination page of the case report

form and includes study discontinuation if it was considered due to an AE as the primary or secondary reason for discontinuation.

As per table 4, overall 226/1977 (11.4%) ESL subjects discontinued a study secondary to an adverse event. 18/528 (3.4%) placebo subjects discontinued a study secondary to an adverse event.

As per Table 4, two placebo subjects (2/107 = ~ 1.9%) and 16/117 (~13.7%) discontinued phase 1 studies. In the phase 2 bipolar studies, 2/51 placebo subjects (3.9%) and 12/148 ESL subjects (~ 8%) discontinued a study secondary to an AE. In the bipolar recurrence study, there was no placebo arm. 11.5% of the ESL subjects discontinued the study secondary to an AE.

As per Table 4, for epilepsy studies, in the phase 2 adult epilepsy study, 4/47 (8.5%) of placebo subjects and 8/96 (8.3%) of ESL subjects discontinued the study secondary to an adverse event. There was no placebo arm in the pediatric study (study 202). 2/31 ESL subjects discontinued the study secondary to an AE. In the controlled part of phase 3 epilepsy studies, 10% of ESL subjects in study 301, 17.3% of ESL subjects in study 302, and 10.3% of ESL subjects in study 303 discontinued secondary to an AE compared to 2.9% of placebo subjects in study 301, 3 % of placebo subjects in study 302, and 4.6% of placebo subjects in study 303.

Discontinuations are discussed per phase in this section.

Table Xx

**Table 4: Summary of Discontinuations due to Adverse Events in the Entire Eslicarbazepine Acetate Development Program and by Study within each Development Phase**

| Study # (Study Type) | Discontinuations due to AEs | |
|---|---|---|
| | Placebo | ESL |
| | n / N (%) | n / N (%) |
| All Studies | 18 / 528 (3.4%) | 226 / 1977 (11.4%) |
| Phase I Studies | | |
| 2093-105 | -- | 1 / 29 (3.4%) |
| 2093-107 | 1 / 13 (7.7%) | 0 / 13 (0%) |
| 2093-110 | -- | 2 / 12 (16.7%) |
| 2093-111 | -- | 1 / 17 (5.9%) |
| 2093-114 | -- | 2 / 19 (10.5%) |
| 2093-116 | 0 / 64 (0%) | 10 / 66 (15.2%) |
| 2093-117 | -- | 1 / 18 (5.6%) |
| 2093-118 | 0 / 4 (0%) | 6 / 12 (50%) |
| 2093-119 | -- | 2 / 31 (6.5%) |
| 2093-120 | -- | 2 / 32 (6.3%) |
| 2093-121 | -- | 2 / 32 (6.3%) |
| 2093-123 | 1 / 26 (3.8%) | 0 / 26 (0%) |
| 2093-126 | -- | 1 / 20 (5%) |
| Phase II Epilepsy Studies | | |
| 2093-201 (Adult) | 4 / 47 (8.5%) | 8 / 96 (8.3%) |
| 2093-202 (Pediatric) | -- | 2 / 31 (6.5%) |
| Phase II Bipolar Studies | | |
| 2093-203 | 1 / 40 (2.5%) | 8 / 121 (6.6%) |
| 2093-204 | 1 / 11 (9.1%) | 4 / 27 (14.8%) |
| 2093-205 | -- | 12 / 104 (11.5%) |
| Phase III Epilepsy Studies | | |
| 2093-301 | | |
| Part 1 | 3 / 102 (2.9%) | 30 / 300 (10.0%) |
| Part 2 | -- | 10 / 314 (3.2%) |
| 2093-302 | | |
| Part 1 | 3 / 100 (3.0%) | 51 / 295 (17.3%) |
| Part 2 | -- | 41 / 325 (12.6%) |
| 2093-303 | | |
| Part 1 | 4 / 87 (4.6%) | 17 / 165 (10.3%) |
| Part 2 | -- | 13 / 196 (6.6%) |

Abbreviations: AE=adverse event, ESL=eslicarbazepine acetate.
Note: Discontinuation due to adverse event as reported on the termination page of the CRF as either primary or as a secondary reason for discontinuation.
Note: Subjects who discontinued due to adverse event are counted under the treatment that corresponds to the last known period they entered.
Note: Subjects are counted once within each study they participated in; therefore, a subject can contribute to the overall denominator more than once. This occurs in 85 subjects.
Note: Studies not listed had no subjects discontinue due to an AE.
Note: No placebo arm was included in studies noted with '--'.
Reference: Attachment 1 Table 2.2



## EPILEPSY

### Phase 3, part 1 data (controlled phase), As per the Sponsor's analysis

In the controlled phases (titration, maintenance, taper) of the phase 3 epilepsy studies, the discontinuation (of study medication) rate secondary to adverse events was dose related with increasing discontinuations with ESL and with increasing doses of ESL. The difference in incidence of discontinuation between placebo and ESL subjects in study 303 was not as great as that seen in the pooled data from studies 301-302.

In combined studies 301-302, 4% placebo, 8.7% of the ESL 400 mg group, 14.6% of the ESL 800 mg group, and 23% of the ESL 1200 mg group discontinued secondary to an AE (SU EOT Table 5.5.1.1). In study 303, 8%, 9.4%, and 11.3% of placebo, ESL 800 mg, and ESL 1200 mg subjects discontinued due to an adverse event (SU EOT Table 5.5.1.2). There are possible limitations to dose response statements given the titration schedule.

Pooled 301-302 data: The sponsor's Table 4.1.4.3-1 is a table of discontinuation of study medication reported in ≥ 2% of subjects in any dose group in part 1 of the phase 3 epilepsy studies and is reproduced later in this section. As per this table, most discontinuations in combined studies 301-302 in ESL subjects were from events in the SOC Nervous System (dizziness 5.5%, abnormal coordination 2.5%, somnolence 1.7%, headache 0.8% and convulsion 0.3%). Combining similar terms for these events increases the incidence. For the terms dizziness + vertigo (n=5 subjects), the incidence is 38/595 = ~ 6.4%. For abnormal coordination + ataxia + cerebral ataxia + balance disorder + gait abnormal there are 21/595 (3.5%). For somnolence + sedation, the incidence is 1.8%. For seizure terms, there is also an ESL discontinuation for complex partial seizures. Adding convulsion + partial complex seizure would increase the incidence to 0.5% in this study (Data for combined terms is from SU EOT Table 5.5.1.1). In placebo subjects, 3 subjects discontinued secondary to a term coded to the SOC Nervous System. One was for dizziness (0.5%). There were no placebo events of vertigo, so combining the terms does not change the incidence. The other two Nervous System discontinuations in placebo subjects were for headache. Combining terms for coordination abnormal is still 0% in the placebo group. Combining terms for somnolence + sedation is still 0% in placebo. (Data from SU EOT Table 5.5.1.1)

Study 303: Based on the sponsor's Table 4.1.4.3-1, for study 303, the most common events in the ESL group were coordination abnormal (2.4%), dizziness (2.4%), headache (1.8%), and sedation (1.2%) There were no ESL discontinuations attributed to convulsion or seizure (compared to 2 placebo). For this study, combining like terms gives incidence of 5/165 (3%) for coordination abnormal + gait disturbance and 7/165 (4.2%) for dizziness + vertigo (data from SU EOT Table 5.5.1.2). Singular events of cerebellar syndrome, memory impairment, paresthesia, somnolence, and tremor led to discontinuation. In placebo subjects, 5 are noted as discontinuation for an event classified under the SOC of Nervous System Disorder (1 coordination abnormal, 2 dizziness, 2 headache, 2 somnolence (2.3%), and 2 convulsion) (EOT Table 5.5.1.2). Combining similar terms for sedation, (sedation + somnolence + hypersomnia) increases the incidence to ~ 3.5% (data SU EOT Table 5.5.1.2). Combining terms for coordination abnormal using terms combined for studies 301-302 does not change the incidence. Combining terms of dizziness and vertigo does not change the incidence.

Table xx

**Table 4.1.4.3-1: Discontinuation of Study Medication Due to TEAEs Reported in ≥2% of Subjects in Any Dose Group by Overall Treatment Group for Part 1 of the Phase III Studies (2093-301 and 2093-302 Pooled vs 2093-303) (Safety Population)**

| MedDRA[A] SYSTEM ORGAN CLASS Preferred term | Studies 2093-301 and 2093-302 Pooled | | | | Study 2093-303 | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo (N=202) | | Total ESL (N=595) | | Placebo (N=87) | | Total ESL (N=165) | |
| | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n |
| AT LEAST 1 TEAE LEADING TO DISCONTINUATION OF STUDY MEDICATION | 8 (4.0) | 14 | 92 (15.5) | 215 | 7 (8.0) | 18 | 17 (10.3) | 42 |
| NERVOUS SYSTEM DISORDERS | | | | | | | | |
| Dizziness | 1 (0.5) | 1 | 33 (5.5) | 34 | 2 (2.3) | 2 | 4 (2.4) | 4 |
| Abnormal coordination | 0 | 0 | 15 (2.5) | 15 | 1 (1.1) | 1 | 4 (2.4) | 4 |
| Somnolence | 0 | 0 | 10 (1.7) | 10 | 2 (2.3) | 2 | 1 (0.6) | 1 |
| Headache | 2 (1.0) | 2 | 5 (0.8) | 5 | 2 (2.3) | 2 | 3 (1.8) | 3 |
| Convulsion | 0 | 0 | 2 (0.3) | 2 | 2 (2.3) | 2 | 0 | 0 |
| GASTROINTESTINAL DISORDERS | | | | | | | | |
| Vomiting | 1 (0.5) | 1 | 22 (3.7) | 23 | 0 | 0 | 5 (3.0) | 5 |
| Nausea | 1 (0.5) | 1 | 16 (2.7) | 16 | 0 | 0 | 4 (2.4) | 4 |
| EYE DISORDERS | | | | | | | | |
| Diplopia | 0 | 0 | 16 (2.7) | 16 | 0 | 0 | 2 (1.2) | 2 |
| Blurred Vision | 0 | 0 | 8 (1.3) | 8 | 0 | 0 | 2 (1.2) | 2 |
| GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS | | | | | | | | |
| Fatigue | 0 | 0 | 5 (0.8) | 5 | 1 (1.1) | 1 | 0 | 0 |
| EAR & LABYRINTH DISORDERS | | | | | | | | |
| Vertigo | 0 | 0 | 4 (0.7) | 4 | 0 | 0 | 3 (1.8) | 4 |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; SU=120-day safety update.
A Reported AE terms were coded using the MedDRA version 7.0 dictionary for Study 2093-301 and version 9.0 for Studies 2093-302 and 2093-303.
Note: The titration, maintenance, and tapering-off periods were combined. Study 2093-302 did not have a tapering-off period. Treatment-emergent adverse events are those that occurred on or after the date of first dose, or the date of randomization if the date of the first dose was missing. Adverse events with missing or incomplete onset dates were considered to be treatment emergent unless it could be determined that the event began before the treatment period.
Note: Subjects were counted at most once within each system organ class and preferred term.
Note: Pre-existing AEs leading to discontinuation were included in this summary.
Note: Adverse events were updated with delayed reports of 59 AEs from Part 2 studies that had onset dates in Part 1.
Reference: SU EOT Tables 5.5.1.1 and 5.5.1.2



**Reviewer's evaluation of sponsor's data:**

There are several places to obtain summarized information as to the number of subjects experiencing discontinuation secondary to an AE. These include the ISS narratives (counting them), Table 4 of xx, and Table 4.1.4.3-1 of xx. I compared the numbers of subjects from these sources for parts 1 and 2 of the phase 3 epilepsy studies. This comparison shows some differences between the tables. Given the discrepancies noted

between the numbers in the tables, the sponsor was asked to clarify. This clarification was submitted and received preliminary review.

In part 1 of phase 3 studies, 10 to 15 placebo subjects discontinued a study or study medication compared to 98 to 109 ESL subjects.

| | **Narratives** | | **Table 4** | | **Table 4.1.4.3-1** | |
|---|---|---|---|---|---|---|
| **Study** | Placebo | ESL | Placebo | ESL | Placebo | ESL |
| 301 | 4 | 31 | 3 | 30 | | |
| 302 | 3 | 56 | 3 | 51 | | |
| 301 + 302 | 7 | 87 | 6 | 81 | 8 | 92 |
| 303 | 6 | 17 | 4 | 17 | 7 | 17 |
| Total | 13 | 104 | 10 | 98 | 15 | 109 |

**Narratives from ISS 3-39-09, Table 4 from 8-28-09 information amendment and is discontinuation from study, table 4.1.4.3-2 from 8-28-09 120-day safety update and is discontinuation from study drug. Narratives seem to be discontinuation from study (Language in the ISS implies that narratives are discontinuations from study ("A summary of TEAEs leading to subject discontinuation from Part 2 of Study 2093-301 is included in Section 21.1.3 and corresponding narratives are provided in Appendix 25.1.1." (p. 76 of the ISS)).**

Dataset ADAE2.xpt: Review of the dataset ADAE2.xpt using part 1 (excluded pre-dose events) events indicates that in the combined data of studies 301-302, the most common SOCs for ESL events leading to discontinuation were Nervous System, GI Disorders, Eye, and Psychiatric. For placebo, the most common were Nervous System and GI Disorders. In study 303, the most common SOCs with events leading to discontinuation were Nervous System and GI for ESL subjects and Nervous System and Psychiatric for placebo.

Table xx

| | Studies 301 and 302 | | | | Study 303 | | |
|---|---|---|---|---|---|---|---|
| | Placebo events | 400 | 800 | 1200 | placebo | 800 | 1200 |
| DEATH | 1 | 0 | 0 | 0 | | | |
| EAR | 0 | 0 | 0 | 1 | | | |
| IMMUNE "allergic reaction" | 0 | 0 | 1 | 0 | | | |
| INDETERMINATE | 0 | 0 | 0 | 1 | | | |
| INFECTION | 0 | 1 | 0 | 0 | | | |
| MUSCULAR | 0 | 0 | 0 | 1 | | | |
| NEOPLASM | 0 | 0 | 1 | 0 | | | |
| REPRODUCTIVE | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| VASCULAR | 0 | 1 | 0 | 0 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AED TOXICITY | 0 | 1 | 1 | 0 | | | |
| CARDIAC | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| INJURY | 1 | 0 | 0 | 1 | | | |
| UNDETERMINED | 0 | 0 | 0 | 2 | | | |
| LAB | 0 | 0 | 2 | 1 | 0 | 1 | 0 |
| VITAL SIGN | 0 | 1 | 0 | 2 | | | |
| SKIN | 1 | 1 | 0 | 6 | | | |
| GENERAL | 1 | 0 | 1 | 8 | 1 | 2 | 2 |
| PSYCHIATRIC | 0 | 6 | 0 | 12 | 4 | 0 | 1 |
| EYE | 0 | 2 | 8 | 15 | 0 | 2 | 2 |
| GI DISORDERS | 2 | 3 | 16 | 25 | 0 | 5 | 4 |
| NERVOUS SYSTEM | 5 | 7 | 27 | 51 | 10 | 8 | 15 |

Discontinuations per ADAE2.xpt, part 1 not pre-dose. AEACN (action taken with study treatment)=262 rows (109 unique subjects) as discontinuation.

Using ADAE2.xpt and variables for discontinuation of study medication or other action taken (choices are none, medication, patient withdrawn, surgery), there are 224 events leading to discontinuation in studies 301 and 302. Of these 121 are in titration, 99 are in maintenance, and 4 are in tapering. {Of note, subjects in 302 did not taper off study medication, so all events in taper should be in study 301}. For study 303, there were 60 events leading to discontinuation; 33 were in titration, 24 in maintenance, and 3 with tapering.

Narrative Review: The table below is based on my count of ISS narratives for discontinuation (they are not numbered/indexed) and shows the number of subjects per dose group discontinuing secondary to an AE. The ISS narrative information regarding dose group is noted by the sponsor to be the most recent dose, not necessarily the randomized dose group.

13 placebo subjects, 29 subjects on ESL 400 mg, 5 subjects on ESL 600 m, 45 subjects on ESL 800 mg, and 25 subjects on ESL 1200 mg discontinued secondary to an AE.

| **Study** | **Placebo** | **400 mg ESL** | **600 mg ESL** | **800 mg ESL** | **1200 mg ESL** | **Total ESL** |
|---|---|---|---|---|---|---|
| 301 | 4 | 12 | -- | 9 | 10 | 31 |
| 302 | 3 | 12 | -- | 33 | 11 | 56 |
| 303 | 6 | 5 | 5 | 3 | 4 | 17 |
| **Total** | 13 | 29 | 5 | 45 | 25 | 104 |

Based on review of AE terms for the individual subject narratives in the ISS, there is evidence of ESL related adverse reactions and/or drug toxicity such as vomiting, abdominal pain, dyspepsia, dizziness, diplopia, headache, vertigo, blurred vision and ataxia. Patients often had more than one of these symptoms. One such patient

experienced decreased appetite, somnolence, fatigue, dizziness, diplopia, nausea, vomiting, and one episode of “moderate” hypotension (302-331-80131). One subject initially (one day after starting study medication) experienced diplopia, dizziness, and abnormal coordination. About 7-8 days later, this subject also had CPK elevations (302-351-80012-ESL 800mg). One subject experienced intermittent abnormal coordination, fatigue, aphasia, and nausea 17 days after first starting ESL (302-313-80262). This subject’s events are reported as resolved although it is not specifically stated whether study medication was stopped.

As indicated above, in some patients, there is a constellation of symptoms consistent with drug toxicity (also subjects, 301-142-90178, 302-351-80059) or called simply “drug toxicity”(301-141-90171, also an SAE) or with the term “drug toxicity” as part of the description (302-421-80778, also an SAE). The term “Cerebellar Syndrome” was used for a patient who discontinued in study 303 (303-703-70374). This was also a serious adverse event.

Several subjects experienced either confusion with dizziness (301-392-80383 confusion resolved day after stopping study medication), or events described as disturbance of attention (one as a single event term, subject 302-315-80253, and one with term “sedation”, 302-351-80060). Subject 302-315-80253 experienced “disturbance of attention” beginning in March, specific date was not recorded (dosing started March 16) and discontinued from the study June 28. The subject’s event was not considered resolved until Oct 14 of the same year. Subject 302-351-80060’s attention problem is reported as resolved the same day of his last dose of study medication.

There are cases of rash and drug hypersensitivity reactions. One involved LFT elevations (301-111-90341). “Hypersensitivity” is the event term for one ESL 800 mg patient (302-423-80744). The verbatim term in the dataset ADAE2.xpt is “allergic reaction.” Facial edema and paresthesia was described for one patient on ESL 400 mg (303-506-70094). Facial edema can be consistent with angioedema.

Liver enzyme elevations were also seen in another subject without rash and reported as discontinuation due to “Gamma glutamyltransferase Increased” in the narrative (301-141-90212). This patient also had increased AST and ALT (about 2x and 1.5x ULN respectively) with bilirubin lower or within reference range (not meeting Hy’s law).

Cardiac events of angina pectoris and Wolf-Parkinson-White (WPW) Syndrome led to discontinuation of one subject each, although for the WPW, this was seen pre-dosing (see narrative) . Events of hypertension led to discontinuation in two subjects (one with hypertensive crisis) and hypotensive events were involved in the discontinuation of two other subjects.

Four subject discontinuations involved the event term “tremor”, 301-174-90449 and 302-338-80154 (1200 mg) and 302-338-80236 and 303-605-70330 (800 mg). Subject 90449 also experienced alopecia. One subject’s event terms are bradypsychism and

tremor in subject 302-338-80154 on ESL 1200 mg. Intermittent dystonia is reported in one ESL subject (301-153-90512) that reportedly resolved a day after study discontinuation. A placebo subject is reported as experiencing blepharospasm leading to discontinuation.

Constipation led to discontinuation in two subjects (302-331-80152 on 400 mg and 302-393-80415 on ESL 800 mg).

Two discontinuations, one of which was also an SAE, involved hyponatremia (302-306-80614-SAE and 303-703-70231).

Hypersensitivity or Rash or Pruritus

| | | |
|---|---|---|
| **301-102-90176-1112** | ESL 400 mg | **Exanthem**, first day of dosing-treated with betamethasone and cetirizine |
| **302-395/80389** | **ESL 400 mg** | **Pruritus** |
| **301-111-90341-1256 SAE** | ESL 800 mg | **Exanthem** (also fever and increased AST, CRP, decreased WBC, increased CRP) |
| **302-351/80059** | **ESL 800 mg** | **Erythema Nodosum, Headache, Fatigue, Coordination Abnormal, Asthenia, Dizziness Dysathria, and Nausea**<br>36-year-old F received her first dose of study medication (ESL 800 mg) on 5-2-05. On 4-4-05 (prior to first dose administration), the subject experienced erythema nodosum, which was assessed as moderate in intensity. Treatment was not required. 5-2-05(the same day as first dose administration), the subject also experienced moderate headache and fatigue and severe abnormal coordination. None of the events required treatment. On 5-3-05 (1 day after starting study medication), the subject experienced severe asthenia, moderate dizziness, severe dysarthria, and moderate nausea. All events were assessed as continuous infrequency and none required treatment. The subject was discontinued from the study on 5-4-05 due to these events. The abnormal coordination, asthenia, dizziness, dysarthria, and nausea events were considered resolved on that day. The erythema nodosum, headache, and fatigue events were considered ongoing at time of analysis. |
| **302-395/80787** | **ESL 800 mg** | **Rash, Vision Blurred,Dizziness, Nausea, Somnolence, Vomiting, and Headache** |
| **302-401/80344** | **ESL 800 mg** | **Rash** |
| **302-423/80744** | **ESL 800 mg** | **Hypersensitivity-** treatment not required |
| **303-506/70094** | ESL 400 mg | **Paresthesia and Face Edema-**paresthesia bilateral hands after first dose, then “mild” facial edema, treated with hydroxyzine and clemastine |

Lab abnormality as part of events:

| | | | |
|---|---|---|---|
| **301-141/90212/1193** | **ESL 1200 mg** | **Gamma-glutamyl transferase Increased** | 54 F 1st dose on 3-10-05, increased to 800 on 3-17-05, then 1200 on 3-24-05. May 13, 2005-labs with ↑GGT, AST and ALT at about 2 and 1.5 x ULN respectively, bilirubin below to WNL. Discontinued due to this event. Event considered resolved on 6-16-05. On concomitant AEDs. |
| **303-703/70231** | **ESL 400 mg** | **Hyponatremia** | Screening sodium 139. One day after first dose of 400 mg ESL, sodium 127. No treatment required. 8 weeks later, sodium 120. SM stopped and 9-10 days later, sodium 133. One month after this, hyponatremia considered resolved. Concomitants include CBZ and phenobarbital. |
| **SAE 302-306/80614** | **ESL 800 mg** | **Coordination Abnormal, Hyponatremia and Vomiting** | See SAE narrative |
| **302-351/80012** | **ESL 800 mg** | **Diplopia, Dizziness, Coordination Abnormal, and Blood Creatinine Phosphokinase Increased** | 37-year-old F first dose of study medication (ESL 800 mg) on 3-08-05. 1 day after starting study medication, the subject experienced diplopia, dizziness, and abnormal coordination. All events assessed as severe in intensity. Treatment was not required. Received last dose of study medication on 3-09-05. The diplopia, dizziness, and abnormal coordination considered resolved 3-10-05. On 3-16-05 (7 days after stopping study medication), the subject experienced an increase in blood creatinine phosphokinase. CPK levels 682 U/L on that day, above the upper limit of the normal range but reference range not provided. This event was assessed as moderate in intensity and treatment was not required. Discontinued from the study due to these events on 3-16-05. The increase in CPK considered resolved 4-13-05. Medical history significant for gynecologic surgery and a cesarean section. Concomitant medications at the time of event onset included carbamazepine and lamotrigine. |

Cardiovascular related term

One subject experienced angina (this was an SAE). Two subjects experienced events that included high blood pressure. One case is not from the ISS narratives but was found in Listing 6.3 (xx). One was also an SAE. Orthostatic hypotension was an adverse event term in one narrative.

| | | | |
|---|---|---|---|
| **SAE 301-145/90194/1398** | **ESL 800 mg** | **Angina Pectoris** | Narrative in appendix |
| **302-301-80637** | **? Prior to treat** | **Wolf-Parkinson-White Syndrome** | 55 year old male with reported worsening of WPW syndrome 15 days prior to starting study medication. Event was continuous and moderate and led to discontinuation 115 days later during part 1, for this |

| | | | |
|---|---|---|---|
| | | | event. History of WPW and paroxysmal tachycardia. |
| SAE **301-124/90485/1243** | **ESL 1200 mg** | **Diplopia, Hypertensive Crisis, and Nausea** | Narrative in appendix |
| ****301-211-90059** | **ESL 1200 mg** | **Arterial Hypertension, Dizziness, and Diplopia (all at 400 mg), Ataxia at 1200** | No CRF, No narrative in ISS or SU narrative sections In listing 6.3. Listing is confusing. All events listed have "none" under the action taken column and the column with treatment information does not indicate withdrawal. Study report for 301a1-legacy-narratives in section 15.3.2.4 indicate withdrawn secondary hypertension and ataxia |
| **302-372/80363** | **ESL 400 mg** | **Orthostatic Hypotension** | A 44 year old female experienced "orthostatic hypotension" 51 days after starting study medication. She received her last dose of study medication 1-30-05 and was discontinued on 2-1-05. Event considered resolved on 2-7-05. Event assessed as moderate and not requiring treatment. CRF –on 1-29-05 through 2-7 seems- events of dizziness and palpitations crossed out and printed as "not to be considered". CRF pages for early discontinuation are blank including one with vital signs. Visit 4 was 2-7- blood pressure 90/70, pulse 74. Post study visit was 3-15. No comments. CRF seems to poorly document or explain event. |
| **302-331/80131** | **ESL 800 mg** | **Decreased Appetite, Somnolence, Fatigue, Dizziness, Diplopia, Nausea, Vomiting, and Hypotension** | 24 year old female, 1st day of dosing ESL 800 mg, patient experienced first 5 listed symptoms, then the next day (1-18-05), nausea and vomiting. Discontinued study medication 1-19. "Moderate" hypotension on 1-21. |
| **303-606-70163** | **P** | **Anxiety, Dizziness, Fatigue, Headache, and Tachycardia** | |

**** Narrative not seen in ISS or SU for this subject. This subject is listed in Listing 6.3 of 9-29-09 submission. This listing is labeled "All Treatment Emergent Adverse Events in Subjects Discontinued Due to Adverse Event Safety Population". P=placebo**

Neurologic and/or Psychiatric Event Terms:

Combined Studies 301-302

Common terms were discussed earlier in this section. There were singular event terms of dysarthria, aphasia, dystonia, and vasculitis cerebral (SU EOT Table 5.5.1.1)

Study 303:
Common terms were discussed earlier in this section. There were singular terms of memory impairment and paresthesia.

There was a discontinuation for either abnormal coordination (based on discontinuation narrative in the ISS) or for cerebral vasculitis (as per the SAE narrative in the ISS) of a

subject with an SAE of cerebral vasculitis (302-351-80013). A brief description of this patient's events is below.

| | | | |
|---|---|---|---|
| **302-351 /80013** | **ESL 400 mg** | **Coordination Abnormal and Vasculitis Cerebral** | 38 year old male with one-year history of epilepsy and medical history of MRI findings of high intensity foci in white matter and lab findings of increased antinuclear antibodies. 78 days after receiving his first dose of ESL, the subject presented with worsening headache. Hospitalized on (b) (6). Reportedly, MRI and CSF "confirmed" cerebral vasculitis and maxillary sinusitis on the right. Treatment included prednisolone. The subject was discontinued from the study due to the event (SAE narrative). Last dose of study medication on 6-7-05. Abnormal coordination on 6-7-05 and discontinued secondary to this (per ISS discontinuation narrative). |

Four subject discontinuations involved the event term "tremor".

| | | | |
|---|---|---|---|
| **301-174/90449 /1441** | **ESL 1200 mg** | **Dizziness, Gait Abnormal, Alopecia, and Tremor** | 46 year old female, 57 days after starting study medication, dizziness, abnormal gait, alopecia, and tremor all assessed as mild and not require treatment. Discontinued 8 days after onset of AEs. Gait resolved two days after discontinuation but other events ongoing. History + for hypothyroidism. CRF indicates dizzy and somnolent in April, then events leading to discontinuation were in June (dizzy, gait disorder, hands trembling, and losing hair). DC events assessed as mild. |
| **302-338/ 80154** | **ESL 1200 mg** | **Bradyphrenia and Tremor** | 37 year old male, medical history of migraine, hypotension, and abdominal pain on concomitant phenytoin, phenobarbital, and metamizole. 56 days after starting study medication, experienced bradyphrenia and tremors, considered moderate, no treatment required. Discontinued 42 days after AEs onset due to events, which were considered resolved that day. CRF AE is "bradypsychism" made as a data clarification entry. This event and tremor started 3-3 with tremor intermittent and bradypsychism continuous. Handwritten note in CRF page 152 states patient worse since beginning protocol, dizzy, somnolent, headache, bradypsychism, and tremors and seizures same frequency. |
| **302-338/ 80236** | **ESL 800 mg** | **Convulsion and Tremor** | 34-year-old Caucasian male who received his first dose of study medication (ESL 800 mg) on 5-24-05. dosage increased to 1200 mg ESL on 6-14-05. On the same day (21 days after first starting SM), the subject experienced convulsions and tremors, both assessed as moderate in intensity. Treatment not required. The subject received his last dose of study medication on 21 June 2005. Discontinued from the study due to these events on 30 June 2005 (16 days after AE onset). Convulsion event considered resolved on 6-21-05, while the tremor event considered resolved on 6-22-05. Medical history significant for an orthopedic procedure and leukopenia. Concomitant medications at the time of event onset included carbamazepine and clobazam. CRF-diplopia on 5-24, leukopenia on 5-17 but marked out on CRF, |

| | | | |
|---|---|---|---|
| | | | tremor and seizure worsening on 6-14. DCF indicates leukopenia at visit 1 on 3-31 also (3 u/L→2.7 u/L). |
| **303-605/70330** | **ESL 800 mg** | **Sedation, Malaise, and Tremor** | 53 year old female, medical history includes head injury and eye excision, on carbamazepine, pregabalin, and fluvastatin also, started ESL at 400 mg on 11-30-05 and escalated to 800 mg on 12-16-05. On 12-21, subject experienced sedation, malaise, and tremor assessed as moderate. Subject was discontinued on 12-22-05 and events considered resolved on 12-23-05. |

The AE term "dystonia" was noted for one ESL patient (800 mg ESL, 301-153-90512) and "blepharospasms and rash" in patient 301-181-90144 (placebo).

| | | | |
|---|---|---|---|
| **301-153/90512/1334** | **ESL 800 mg** | **Dystonia and vomiting** | 35 M -15 days after starting SM and day of increase to 1200 mg, subject with intermittent dystonia and vomiting. Treatment not required. Subject discontinued 8 days after AE onset due to events. Events considered resolved the day after discontinuation. Also on carbamazepine. |
| **301-191/90144/1389** | **Placebo** | **Blepharospasm and Rash Vesicular** | 40 F, 59 days after starting study medication, rash, mild, resolved 24 days after study medication discontinuation. Mild blepharospasms started 64 days after staring study medication, intermittent and resolved 15 days after discontinuation. |

Seizure related terms were present in the discontinuation of three subjects in 301-302 (per dataset ADAE2.xpt) and two in study 303 (please see listing below).

| UUBJID | Treatment assigned | AETERM | AEPERIOD |
|---|---|---|---|
| 2093301-193-90148 | ESL 1200 mg | Exacerbation of seizures | Maintenance |
| 2093302-338-80236 | ESL 1200 mg | Seizure worsening | Maintenance |
| 2093302-306-80607 | ESL 400 mg | Increased seizures | Titration |
| 2093303-613-70131 | Placebo | Exacerbation of seizures | Maintenance |
| 2093303-517-70106 | Placebo | Increased intensity of seizures | Maintenance |

<u>Psychiatric events or events involving concentration/cognition/mental status were seen;</u>
(Some events in this listing could have been placed also in neurologic events instead.)

| | | | |
|---|---|---|---|
| **303-517/70106** | **Placebo** | **Aggression, Headache, and Convulsion** | 43 year old male 15 days after starting SM. Convulsions considered severe.Treatment not required. No significant medical history. Concomitant medications CBZ and clobazam. |
| **303-606/70163** | **Placebo** | **Anxiety, Dizziness, Fatigue, Headache, and Tachycardia** | |

| | | | |
|---|---|---|---|
| **303-622/70333** | **Placebo** | **Irritability, Restlessness, and Somnolence** | |
| **303-618/70185** | **Placebo** | **Libido Decreased** | |
| **301-101/90185/1197** | **ESL 400 mg** | **Insomnia** | |
| **301-124/90358/1213** | **ESL 400 mg** | **Depression and Influenza** | 41 year old male,1st dose on 12-13-04, 103 days later (3-26-05) continuous depression and single episode flu. Both severe. Depression not treated. Subject discontinued 4-18-05 due to events. Flu resolved. Depression ongoing. Medical history reported + for depression. |
| | | | |
| **301-211/90046/1093** | **ESL 400 mg** | **Depression (Narrative in CSR also asthenia)** | 43 year old female, no listed medical history of depression. 28 days after starting SM, moderate depression. Discontinued from study 2 days later. Treated with amitriptyline and event resolved about month after onset. |
| **SAE 302-382/80440** | **ESL 400 mg** | **Psychotic Disorder** | Two events with SAES- Nervousness, dizziness, diplopia, psychotic disorder- ELS 400 mg- 40 year old male with 23-year history of epilepsy and history of skull fracture in 1982, received first dose of ESL 400 mg on 7-4-2005. On (b) (6) the subject was hospitalized with nervousness, dizziness, and diplopia. No medications were given as treatment. Carbamazepine and valproic acid levels are reported as within therapeutic. These events are reported resolved on (b) (6). On 9-4-2005, the subject became aggressive, accusative, and paranoid. Symptoms continued until (b) (6) at which time he was hospitalized. He is reported to have been fully oriented and clinically normal except "his thought disorder was interfering in his social interactions". Carbamazepine levels are reported as within normal. No treatment medication was reported. The subject was discontinued from the study with the last dose of study medication on (b) (6). The event of psychotic disorder is reported to have resolved as of (b) (6) and the subject was discharged from the hospital. |
| **302-412/80592** | **ESL 400 mg** | **Depressed Mood and Stress** | |
| **303-614/70298** | **ESL 600 mg** | **Diplopia, Headache, Memory Impairment, and Nausea** | 28 year old female no stated history of cognitive impairment and on concomitant valproic acid and carbamazepine, received first dose of ESL on 11-7-05 and experienced headache and diplopia. 14 days later, she experienced memory impairment and nausea. She was discontinued on 1-4-06 due to these events which were reportedly resolved on 1-3-06. CRF indicates odynophagia on 11-18-0-5 and 11-21-05 |
| **302-315/80253** | **ESL 800 mg** | **Disturbance in Attention** | 34 year old male, Date of event not specified more than by month, which was month of starting SM. Subject discontinued 3 months later due to event and event considered resolved about 3.5 months after discontinued study. |
| **302-385/80427** | **ESL 800 mg** | **Weight Increased and Depression** | |
| **302-** | **ESL 800 mg** | **Confusional** | 33-year-old female received her first dose of study medication |

| | | | |
|---|---|---|---|
| **392/80383** | | **State, Dizziness, and Fall** | (ESL 800 mg) on 3-21-05. The next day ,the subject intermittently experienced a confusional state, dizziness, and falls. All events were assessed as moderate in intensity. Treatment not required. Discontinued from the study on 4-4-05 (13 days after AE onset) due to these events, which were considered resolved on 4-5-05. CRF-adverse events of dizziness, frequent falls, and confusion on 3-22-05, medication was discontinued but date not clear from AE page of CRF. |
| **301-192-90258** | **ESL 1200 mg** | **Apathy, Insomnia, Irritability, Nervousness** | 36 year old Caucasian female, no significant other medical history, started ESL 400 mg on 5-17-05. Narrative reports discontinuation on 7-20-05, discontinued by Investigator. 8-18-05, subject experienced reported events. CRF AE page shows events on 8-18 and notes medication discontinued and patient withdrawn. Outcome unknown. |
| **302-351/80060** | **ESL 1200 mg** | **Fatigue, Disturbance in Attention, and Sedation** | 41 year old male, no reported history of cognitive disorder, on concomitant valproic acid and dexamethasone, experienced fatigue 6-14-05, one day after starting ESL 800 mg dosing. 6-24-05, subject experienced "severe disturbance in attention" and "severe sedation". Received his last dose of study medication on 7-4-05. Events reported resolved 7-4-05. CRF documents events of "tiredness", "tranquilization" – 2 events, "disturbance of concentration". |
| **302-337/80221** | **ESL 1200 mg** | **Dizziness, Crying, Insomnia, Irritability, and Nervousness** | |

**Part 2 of the phase 3 epilepsy studies (Open-label):**

The numbers of subjects discontinued in part 2 due to an adverse event as reported in three different sources (ISS and SU narratives counted as 1 source) were compared. The sources were ISS and SU narratives, Table 4 of the 8-28-09 information amendment, and Table 5.5.3-1, "Discontinuation of Study Medication Due to TEAEs Reported in > 1 Subject in Any Study Grouping for the Phase III Extensions (Part 2 of 2093-301, 2093-302, and 2093-303, Safety Population", of the 120-day safety update.

The number of subjects discontinued from the study or study medication was 60-71.

| | **ISS + SU** | **Table 4** | **Table 5.5.3-1** |
|---|---|---|---|
| **301** | 16 | 10 | |
| **302** | 42 | 41 | |
| **301 + 302** | 58 | 54 | 50 |
| **303** | 13 | 13 | 10 |
| **Total** | 71 | 67 | 60 |

The sponsor's summary table of part 2 events in the SU was of discontinuation of study medication due to TEAEs reported in >1 subject in any study grouping for the phase 3 extensions. As per this table (not duplicated in this review), 50 subjects with 78 events discontinued secondary to adverse events in combined studies 301-302 and 10 subjects with 15 events discontinued in study 303. Based on exploration of the dataset

ADAE2.xpt (open-label period, action taken as discontinuation or action other of withdrawn), 97 events are found for 63 subjects. Sixteen were from study 301, 37 from study 302, and 10 from study 303.

As per the SU, the incidence of TEAEs causing discontinuation of study medication in one of the phase 3 studies (301, 302, or 303) was 7.2% in part 2. The sponsor reports the most common TEAEs causing discontinuation in part 2 as dizziness (1.1%), convulsion (0.5%), vomiting (0.5%) and diplopia (0.5%). Adding similar terms, such as dizziness + vertigo, likely would increase these incidences. The median time to onset of any TEAE leading to discontinuation is reported as 66 days. For dizziness, the median time was 55 days (9 subjects).

SU end-of-text tables, classifications, most discontinuations in part 2 of the phase 3 studies were due to events classified under the SOC Nervous System Disorders for both combined 301-302 and 303 followed by GI and General Disorders in combined 301-302 compared to General in 303.

A discontinuation secondary to pancreatitis is reported (301-121-90348). The subject reportedly was on concomitant valproic acid and the narrative is not that detailed. The subject appears to have resolved and the narrative indicates that study medication probably was stopped before resolution. I was unable to locate a case report form for this subject in either the ISS or SU CRF locations. An insulinoma led to discontinuation (302-338-80164) in a subject who reportedly was experiencing hypertension and hypoglycemia at study entry (CRF glucose is low at visit 1 of the study in part 1 and blood pressure was 120/80 at visit 1 and 150/90 at visit 2). There is one event of increased hair growth and one subject who experienced alopecia.

Hyponatremia led to discontinuation of one subject (in study 303). Five other subjects discontinued due to events involving laboratory abnormalities.

An event of intermittent hemiparesis led to discontinuation (302-351/80008). The narrative is not optimal but indicates that this was an increase in a pre-existing event versus a new onset event.

Psychiatric events include events of psychosis (see event listing below).

Table XX
Part 2 AEs leading to discontinuation

| **MedDRA SOC**<br>**Preferred Term** | **Studies 301 and 302 pooled (n=835)** | | **Study 303 (n=196)** | |
|---|---|---|---|---|
| | **subjects** | **events** | **subjects** | **events** |
| **Any TEAE leading to discontinuation of study medication** | **50 (7.8%)** | **78** | **10 (5.1%)** | **15** |
| **Nervous System Disorders** | **25 (3.9%)** | **28** | **3 (1.5%)** | **4** |
| Dizziness<br>Vertigo (different SOC) | 9 (1./4%) 9<br>1 (0.2%) 1 | | ---------- | |
| Convulsion | 4 (0.6%) 4 | | ---------- | |
| ●Status epilepticus | 1 (0.2%) 1 | | ---------- | |
| ●Complex Partial Seizure | 1 (0.2%) 1 | | ---------- | |
| Coordination abnormal | 3 (0.5%) 3 | | ---------- | |
| Dysarthria | 1 (0.2%) 1 | | ---------- | |
| Hemiparesis | 1 (0.2%) 1 | | ---------- | |
| Apraxia | ---------- | | 1 (0.5%) 1 | |
| TIA | ---------- | | 1 (0.5%) 1 | |
| Mental Impairment | | | 1 (0.5%) 1 | |
| **GI Disorders** | **10 (1.6%)** | **11** | **1 (0.5%)** | **1** |
| Vomiting | 4 (0.6%) 4 | | ---------- | |
| Nausea | 2 (0.3%) 2 | | ---------- | |
| Pancreatitis | 1 (0.2%) 1 | | ---------- | |
| Dysphagia | ---------- | | 1 (0.5%) 1 | |
| **General Disorders and Administration Site Conditions** | **8 (1./3%)** | **8** | **2 (1%)** | **2** |
| Asthenia | 2 (0.3%) 2 | | 1 (0.5%) 1 | |
| Irritability | 2 (0.3%) 2 | | ---------- | |
| Death or Sudden Death | 2 (0.3%) | | ---------- | |
| Drowning | 1 (0.2%) | | ---------- | |
| **Psychiatric** | **6 (0.9%)** | **7** | ---------- | ---------- |
| **Eye Disorders** | **5 (0.8%)** | **5** | ---------- | ---------- |
| Diplopia | 4 (0.6%) 4 | | | |
| **Skin and Subcutaneous Tissue Disorders** | **4 (0.6%)** | **4** | **1 (0.5%)** | **1** |
| **Cardiac Disorders** | **2 (0.3%)** | **2** | See below | |
| Chest Pain (included under SOC General Disorders) | ---------- | | 1 (0.5%) 1 | |
| **Metabolism and Nutrition Disorders** | **2 (0.3%)** | **2** | **1 (0.5%)** | **2** |
| Hyponatremia | ---------- | | 1 (0.5%) 2 | |
| **Blood and Lymphatic System Disorders** | **1 (0.2%)** | **1** | **1 (0.5%)** | **1** |

| | | | | |
|---|---|---|---|---|
| Lymphocyte count ↓, monocyte count ↓ neutrophil count ↓, WBC ↓- 1 each (under different SOC in studies 301 and 302- Investigations) | **1 (0.2%)** | **4** | ---------- | -------- |
| lymphopenia | ---------- | | 1 (0.5%) | 1 |
| **Injury, Poisoning and Procedural Complications** | **1 (0.2%)** | **2** | 1 (0.5%) | 1 |
| Drug Toxicity | 1 (0.2%) 2 | | ---------- | |
| Multiple Injuries | ---------- | | 1 (0.5%) 1 | |
| **Neoplasms Benign, Malignant and Unspecified (Incl Cysts and polyps)** insulinoma | **1 (0.2%)** | **1** | ---------- | ---------- |
| **Pregnancy, Puerperium and Perinatal Conditions** | **1 (0.2%)** | **1** | ---------- | ---------- |
| **Respiratory, Thoracic and Mediastinal Disorders** | **1 (0.2%)** | **1** | -------- | ---------- |
| **Vascular Disorders** | ---------- | -------- | **1 (0.5%)** | **1** |
| hypertension | ---------- | ---------- | 1 (0.5%) | 1 |
| **Infections and Infestations** | ---------- | ---------- | 2 (1%) | 2 |

Data from EOT table 16.7.1.1 and EOT Table 16.7.1.2 of SU. Coding dictionary MedDRA 9.0 for study 301 and 10 for studies 302 and 303.---- indicates events not occurring in trial (s). Subjects may have had more than one adverse event per SOC and preferred term.

Fatal events: Fatal events leading to discontinuation: There were 3 deaths. Two of these are drowning (301-177-90425 and 302-388-80468) and one was a sudden death (302-313-80267). Narratives of these deaths may be found in the death section of this review.

Rare or Unusual Events: A pancreatitis is reported in the ISS. The narrative is not detailed and indicates concomitant valproic acid use but that there was resolution, maybe after study drug discontinuation (discontinuation date not specified).

| | | |
|---|---|---|
| **301-121/90348** | **ESL 800 mg** | **Pancreatitis-51 year old male randomized to ESL 800 mg in part 1. Received first dose of pat 2 800 mg ESL on 4-13-05. On (b) (6), the subject experienced pancreatitis, assessed as moderate and the subject was treated. History significant for hypertension. The subject was discontinued from the study. Subject was taking concomitant valproic acid. No CRF provided with ISS or 120-day SU.** |
| **SAE 302-338/80164** | **400 mg-1200 mg ESL** | **Insulinoma-narrative reports this 25 year old male was experiencing hypertension and hypoglycemia at study entry with no reported medical history. He received ESL 1200 mg in part 1 and started part 2** |

| | | |
|---|---|---|
| | | **on 6-9-05 at 800 mg daily. In (b) (6), he was hospitalized with insulinoma which required treatment. Study medication was discontinued and the subject is reported recovered as of (b) (6) CRF shows week -8 blood pressure of 120/80, glucose low at 1.2 mmol/L (reference range 3.8-6.1). At visit 2, blood pressure 150/90 and glucose 0.9 mmol/L.** |
| **302-331-80132** | | **sudoresis with other terms, diplopia, fatigue, dyspnea, and dizziness- narrative reports recovery of dyspnea and sudoresis before treatment discontinuation and of diplopia and dizziness sometime in May of 2005. Study medication discontinued 5-31-05.** |
| **302-322-80570** | | **increased hair growth- narrative indicates on legs and that she was withdrawn but study medication was not discontinued but also reports that the last dose of study medication was 4-25-06 and termination was 4-26-06 due to an unacceptable AE.** |
| **302-308-80649** | | **alopecia and bad breathe – treatment discontinued on day 88 and halitosis reported as recovered the next day. Alopecia was ongoing.** |

Cardiac Events:

| | | |
|---|---|---|
| **303-510/70050** | **400 mg-1200 mg ESL** | **Chest pain** |
| **302-351/80064** | **400 mg-1200 mg ESL** | **Extrasystoles (verbatim is coupled beat (bigeminus)** |

Laboratory value related:

| | | |
|---|---|---|
| **302-382/80444** | **400 mg-1200 mg ESL** | **Blood Sodium Decreased** |
| **302-382/80445** | **400 mg-1200 mg ESL** | **Blood Sodium Decreased** |
| **SAE 302-395/80794** | **400 mg-1200 mg ESL** | **White Blood Cell Count Decreased, Neutrophil Count Decreased, Lymphocyte Count Decreased, Monocyte Count Decreased, and Lymphoma** |
| **302-337/80232** | **400 mg-1200 mg ESL** | **Leukopenia** |
| **303-707/70239** | **400 mg-1200 mg ESL** | **Lymphopenia** |
| **SAE 303-601/70156** | **400 mg-1200 mg ESL** | **Worsening of Hyponatremia** |

**Neurologic non-seizure (excluding dizziness, vertigo, diplopia)**

| | | |
|---|---|---|
| **SAE 303-712/70144** | **400 mg-1200 mg ESL** | **Transient Ischemic Attack (narrative is in SAE section).** |
| **302-412/80597** | **400 mg-1200** | **Dysarthria and Coordination Abnormal** |

| | | |
|---|---|---|
| | mg ESL | |
| 302-411/80396 | 400 mg-1200 mg ESL | Vision blurred, Dizziness, and Hypoesthesia |
| 302-351/80008 | 400 mg-1200 mg ESL | Hemiparesis -54 year old male with history includes excisional biopsy of a cerebral cavernoma and dorsal vertebral fracture as well as epilepsy, was in part 1 on placebo. He started part 2 on 4-27-05 and is reported as having an increased frequency of intermittent right hemiparesis while taking ESL 800 mg daily. Study treatment was discontinued on 4-20 (day 4) and the subject is reported recovered that same day. |
| 302-301/80640 | 400 mg-1200 mg ESL | Anorexia, Asthenia, Coordination Abnormal, Nausea |
| 302-336-80073 from dataset | | AE TERM is BIA 2093 Related CNS Toxicity Syndrome |

**Psychiatric**

| | | |
|---|---|---|
| 301-112/90327 | ESL 800 mg | Depressed Mood |
| 301-175/90417 | ESL 800 mg | Anxiety |
| SAE 301-214/90041 | ESL 1200 mg | Delusional Disorder, Persecutory Type |
| 302-338/80170 | 400 mg-1200 mg ESL | Irritability |
| SAE 302-306/80604 | 400 mg-1200 mg ESL | Schizoaffective Disorder |
| SAE -302-306/80612 | 400 mg-1200 mg ESL | Acute Psychosis |
| 302-315/80253 | 400 mg-1200 mg ESL | Disturbance in Attention |
| 302-335/80202 | 400 mg-1200 mg ESL | Dizziness and Irritability |
| 302-371/80529 | 400 mg-1200 mg ESL | Aggression and Insomnia |
| 303-702/70302 | 400 mg-1200 mg ESL | Mental Impairment, Apraxia, Dysphagia, and Asthenia |

**Phase 2 epilepsy studies:**

●Study 201 (Adult): The ISS reports an overall incidence of discontinuations due to TEAEs as 10.6%, 13%, and 6% of subjects in the placebo, 200 -600 mg ESL BID, and 400-1200 mg ESL QD groups respectively. The sponsor indicates that dose response relationships were not assessable in the phase 2 adult epilepsy study (ISS p 106/582). The most common TEAEs causing discontinuation in the ESL group were nausea and vomiting.

As per the study report, 23 AEs led to premature study discontinuation in 14 patients (5 events in 3 patients in the once-daily group, 10 events in 6 patients in the twice-daily group, and 8 events in 5 patients in the placebo group.

- Placebo events were epigastric pain and nausea in one patient, status epilepticus and viral gastroenteritis in one patient, irritability and insomnia in one patient, and one patient each for pruritic rash and duodenitis
- Once daily dosing events were blurred vision, diplopia, and incoordination in one patient, rash in one patient, and ischemic stroke NOS in one patient
- Twice daily dosing events were dyspepsia and nausea in one patient, vomiting in three patients, headache in one patient, dry mouth in one patient, and dizziness and nausea in one patient (both dizziness and nausea are listed twice for this subject)

| | | |
|---|---|---|
| **201-01/116 (001/9026)** | **Placebo** | **Epigastric Pain and Nausea** |
| **201-05/145 (005/9043)** | **Placebo** | **Status Epilepticus and Viral Gastroenteritis** |
| **201-05/144 (005/9047)** | **Placebo** | **Pruritic Rash** |
| **201-14/080 (014/9154)** | **Placebo** | **Duodenitis** |
| **201-16/010 (016/9118)** | **Placebo** | **Insomnia and Irritability** |
| **201-03/119 (003/09014)** | **ESL 200 mg BID** | **Nausea and Dyspepsia** |
| **201-05/146 (005/09044)** | **ESL 200 mg BID** | **Complex Partial Seizures Increased** |
| **201-08/176 (008/09063)** | **ESL 200 mg BID** | **Headache** |
| **201-11/001 (011/9107)** | **ESL 200 mg BID** | **Nausea, Dizziness, and Nausea** |
| **201-08/179 (008/9064)** | **ESL 200 mg BID** | **Vomiting** |
| **201-11/089 (011/09116)** | **ESL 200 mg BID** | **Dry Mouth and Complex Partial Seizures Increased** |
| **201-06/169 (006/09053)** | **ESL 400 mg BID** | **Vomiting** |
| **201-14/016 (014/09127)** | **ESL 400 mg QD** | **Rash** |
| **201-11/002 (011/9108)** | **ESL 1200 mg QD** | **Diplopia, Blurred Vision, and Coordination Abnormal** |
| **201-14/079 (014/9155)** | **ESL 1200 mg QD** | **Ischemic Stroke NOS** |

**Red font= SAE**

●Study 202 (pediatric): The ISS reports that a total of 2 treatment-emergent adverse events of seizures (worsening of epilepsy) caused discontinuation from the study (subjects 202-114 and 202-201). Both events were considered SAEs. Both patients were in the 30 mg/kg/d group. One was 2 years old and one was 11 years old. Both were females (CSR p.117/2206). Duration of treatment was 71 and 68 days respectively (CSR 117/2206).

**Ongoing and clinically completed but not reported studies' events up to March 30, 2009 as reported in 2-4-10 submission:**

301, part 3 (epilepsy)-there were three events: brain edema, status epilepticus, and acute psychosis.

301, part 4 and 302 part 3 (epilepsy)-are stated to have no discontinuations of study medication due to an AE reported.

304, part 1 (epilepsy) – two subjects with 3 events: pregnancy in one and one with

305, part 1: five events are reported in the observational pre-randomization period. These include a "decrease T4 level" and in a different subject, increasing TSH.

**NON- EPILEPSY**

**Phase 1:**
As noted in the table above, and not unexpected for phase 1, most studies were not placebo controlled. As per the sponsor's Table 4 of the 8-28-09 submission, there were a total of 32 discontinuations secondary to an adverse event in phase 1 studies; two were in placebo subjects (2/107 in the 4 placebo controlled trials, ~1.9%) and 16 were in ESL treated patients in these same 4 trials (16/117~13.7%). The remaining 14 events ESL occurred in uncontrolled phase 1 studies.

Listing 5.3 in the 1-25-10 document is a listing of "All Treatment Emergent Adverse Events in Subjects Discontinued Due to Adverse Event" in phase 1 studies (40 pages long). Discontinuation data for the phase 1 trials indicates that in ESL subjects there was one discontinuation for worsening of hypertension, 11 for the terms "hypersensitivity reaction" (possibly all with ESL and a concomitant AED) or rash/urticaria/generalized rash, and one rash that include LFT elevations (110-000-11). Some rashes were treated with either steroids or an antihistamine or both. Vomiting led to discontinuation in about 8 subjects.

Depressed level of consciousness was the cause of one discontinuation at ESL 2400 mg (116-1-7). A constellation of symptoms that include somnolence (+ dizziness, or paresthesia, and one + rash) resulted in the discontinuation of 4 subjects. "Mood Altered" is reported in the ISS narrative as leading to discontinuation in a subject on ESL 1200 +TPM 200 mg (120-17). (Dose group is ESL 600mg in listing 5.3 with no event noted as leading to discontinuation).

A more detailed table summarizing events may be found in the appendix of this review.

Table xx Summary of events leading to discontinuation as per Listing 5.3 or ISS narrative

| | | |
|---|---|---|
| 1 | 105-000-00005 | **ESL 600 mg- day after, "sudden cardiovascular failure" (Death).** |
| 2 | 107-000-00011 | **ESL 1200 mg- Hypertension worsened**, description is in SAE section of this review |
| 3 | 110-000-00001 | **ESL 900 mg-urticaria** on 11-12-2003, then **diffuse macular rash** on 11-24-2003 on ESL 450 BID |
| 4 | 110-000-00011 labeled in ISS narrative as trileptal in heading | **Trileptal as per ISS narrative bolded header information, but highest elevations on ESL.** The following is from information in either the ISS narrative, Listing 5.3, the CRF, or the study report. This 27 year old male, with baseline AST within normal and baseline ALT a little high (56 IU/L, high end of normal for males is 41 IU/L), experienced transaminases elevations in period 1 on ESL (11-7-03 to 11-14-03), however the values for the LFT elevations are not provided in the ISS |

| | | |
|---|---|---|
| | | narrative. Review of labs indicates that AST and ALT were about 3.6 x and 8 x ULN, respectively based on reference ranges in the study report (AST was135 U/L and ALT was 327 U/L). Transaminases were going down before starting Trileptal and AST was within normal and ALT was a little high (62 IU/L) at admission for Trileptal dosing. Transaminase elevations again occurred on Trileptal (81 IU/L AST and 221 IU/L ALT) and the subject was discontinued and did not go to period 3 of the study which would have been dosing of ESL 900 mg once daily. Neither direct nor total bilirubin was above the reference range during the dosing periods. ALP remained within the reference range. Listing 5.3 shows multiple events with none having an action taken of medication being stopped or patient discontinued. Based on information in listing 5.3, the CRF, and/or the study report, this subject experienced vasovagal reaction and dizziness in dosing period 1 on ESL 450 mg BID daily. About 4 days later and still on ESL 450 mg BID, the AST and ALT elevations occurred. On 12-2, the subject had RU quadrant pain (on ESL or in washout). On 12-3, on active control, the subject had a single episode of abdominal pain and loose stools and on 12-9 is noted to have nystagmus and AST & ALT increases (81 and 221 IU/L respectively). CRF indicates the subject had LFTs of 5xULN (handwritten note on page 159/220 of CRF) that led to discontinuation with hypothesis of Wilson's disease (reported low plasma ceruloplasmin) or unspecified hepatitis and that the subject was referred for gastroenterology consultation. I am not able to locate the ceruloplasmin values or any other reference to them in the study report. |
| 5 | 111-000-00009 | **ESL 800 mg- hepatic encephalopathy and abdominal pain and nausea** in the about 7-8 days after hepatic encephalopathy. |
| 6 | 114-000-00007 | **ESL 1200 mg- Somnolence + Dizziness+ Concentration Impaired and Facial Paresthesias-** onset date of 3-21. On 4-5, CPK is increased. |
| 7 | 114-000-00014 | **ESL 1200 mg- Paresthesia Lips, Lightheadedness, Palpitations, Somnolence, and Erythematous Rash** -on 3-21, lightheaded and paresthesias of lips. 3-22, palpitations & recurrent somnolence, and on 3-28, generalized erythematous rash with pruritus. erythematous rash, treated with steroid and antihistamine. Narrative states listing not clear which event causing discontinuation. |
| 8 | 115-000-00009 | **R-lic 450 mg Visual Disturbance, Dizziness, Oral Dryness, and Leg Pain,**Active Control-five events, recurrent visual disturbance, dizziness, dry mouth, visual disturbance, and leg pain, none noted as leading to medication withdrawal. |
| 9 | 115-000-00010 | **S-lic 450 mg Tooth Extraction** Active Control-dosing stopped. |
| 10 | 116-001-00004 | **ESL 2400 mg- Fatigue, Vomiting, and Abdominal Distention** |
| 11 | 116-001-00007 | **ESL 2400 mg- Depressed Level of Consciousness-**discontinued on 4-12-07. Other events on 4-12 are paresthesia and vomiting. On 4-14, patient with headache and weak lower extremities.. |
| 12 | 116-001-00008 | **ESL 2400 mg-Somnolence, Paresthesia Oral, and Dizziness** |
| 13 | 116-001-00013 | **ESL 2400 mg-Vomiting-** preceded day before with sleepiness, dizziness, oral paresthesia. |
| 14 | 116-001-00015 | **ESL 2400 mg –Nausea-** Listing ESL 1200 mg- discontinued with headache. |
| 15 | 116-001-00020 | **ESL 2400 mg- Paresthesia Oral and Vomiting Indeterminate as to which event led to discontinuation in the listing (5.3)**- events on ESL 1200 mg, placebo, ESL 2400mg. On ESL 2400 mg, patient on same day reported, somnolence, paresthesias of lips, |

| | | |
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| | | nausea, vomiting, and two days later pruritus |
| 16 | 116-001-00021 | **ESL 2400 mg-Back Pain, Constipation, Somnolence, Dizziness, and Vision Blurred -**Listing 5.2 subject on **Placebo** |
| 17 | 116-001-00023 | **ESL 1200 mg- Pruritus and Rash**<br>**ISS narrative indicates** subject treated with aminoalkyl ethers and corticosteroids. |
| 18 | 116-001-00034 | **ESL 1200 mg Rash**<br>also had headache and fever on 5-5. ISS narrative rash moderate. |
| 19 | 116-001-00066 | **ESL 2400 mg Vasodilation, Blood pressure increased, Abdominal Pain Upper, Headache, and Rash** |
| 20 | 117-000-00005 | **ESL 800 mg –Pregnancy** |
| 21 | 118-001-00105 | **ESL 3600 mg Vomiting**<br>Other events with onset 1-12 are paresthesia, dizziness, and somnolence. |
| 22 | 118-001-00106 | **ESL 3600 mg-Vomiting-** |
| 23 | 118-001-00108 | **ESL 3600 mg-Vomiting** |
| 24 | 118-001-00203 | **ESL 3000mg-Vomiting** |
| 25 | 118-001-00204 | **ESL 3000 mg- Vomiting** |
| 26 | 118-001-00207 | **ESL 3000 mg-Vomiting** |
| 27 | 119-000-00004<br>SAE | *Listing 5.3-ESL 1200 mg* does not state which event led to discontinuation in the listing although action taken secondary to hypersensitivity, multiple events, abdominal pain, constipation, hypersensitivity reaction (considered severe), dizziness, headache, paresthesia. **ISS narrative: treatment group listed as ESL 1200mg + LMT 150 mg**. 30 year old male, 9 hours after receiving dose 18, severe hypersensitivity, treated with steroids and antihistamines. CRF indicates transferred to hospital on (b) (6) due to swelling of face, difficulty swallowing also on (b) (6) At some point, subject with macular rash, ulceration lower lip mucosa, skin peeling, swollen lips, fever ALT , ALT, GGT, LDH increased. |
| 28 | 119-000-00023 | *ESL 1200 mg*, does not state which event led to discontinuation but only two events, dry lips and hypersensitivity reaction (moderate). ISS narrative: lists treatment as **ESL 1200 + LMT 150 mg** and event as hypersensitivity. treated with diphenhydramine. |
| 29 | 120-000-00015 | *ESL 1200 mg* –multiple events but only one with an action as "y", this is **generalized rash. ISS narrative: indicates treatment group as ESL 1200 mg + TPM 100 mg** |
| 30 | 120-000-00017 | Indeterminate which event led to discontinuation. Event(s) on DDI alone, "No Dose", and 600 mg ESL 600. **ISS narrative: Group B – ESL 1200 mg + TPM 200 mg, event "mood altered"** |
| 31 | 121-004 | *Not in listing 5.3.* ISS narrative indicates **ESL1200 mg** with diarrhea leading to discontinuation. |
| 32 | 121-000-00017 | *ESL 1200 mg*- Dental abscess on ESL 1200 mg has "Y" in action taken.. **ISS narrative: ESL 1200 mg + PHT 300 mg** |
| 33 | 121-000-00028 | *Listing 5.3 is indeterminate* which event led to discontinuation. There are multiple treatments listed (DDI alone, ESL 1200 mg). On ESL 1200 mg, there is term "hypersensitivity syndrome" on 2-20, this is preceded in 10 days before with events of rash, headache, dizziness, and "muscular spasm upper right arm". Appears to have used DDI alone earlier in trial and reported events of somnolence and palpitations. **ISS narrative: ESL 1200 mg + PHT 300 mg,** discontinuation for "hypersensitivity syndrome" |
| 35 | 121-000-09013 | **Placebo- pharyngolaryngeal pain** |

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| | | in the four days preceding, patient on placebo and with rash. |
| 36 | 126-000-00007 | **ESL 1200 mg Generalized Urticarial Rash** |

**Data in this table are from Listing 5.3 of 1-25-10 submission amendment and narratives in the ISS or SU**. Red font indicates SAE.

## Phase 2 Bipolar

Acute mania studies: In the bipolar studies (studies 203 and 204), the dosing was different in each study (dose-titration in study 203 and fixed, multiple doses in study 204).

As per CSR information, in study 203 there was no dose response for the occurrence of treatment-emergent AEs (14/40 (35%) of placebo, 34/64 (53.1%) of ESL 600 mg, and 29/57 (~51%) of 800 ESL For discontinuation due to an AE, there was a dose relationship (1/40= 2.5%, 3/64=4.7%, and 4/57=7% for placebo, ESL 600mg, and ESL 800 mg respectively (CSR, Table 3, p. 49/3972). In study 204, there was no dose relationship for the occurrence of treatment-emergent AEs (7/11 placebo, 4/8 ESL 600 mg, 9/9 ESL 1200 mg, and 10/10 ESL 1800 mg (page 44/1987 CSR). There was no dose response for discontinuation secondary to an AE (1/11 placebo compared to 0/8, 2/9, and 2/10 for ESL 600 mg, 1200 mg, and 1800 mg respectively (Table 10-1 CSR).

- Study 203-

ISS narratives indicate nine subjects discontinued secondary to adverse events; eight were on ESL and one was on placebo (influenza two days after starting study medication). One subject in the ESL 1800 mg group discontinued secondary to leukopenia (this was an SAE, subject also with hyponatremia). Allergic reactions resulted in discontinuation of three subjects (one subject each 1600 mg group discontinued secondary to “Dermatitis Allergic” and “Drug Hypersensitivity” and one 2400 mg subject,secondary to “Drug Hypersensitivity”). Per ISS text, the three subjects with what appear to be drug hypersensitivity reactions had onsets of rash at 11, 8, and 9 days after starting study medication. In one subject with rash, there was also low blood pressure. Two rashes were treated ( one with steroids).

Two 1200 mg subjects discontinued (one each) secondary to vomiting and “Adverse Event Leading to Discontinuation Not Defined”). The text of the ISS narrative (and the AE listing 28a in the CSR) indicates the patient who discontinued with vomiting also had increased liver enzymes and bilirubin, raising the possibility of hepatitis. The subject with the ISS narrative bolded heading of “Adverse Event Leading to Discontinuation Not Defined” had 5 reported event terms. Two subjects discontinued due to psychiatric events; one 800 mg with “Bipolar Disorder” and one 1200 mg secondary to mania.

● **203-301-203215 ESL 1800 mg** - **Leukopenia and hyponatremia**-narrative summarized in SAE section of this review. Both lab values low 11 days after receiving first ESL dose. The subject was discontinued from the study on the day of low lab values and hospitalized where she was treated with sodium chloride for the hyponatremia and valproic acid as concurrent AED. About 3 days after

hospitalization, the hyponatremia is reported as resolved. About 7 days after hospitalization, the WBC count reported is within normal.

● **203-337-203058 ESL 1200 mg - Vomiting- drug – reviewer notes this event is consistent with drug induced effect-** 57 year old female with reported concomitant medical conditions of chronic pancreatitis and hypertension. The subject started ESL on 5-10-05. Three days after starting study medication, the subject experienced severe vomiting. She was discontinued from the study 2 days later due to this with the narrative stating the event was reported resolved that day. On the day of discontinuation, AST was 1447 U/L, ALT 1154 U/L, bilirubin was 43.8 mcmol/L and direct bilirubin was 30.30 mcmol/L. No reference ranges are given but these are noted in the ISS narrative as "positive" for clinically significant increases. At the post-study visit four weeks later, as per the narrative, levels are reported as normal. VPA was stopped before randomization (5-5-06 per listing 19 of the study report) and restarted on 5-18-06. (study report listing 21). **CRF** has adverse events of vomiting and diarrhea on 5-13 and elevated ALT, AST, total and direct bilirubin on 5-15. Lab form indicates ALP high but not considered clinically significant. Patient was noted to be pale and weak at the early discontinuation visit. Post study visit (6-16-06) lab values for AST, ALT, ALP, and total bilirubin are noted as within the range. There was a visit on 5-23-06 (between the discontinuation visit and post-study visit). On 5-23-06, all values except ALT were within the reference ranges. AST, was about 18, ALT was much lower but still high at 68. Total bilirubin was down to <10 and direct bilirubin was down to about 2. Pancreatic enzymes are not described.

● **203-343-203134 ESL 1200 mg – Adverse Event Leading to Discontinuation Not Defined-** 67 year old male who experienced asthenia, upper abdominal pain, vomiting, and syncope 5 days after starting study medication. Syncope is reported as a single event. No events required treatment. Seven days after starting study drug, the subject experienced anxiety that was considered mild and not to require treatment. The subject was discontinued on the day of the onset of anxiety (3-7-06). All events were considered resolved by 3-10-06.

## Hypersensitivity reactions:

●**203-331-20382-ESL 1600 mg-Dermatitis Allergic-**52 year old Caucasian female who experienced an allergic rash considered moderate, 9 days after starting ESL. Treatment was not required. The subject was discontinued 2 days after onset of the adverse event due to the event. Two days after discontinuation, the event was considered resolved. The subject had no significant medical history and no concomitant medications were reported. CRF AE page shows skin rash on 7-16., "whole body rash" on EDV exam on 7-18 (p.123/192). EDV labs BUN, CR, AST, ALT, ALP, and total bilirubin marked as within range

●**203-346-203107-ESL 1600 mg-Drug Hypersensitivity-** 22 year old Caucasian female who experienced "postdrug allergic cutaneous reaction" beginning 11 days after starting study medication. She was treated with loratidine, cyproheptadine, and hydrocortisone butyrate. 3 days later, on physical examination, erythematous macular and popular eruption on the superior and inferior limbs, trunk, and neck was noted. The subject's blood pressure was low at 90/60. She was discontinued on the day of the exam. The event was considered resolved 3 days after discontinuation. Concomitant medications at the time of event onset were not reported. CRF admission blood pressure on 6-6-06 was 90/65 and 95/60 on 6-14. EDV was 6-22. 6-22 labs AST, LT, ALP, total bilirubin, BUN, and Creatinine indicated as within range.

●**203-346-203171- ESL 2400 mg- Drug Hypersensitivity-** 27 year old Caucasian male who received first dose of ESL (800 mg) on 6-16-06 with increase up to 2400 mg on 6-22-06. 8 days after starting study medication, the subject experienced "moderate postdrug allergic cutaneous reaction". Two days later, exam findings were of erythematous macular eruption on the trunk, face, neck, palms, and thighs. Subject treated with antihistamines and discontinued from the study 6-26-06. Concomitant medication of lorazepam. Event considered resolved 7-2-06. CRF EDV on 6-26-06, AST, ALT, neutrophils, and

lymphocytes marked as out of range but not clinically significant. Eosinophils not out of range. Visit 8 on 7-4-06- no rash on exam. Labs ALT out of range, CBC not out of range, aPTT out of range but not considered clinically significant and also out of range on admission. Post Study Visit on 8-9-06. Physical exam not indicate rash. AST, ALT, neutrophils, lymphocytes in range. Basophils out of range but not considered clinically significant.

- Study 204- As per the ISS narratives, six subjects were discontinued secondary to adverse events. One patient in the placebo group discontinued secondary to mania (SAE). Five ESL treated patients discontinued; 3 in the ESL 1200 mg group and 2 at ESL 1800 mg dose. The three discontinuations in the ESL 1200 mg group are: fatigue and lethargy; somnolence, depression, and disturbance in attention; and intentional overdose. The two discontinuations in the 1800 mg group are hypersensitivity and mania (SAE). There were what appear to be small liver enzyme changes with the hypersensitivity reaction that resolved

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| **204-470/103** | **ESL 1200 mg QD** | **Fatigue and Lethargy**<br>CRF indicates these on 6-9-06, Nausea on 5-31, headache and vomiting on 6-2-06 and dizziness on 6-6. Narrative indicates that day of first dose is not reported. |
| **204-472/115** | **ESL 1200 mg QD** | **Somnolence, Depression, and Disturbance in Attention**<br>Narrative indicates that first day of dosing was not reported. CRF AE page indicates somnolence on 7-20, depression and loss of concentration on 7-23. Somnolence categorized as severe. All three events noted to have action taken as withdrawn. |
| **204-476/137** | **ESL 1200 mg QD**<br><br>**or**<br><br>**ESL 900 mg** | **Intentional Overdose**<br>Two narratives in discontinuation section. One for patient 204-476-137 refers to study 205 narrative for this patient study 205-576-204137. The study 205 narrative header indicates subject on ESL dose of 900 mg QD in part 1 and not randomized into part 2. This 37 year old female subject reportedly intentionally overdosed on clonazepam 11 days after starting study medication. The clinical study report notes subject on 1200 mg (p.47/1987). Two CRFs with referenced subject numbers. In both CRFs, AE is dated 7-25 and listed as intentional overdose of clonazepam with action of patient withdrawn. |
| **204-452/153** | **ESL 1800 mg QD** | **Hypersensitivity-**Narrative indicates first day of dosing not reported.<br>63 year old male with history of penicillin allergy and possible food allergy experienced an event of allergic reaction beginning 5-8-06, described as moderate and required treatment with dexamethasone. Discontinued 9 days after AE onset. Event considered resolved in June, date not specified. On physical examination on 5-16 EDV, an allergic reaction was noted. CRF indicates adverse events, "flu" on 5-7-06, "allergic reaction" on 5-8-06, and "acute bronchitis" on 5-17-06. No event has action taken as withdrawn although DCF indicates due to allergic reaction. Dexamethasone IM given 5-12-06. On 5-12: Listing 16.2.8-1 (CSR) indicates that AST out of range but not CS (15, no RR given, normal at screening). On 5-16, ALT and ALP out of range but not considered clinically significant. Labs of 5-24-06 and 6-17-6, ALT, ALP, and eosinophils no longer out of range. Neutrophils still out of range but not considered clinically significant. |

**Bolded event terms are as per the ISS narratives. EDV=early discontinuation visit, DCF=data clarification form, CS=clinically significant, RR=reference range, CRF=case report form, CSR=clinical study report.**

Study 205- This was an extension of studies 203 and 204 to assess the

ability to prevent the recurrence of bipolar symptoms. The study had two parts; part 1 was open-label and part 2 was double-blind, parallel group, without placebo, of 3 doses of ESL. 20 patients reported 40 AES in the open-label part of the study. During the blinded portion of the study, 14 patients experienced 27 AEs in the 300 mg group, 14 patients experienced 25 AES in the 900 mg group, and 18 patients experienced 42 AEs in the 1800 mg. More of the 1800 mg group discontinued the study for any reason when compared to the other two ESL group (73% versus about 54% each for the two other groups), however, this was not the case with discontinuation in the blinded part of the study for discontinuation secondary to an adverse event: 14.3% (5/35) of the 300 mg group, 26.9% (7/26) of the 900 mg group, and 7.7% (2/42) of the 1800 mg group discontinued secondary to an AE. (paragraph information from the clinical study report).

As per the ISS narratives, 18 subjects on a study medication discontinued secondary to an AE (there are an additional two narratives labeled as prior to treatment). These were distributed as 5 in the 300 mg group, 11 in the 900 mg group, and 2 in the 1200 mg group. 12 of these 18 subject discontinuations were for psychiatric related event terms (depression, mania, disease progression) and were distributed as 2 of 5 subject discontinuations in the 300 mg group, 7 of 11 subject discontinuations in the 900 mg group, and both of the discontinuations in the 1200 mg group. 7 of the 18 events were also considered SAEs: one mania SAE in the 300 mg group, the event labeled anemia in the 900 mg group as well as four of the psychiatric events, and one of the events in the 1200 mg group.

Due to the indication of the trial, the table below is limited to non-psychiatric events. Data and information are from the events reported as per the ISS unless otherwise noted.

| | | | |
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| **205-501/203101** | **ESL 300 mg QD** | **Hepatic Steatosis** | 26 year old female, with history of hepatitis A, cholecystectomy, hypertension, obesity, and iodine allergy was on ESL 900 mg in part1 with dose decreased to 300 mg in part 2. "Hepatic steatosis" considered moderate and noted as onset 210 days after starting study medication (CRF date is 1-12-07). Subject was discontinued 5 days after event, which narrative states was considered resolved with sequelae. Narrative no details as to how diagnosis made or lab values. CRF labs - AST, ALT, ALP marked as within range at admission and EDV. CRF AE page does not provide details of diagnosis nor does page labeled "Additional Information". CRF AE page has an event of "gallbladder inflammation" on 9-10-06. |
| **205-571/204109** | **ESL 300 mg QD** | **Malaise** | 27 year old male who received ESL 900 mg in part 1 on 8-8-06 and was randomized to part 2 on 8-21-06 at which time dose decreased to 300mg. Subject experienced malaise beginning 102 days after starting study medication. Treatment was not required but the subject was discontinued 16 days after onset for the event which was ongoing. |
| **205-531/203081** | **ESL 900 mg QD** | **Sinus Tachycardia** | 34 year old male, 1st ESL in part 1 (900mg) on 6-22-06 and randomized to part 2 on 7-4-06 with dose remaining at 900 mg QD. No concomitant medications reported during open-label or double-blind periods (per CSR p.68/5893). Event started on 7-4-06, considered moderate, not treated for the event, but discontinued about two weeks after onset. Event considered resolved on 8-18-06. The CSR EKG listing noted the rate as 108 at v2 (68 at v1). In the CRF, on the EKG section under the sinus tachycardia notation, left bundle branch block is also written. At the |

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| | | | discontinuation visit on 7-17, only sinus tachycardia noted in EKG section of CRF. A data clarification (p.132/135) query for visit 2 and EDV notes the EKG showed clinically relevant abnormality and asked for verification that AE was capture. The response was to change the clinical relevance to no, "after consultation with a cardiologist". |
| **SAE 205-543/203144** | **ESL 900 mg QD** | **Anemia** | Narrative in SAE section of this review. Anemia reported in narrative as event leading to discontinuation. Subject also with event term "esophageal stenosis". |
| **205-552/204157** | **ESL 900 mg QD** | **Vomiting , Bronchitis, and Headache** | 50 year old female who experienced vomiting and headache, considered moderate, 8 days after starting study medication. About 14 days after starting study medication (on 10-5-06), the subject experienced bronchitis considered moderate and treated with antibiotic. Discontinuation was 10-14-06. The narrative states that vomiting and headache were resolved on 10-4 and bronchitis on 10-12. |
| **205-576/204137** | **ESL 900 mg QD** | **Intentional Overdose** | 37 year old female who received 900 mg ESL daily in part 1 but was not randomized to part 2. This is the subject who was described as intentional overdose of clonazepam in study 204. |

**Ongoing and clinically completed but not reported studies' events up to March 30, 2009 as reported in 2-4-10 submission**

The sponsor submitted updated discontinuation information for events on 2-4-10 (Table 4). Quality issues regarding the presentation of this data in the NDA are discussed elsewhere in this review. The discontinuation table submitted 2-4-10 has received only cursory review. As with the SAE information, no dose relationships are made or implied as the data from the sponsor is not final, my review is not final, and there are no sample sizes or denominators.

For study 127, (plasma and CSF PK, clinically completed 2-7-09), it is stated that no discontinuations of study medication due an AE were reported. For study 128 (DDI with oral contraceptive, clinically completed 11-14-08, there is one discontinuation for a generalized cutaneous rash with pruritus.

For study 206, 4 events from the observational baseline period, 82 from the double blind period, and 7 from the open-label period are reported. In the double-blind period, 7 events are in placebo subjects, 15 are in ESL 400 mg BID subjects, 8 are in ESL 800 mg daily subjects, 11 are in ESL 600 mg BID subjects, 17 are in ESL 1200 mg subjects, and 24 events are in ESL 800 mg BID subjects.

Double-blind: Placebo discontinuation events are hypoglycemia, gastritis-stomach pain, diarrhea (2), nausea, exacerbation of pain, and coordination abnormal. In ESL treated patients, there were at least 8 events of discontinuation attributed to either rash/pruritus/itching, at least six involved vomiting or nausea, at least three with terms consistent with possible angioedema (face edema/ face edema and eyelids, /edema of the tongue), at least two with cardiovascular terms (suspected angina pectoris although a foot note states it was before first dosing, non-ST wave MI, cardiac decompensation, hypertension), at least two with cognitive-behavioral terms (disorientation, disturbance

in attention and memory impairment), several with terms consistent with a gait difficulty and/or abnormal coordination, several with dyspnea, a couple with terms suggesting blood glucose control was fluctuating or worse, a loss of consciousness, at least one constipation, one with increased hepatic enzymes, and one with "paraparesis of lower limbs".

In study 207, there is are two events of hyponatremia, one of esophageal stenosis, one of hepatopathy, and events similar to those seen in 206 (e.g. MI, rash, nausea and vomiting). Additionally, there is a "suicide attempt" (OL), an obstipation (OL), an iritis (double-blind), a liver enzyme elevation, a subject with increasing "CK-NAC" and decreased chloride (DB period), peripheral edema, a subject with biliary tract infection, one with "tremoring in both hands", and one subject with "ulerythema, desiccation scin, and pruritus of the skin".

### 7.3.4 Significant Adverse Events

A patient is reported as having pancytopenia in the SU (p. 160). This is subject 2093-303-701-70290. There is no narrative for this subject in either the SAE or SU, so it is unclear exactly what the details are. The page indicating this event only states that this was as 38 year-old female who received ESL 1200 mg for 155 days and experienced pancytopenia. She is reported as being on concomitant valproic acid.

Otherwise, events classified by the sponsor severe are described below.

Bipolar:

Study 203-The ISS reports that severe events were reported by 7.5%, 6.3%, and 3.5% of placebo-treated, 600 mg ESL-treated, and 800 mg ESL-treated subjects respectively. Two subjects each are noted to have reported severe mania or vomiting (both in the 600 mg ESL QD group). Severe agitation was reported for one placebo and one 800 mg ESL QD patient. One subject each is noted to have severe ALT increased, AST increased, Bipolar I disorder, diarrhea, fatigue, headache, hematemesis, insomnia, and ischemic stroke.

Study 204: 5 severe events are reported in the ISS: intentional overdose (1200 mg ESL), mania (one subject each placebo and 1800 mg ESL), somnolence (1200 mg ESL), and syncope (1800 mg ESL).

Study 205: 5 severe events are reported during the double-blind period: unilateral deafness (ESL 900 mg ESL "an ongoing event" since 1986), disease progression (one each in 300 mg and 1800 mg ESL), malaise (300 mg ESL), and mania (300 mg ESL).

The open-label period of 205 is not addressed.

Phase 2 epilepsy study 201-severe events were reported by 8.5%, 2.2%, and 2% of placebo, BID-treated, and QD-treated subjects respectively. The ISS reports that "at most" one subject per treatment group reported the following; chest pain (placebo as per the study report), creatinine kinase increased (placebo as per the study report Table 91), headache (BID ESL dosing as per the study report), ischemic stroke NOS (daily ESL as per the study report), radius fracture (placebo, as per the study report), and status epilepticus (placebo, as per the study report).

Phase 2 pediatric epilepsy study 202- Seizures were reported as severe in a subject in the 2-6 year old age group and in a subject in the 7-11 year old age group, both during 30 mg/kg/d treatment. Acute pharyngitis is reported in the 12-17 year age group during down titration.

Phase 3 epilepsy:

The sponsor presented the table below in the SU. 4.5 % of placebo subjects and 9.7% of ESL subjects in pooled study data 301-302 compared to 5.7% of placebo and 10.3% of ESL subjects reported at least 1 severe TEAE.

**Table 4.1.4.6-1: Severe Treatment-Emergent Adverse Events Reported in ≥2% of Subjects in Any Dose Group by Overall Treatment Group for Part 1 of the Phase III Studies (2093-301 and 2093-302 Pooled vs 2093-303) (Safety Population)**

| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | Studies 2093-301 and 2093-302 Pooled | | Study 2093-303 | |
|---|---|---|---|---|
| | Placebo (N=202) | Total ESL (N=595) | Placebo (N=87) | Total ESL (N=165) |
| | Subjects n (%) | Subjects n (%) | Subjects n (%) | Subjects n (%) |
| AT LEAST 1 SEVERE TEAE | 9 (4.5) | 58 (9.7) | 5 (5.7) | 17 (10.3) |
| NERVOUS SYSTEM DISORDERS | | | | |
| Dizziness | 0 | 13 (2.2) | 2 (2.3) | 6 (3.6) |
| Somnolence | 1 (0.5) | 3 (0.5) | 1 (1.1) | 4 (2.4) |
| Headache | 0 | 4 (0.7) | 1 (1.1) | 3 (1.8) |
| Coordination abnormal | 0 | 10 (1.7) | 0 | 3 (1.8) |
| Convulsion | 0 | 4 (0.7) | 2 (2.3) | 0 |
| GASTROINTESTINAL DISORDERS | | | | |
| Nausea | 1 (0.5) | 3 (0.5) | 0 | 3 (1.8) |
| Vomiting | 2 (1.0) | 8 (1.3) | 0 | 1 (0.6) |
| GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS | | | | |
| Gait disturbance | 0 | 1 (0.2) | 0 | 2 (1.2) |
| EAR & LABYRINTH DISORDERS | | | | |
| Vertigo | 0 | 2 (0.3) | 0 | 3 (1.8) |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; SU=120-day safety update; TEAE=treatment-emergent adverse event.

a Reported AE terms were coded using the MedDRA version 7.0 dictionary for Study 2093-301 and version 9.0 for Studies 2093-302 and 2093-303.

Note: The titration, maintenance, and tapering-off periods were combined. Study 2093-302 did not have a tapering-off period. Treatment-emergent adverse events are those that occurred on or after the date of first dose, or the date of randomization if the date of the first dose was missing. Adverse events with missing or incomplete onset dates were considered to be treatment emergent unless it could be determined that the event began before the treatment period.

Note: Potentially-related events as those assessed by the Investigator as having a definitely, probably, possibly, unlikely, or unknown/missing relationship to treatment.

Note: Subjects were counted at most once within each system organ class and preferred term.

Note: Adverse events were updated with delayed reports of 59 AEs from Part 2 studies that had onset dates in Part 1.

Reference: SU EOT Tables 5.2.1.1 and 5.2.1.2

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The SU reports that overall, there was not a dose response for TE AEs of a severe intensity in part 1 of studies 301-302 or part 1 of study 303. For studies 301-302 pooled data, the most common severe events in ESL groups are reported as dizziness (0%, 0.5%, 1%, and 5% of subjects for the respective placebo, 400 mg ESL, 800 mg ESL, and 1200 mg ESL groups) and vomiting (1, 0.5%, 1.5%, and 2 % of subjects respectively). In study 303 part 1, the most common severe events in ESL patients were dizziness (not dose responsive), somnolence (not dose responsive), headache (not dose responsive), abnormal coordination (0, 1.2%, and 2.5% placebo, 800 mg, and 1200 mg respectively), nausea (not dose responsive), and vertigo (not dose responsive).

Review of dataset events considered severe in part 1 (titration, maintenance, and double blind) showed a dose group breakdown (based on assigned treatment) of placebo 14 subjects, ESL 400 mg 18 subjects, ESL 800 mg 24 subjects, and ESL 1200 mg 33 subjects. Using verbatim terms, in the 1200 mg group, there is a severe event of

decreased blood pressure (302-337-80228), one of disturbance of concentration( 302-351-80060), one of dysarthria (302-351-80059) two of exanthema (same subject, 301-111-90341, also with severe fever), a GGT increased (301-141-90212), one tremor (302-336-80736), one cerebellar syndrome (303-703-70374), one asthenia (302-351-80059), one “tranquilization” (302-351-80060), one “sickness” (303-605-70361) and a “worsening of seizures” (302-331-80141). The other severe events in this group are GI-related (abdominal cramps, abdominal pain, acute diarrhea, nausea, vomiting), ataxia or gait abnormality, somnolence or sedation, vertigo terms or dizziness terms, diplopia or double vision or blurred vision.

Using verbatim terms, in the 800 mg ESL group there were singular severe events of angina pectoris (301-145-90194), arthralgia, endometriosis, follicular cell lymphoma, fracture of a leg, ovarian cyst, right ankle pain (dislocation), stomach ulcer, stomach discomfort (different subjects with these two stomach complaints), urinary infection, prolong seizures, and worsening of erectile dysfunction. Other terms were terms consistent with possible toxicity or drug side effect (ataxia or equivalent, dizziness or equivalent, diplopia or blurred vision, somnolence, nausea and vomiting, and headache).

Using verbatim terms, in the 400 mg ESL group there was one severe acute asthma (302-336-80072), one asthenia (301-211-90046), one constipation (302-331-80152), one insomnia (301-101-90185), one “further worsening of depression”, one “trigonitis” (also renal colic for this patient-302-336-80072), one “brain contusion and nasal bone fractures” (2 events, one subject, 301-113-90398), two seizure-related events, three infections (upper respiratory and flu), and events possibly reflective of toxicity or drug side effect (intoxication with AEDs, ataxia, dizziness, headache, itch hand, vertigo, vomiting, blurred vision).

Using verbatim terms, in the placebo group, there were singular severe events of anxiety, carries, chest trauma, creatinine phosphokinase increased, death, diarrhea, fatigability, leukopenia, pain chest, sore throat, stomach ache, upper respiratory infection (flu), “hipersomnia”, and xx. There were two events each of dizziness and somnolence and vomiting, and three events related to seizures or increased seizures.

The SU reports that 8.9% of the subjects in pooled study data of 301-302 compared to 7.1% of study 303 subjects reported at least one severe TEAE. The table below, duplicated from the SU, indicates that dizziness and headache were the two most common severe events in studies 301-302 while convulsion was in study 303. Combining the seizure terms (convulsion, complex partial seizures, and status epilepticus) indicates that 10.5% of severe events in 301-302 involved one of these events and 21 % of severe events in study 303 involved one of these events.

**Table 5.5.6-1: Severe Treatment-Emergent Adverse Events Reported in >1 Subject in Any Study Grouping for the Phase III Extensions (Part 2 of 2093-301, 2093-302, and 2093-303) (Safety Population)**

| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | 400-1200 mg ESL QD | | |
|---|---|---|---|
| | Studies 2093-301, 2093-302, and 2093-303 Pooled (N=835) | Studies 2093-301 and 2093-302 Pooled (N=639) | Study 2093-303 (N=196) |
| | Subjects n (%) | Subjects n (%) | Subjects n (%) |
| AT LEAST 1 SEVERE TEAE | 71 (8.5) | 57 (8.9) | 14 (7.1) |
| NERVOUS SYSTEM DISORDERS | | | |
| Dizziness | 11 (1.3) | 10 (1.6) | 1 (0.5) |
| Headache | 11 (1.3) | 11 (1.7) | 0 |
| Somnolence | 5 (0.6) | 5 (0.8) | 0 |
| Coordination abnormal | 5 (0.6) | 4 (0.6) | 1 (0.5) |
| Convulsion | 4 (0.5) | 2 (0.3) | 2 (1.0) |
| Complex partial seizures | 2 (0.2) | 2 (0.3) | 0 |
| Status epilepticus | 3 (0.4) | 2 (0.3) | 1 (0.5) |
| INFECTIONS & INFESTATIONS | | | |
| Influenza | 2 (0.2) | 2 (0.3) | 0 |
| Upper respiratory tract infection | 2 (0.2) | 2 (0.3) | 0 |
| GASTROINTESTINAL DISORDERS | | | |
| Nausea | 3 (0.4) | 2 (0.3) | 1 (0.5) |
| Vomiting | 2 (0.2) | 2 (0.3) | 0 |
| Toothache | 3 (0.4) | 2 (0.3) | 1 (0.5) |
| Dyspepsia | 2 (0.2) | 2 (0.3) | 0 |
| INVESTIGATIONS | | | |
| Weight increased | 2 (0.2) | 2 (0.3) | 0 |
| EYE DISORDERS | | | |
| Diplopia | 2 (0.2) | 2 (0.3) | 0 |
| INJURY, POISONING, & PROCEDURAL COMPLICATIONS | | | |
| Multiple injuries | 2 (0.2) | 0 | 2 (1.0) |
| Skull fracture | 2 (0.2) | 1 (0.2) | 1 (0.5) |
| GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS | | | |
| Drowning | 2 (0.2) | 2 (0.3) | 0 |
| Malaise | 2 (0.2) | 2 (0.3) | 0 |
| MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS | | | |
| Back pain | 3 (0.4) | 3 (0.5) | 0 |
| Arthralgia | 2 (0.2) | 2 (0.3) | 0 |
| REPRODUCTIVE SYSTEM & BREAST DISORDERS | | | |
| Dysmenorrhea | 2 (0.2) | 2 (0.3) | 0 |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; QD=once daily; SU=120-day safety update; TEAE=treatment-emergent adverse event.

a Reported AE terms were coded using the MedDRA version 9.0 dictionary for Part 2 of Study 2093-301 and version 10.0 for Part 2 of Studies 2093-302 and 2093-303.

Note: Subjects may have more than 1 adverse event per system organ class and preferred term. At each level of summarization (global, system organ class, preferred term), a subject was counted once if he/she reported more than 1 adverse event at that level and the adverse event with the greatest severity is presented.

Reference: SU EOT Tables 16.3, 16.3.1, and 16.3.2



Dataset ADAE2.xpt indicates there were 135 severe events (71 subjects) in part 2 of the phase 3 studies. Verbatim terms in open-label show similarities to those in part 1 in terms of events consistent with possible side effect or toxicity (such as ataxia, diplopia, dizziness terms, medication intoxication, BIA 2093 related CNS toxicity syndrome, GI effects). In addition there are several psychiatric related events such as aggression, anxiety, depression, psychogenic paranoid psychosis, and hallucination), events reflective of injury (laceration liver rupture, cranial trauma, fracture of occipital bone and

subdural hematoma, eye trauma). Seizure terms are seen (such as “GTCS x 3”, exacerbation of seizure frequency, status).

Phase 1 study 123-one severe event is reported in a placebo patient (SU, p. 186)

### 7.3.5 Submission Specific Primary Safety Concerns

**MYOCARDIAL INFARCTION AND STROKE**

The ISS reports there was an imbalance of ischemic events in the ESL groups in phase 3 epilepsy studies. The sponsor presents the results of a search of the entire safety database in table 8.6.17-1 below. 12 events are in the table below, 2 of which occurred in placebo patients. Denominator is not given.

**Table 8.6.17-1: All Potential Ischemic Vascular Events in the ESL Studies**

| Potential ischemic event | Eslicarbazepine Acetate | | | Placebo |
|---|---|---|---|---|
| | 400 mg | 800 mg | 1200 mg | |
| Angina pectoris | | 1 | | |
| Cardiac pain | | | 1 | |
| Ischemic cardiomyopathy | | 1 | | |
| Vertebrobasilar insufficiency | 1 | | | |
| Bundle Branch Block Right | | 1 | | 1 |
| Ischemic stroke | | | 1 | 1 |
| Myocardial ischemia | | | 1[a] | |
| Cerebrovascular disorder | | 1 | | |
| Hemiparesis | | 1 | | |
| Monoparesis | | 1 | | |

a Includes 1 subject in Study 2093-203 reported the event 3 days after the last dose of 1600 mg ESL.
Reference: See narratives that follow for references.

By phase, the events are reported as 0, 5, 7 for phase 1, 2, and 3 respectively.

| | | |
|---|---|---|
| Phase 1 | no “potentially ischemic events” | |
| Phase 2 | 5 (3 in study 201) and 2 in study 203 | ESL-cardiac pain (study 201, ESL 1200 mg), ischemic stroke (study 201, ESL 1200 mg), myocardial ischemia (study 203, ESL 1600 mg)<br>placebo-RBBB (study 201), ischemic stroke (study 203) |
| phase 3 | 6 | ESL-Angina, RBBB, ischemic cardiomyopathy, |

| | | |
|---|---|---|
| | | vertebrobasilar insufficiency, cerebrovascular disorder, and hemiparesis, monoparesis |

**From text and/or narrative page 221/582 ISS**

The sponsor included narratives, which are summarized in the table below.

| | | |
|---|---|---|
| 301-145-90194 **ESL 800 mg** | part 1 | 35 year old male, with no prior cardiac history, experienced angina pectoris on day 75 of treatment with ESL 800 mg. Subject was also on topirimate and acetylsalicylic acid. Episode was serious and subject discontinued. No EKG, lab or workup data are presented in the narrative. |
| 301-111-90342 **ESL 800 mg** | part 1 | 53 year old male with history of hyperlipidemia reported "mild ischemic cardiomyopathy" on day 74 of ESL 800 mg. The subject was on concomitant carbamazepine and topirimate. Event considered not serious and no action was taken. The outcome was ongoing. There is no EKG, lab, or workup data in the narrative. |
| 301-112-90323 **ESL 400 mg** | part 1 | 47 year old male with history of pulmonary tuberculosis experienced "mild vertebrobasilar insufficiency" after day 83 of ESL 400 mg treatment. The subject was on concomitant carbamazepine and clonazepam. The event was considered not serious and was treated with "medication". There is no EKG, lab, or workup data in the narrative. |
| 301-112-90326 **ESL 800 mg** | part 1 | 50 year old male, with a history of hyperlipidemia, reported right bundle branch block on the same day as starting treatment with ESL 800 mg. The subject was on concomitant gabapentin and clonazepam. The event was considered not serious, no action was taken, and the EKG changes persisted to the last EKG taken (visit 5). No other EKG data is given. No lab or other workup data are given. |
| 301-124-90357 **ESL** | part 2 | 41 year old female, previously on placebo in part 1, with no stated cardiac history, experienced an episode of "mild hemiparesis" on the right on day 7 of ESL 1600 mg daily. The subject is reported to have mistakenly been prescribed 1600 mg instead of 800 mg ESL and was taking carbamazepine and topirimate also as well as ibuprofen. The event was serious and accompanied by vertigo and walking instability. The subject is reported recovered after 10 days. All AEDs were stopped later "because of drug intoxication". No details are given otherwise. |
| 301-181-90002 **ESL 800 mg** | part 2 | 47 year old male, previously on ESL 1200 mg, reported an episode of monoparesis of right upper limb after day 142 of ESL 800 mg. The subject had a history of hyperlipidemia, traumatic brain injury, and subdural empyema. He was on concomitant phenobarbital and phenytoin. The event was considered not serious and the subject is reported as recovered. No other details (for example, of workup or evaluation) are provided. |
| 301-112-90324 **ESL 400 mg** | part 2 | 49 year old female previously on ESL 800 mg in part 1, reported "mild cerebrovascular disorder" after day 359 of ESL 400 mg daily. She was also taking carbamazepine and topirimate. The subject had "no relevant medical history" although she had reported 2 episodes of blurred vision prior to treatment. The event was considered not serious, treated with "medication", and was ongoing at the time of report. No additional details are given. |
| 201-005-112 **placebo** | | 56 year old male, with history of hypertension. Concomitant medications of enalapril, lamotrigine and vigabatrin, reported "mild right bundle brand block" after day 28 of **placebo** treatment. The event considered not serious, resolved after day 28, and the subject is reported as recovered. No other details are provided. |
| 201-013-062 **ESL 1200mg** | | 51 year old female with no medical history reported experienced "a mild episode of cardiac pain" after day 64 of ESL 1200 mg. The subject was also taking valproic acid and "LMT". The event was not considered serious, resolved after day 64, and the subject is reported as recovered. No other details are provided. |

| | | |
|---|---|---|
| 201-014-079 **ESL 1200 mg** | | 46 year old female with a history of carotid thrombosis, menometrorrhagia, and anemia, hospitalized due to severe ischemic stroke after day 60 of treatment with ESL 1200 mg. The subject was on concomitant "LMT", desogestrel and estrogen. The event was serious, lasted 40 days, and the subject is reported as recovered with sequelae. |
| 203-334-11123 **post- ESL 1600 mg** | | 66 year old male with a screening EKG of RBB and with acute manic episode experienced "mild episode of myocardial ischemia" during follow-up visit after the end of treatment with ESL 1600 mg. The subject was treated with perindopril, glyceryl trinitrate, and acetylsalicylic acid. The event was considered not serious and was ongoing at the time of report. |
| 203-341-203181 **placebo** | | 42 year old female died from ischemic stroke. She experienced the event 21 days after starting placebo. Her medical history was significant for obesity and RBBB. |

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Common adverse events are described in the most cursory manner. As with all safety data at this point, no interpretation is made at this time due to data quality issues.

As displayed by the sponsor, nervous system events were the most common reason adverse events.

**Table 5.5.4-1: Treatment-Emergent Adverse Events Reported in ≥2% of Subjects in Any Study Grouping for the Phase III Extensions (Part 2 of 2093-301, 2093-302, and 2093-303) (Safety Population)**

| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | 400-1200 mg ESL QD | | | | | |
|---|---|---|---|---|---|---|
| | Studies 2093-301, 2093-302, and 2093-303 Pooled (N=835) | | Studies 2093-301 and 2093-302 Pooled (N=639) | | Study 2093-303 (N=196) | |
| | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n |
| AT LEAST 1 TREATMENT-EMERGENT AE | 532 (63.7) | 1762 | 422 (66.0) | 1510 | 110 (56.1) | 252 |
| NERVOUS SYSTEM DISORDERS | | | | | | |
| Dizziness | 141 (16.9) | 172 | 110 (17.2) | 135 | 31 (15.8) | 37 |
| Headache | 97 (11.6) | 133 | 81 (12.7) | 117 | 16 (8.2) | 16 |
| Somnolence | 66 (7.9) | 73 | 47 (7.4) | 53 | 19 (9.7) | 20 |
| Coordination abnormal | 22 (2.6) | 27 | 21 (3.3) | 25 | 1 (0.5) | 2 |
| Convulsion | 17 (2.0) | 17 | 15 (2.3) | 15 | 2 (1.0) | 2 |
| INFECTIONS & INFESTATIONS | | | | | | |
| Nasopharyngitis | 38 (4.6) | 53 | 36 (5.6) | 51 | 2 (1.0) | 2 |
| Influenza | 29 (3.5) | 31 | 20 (3.1) | 22 | 9 (4.6) | 9 |
| Urinary tract infection | 10 (1.2) | 10 | 5 (0.8) | 5 | 5 (2.6) | 5 |
| GASTROINTESTINAL DISORDERS | | | | | | |
| Nausea | 36 (4.3) | 41 | 28 (4.4) | 32 | 8 (4.1) | 9 |
| Vomiting | 36 (4.3) | 38 | 25 (3.9) | 27 | 11 (5.6) | 11 |
| Diarrhea | 25 (3.0) | 28 | 20 (3.1) | 23 | 5 (2.6) | 5 |
| Abdominal pain upper | 20 (2.4) | 26 | 18 (2.8) | 24 | 2 (1.0) | 2 |
| Abdominal pain | 13 (1.6) | 16 | 13 (2.0) | 16 | 0 | 0 |
| INVESTIGATIONS | | | | | | |
| Blood pressure diastolic decreased | 26 (3.1) | 36 | 26 (4.1) | 36 | 0 | 0 |
| Weight increased | 14 (1.7) | 14 | 13 (2.0) | 13 | 1 (0.5) | 1 |
| EYE DISORDERS | | | | | | |
| Diplopia | 43 (5.1) | 52 | 39 (6.1) | 48 | 4 (2.0) | 4 |
| Vision blurred | 25 (3.0) | 27 | 17 (2.7) | 19 | 8 (4.1) | 8 |
| GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS | | | | | | |
| Pyrexia | 13 (1.6) | 18 | 9 (1.4) | 14 | 4 (2.0) | 4 |
| PSYCHIATRIC DISORDERS | | | | | | |
| Anxiety | 10 (1.2) | 10 | 6 (0.9) | 6 | 4 (2.0) | 4 |
| MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS | | | | | | |
| Back pain | 22 (2.6) | 24 | 20 (3.1) | 22 | 2 (1.0) | 2 |
| EAR & LABYRINTH DISORDERS | | | | | | |
| Vertigo | 20 (2.4) | 21 | 18 (2.8) | 19 | 2 (1.0) | 2 |

Abbreviations: AE=adverse event; EOT=end of text; ESL=eslicarbazepine acetate; QD=once daily.
a Reported AE terms were coded using the MedDRA version 9.0 dictionary for Part 2 of Study 2093-301 and version 10.0 for Part 2 of Studies 2093-302 and 2093-303.
Note: Treatment-emergent adverse events are those that occurred after the date and time of the first dose of open-label study medication.
Note: Subjects were counted at most once within each system organ class and preferred term.
Reference: SU EOT Tables 16.1, 16.1.1, and 16.1.2



### 7.4.2 Laboratory Findings

No TSH measures were acquired. The PCS value for cholesterol high value is too high (≥ 300 mg/dL).

Consistent across the development program is that sodium, and it appears, chloride decrease with ESL use. There were serious adverse events involving hyponatremia.

Study 111 included subjects with hepatic impairment as well as healthy volunteers. Mean sodium values decreased from baseline to all study visits in both subjects with hepatic impairment and healthy volunteers. Decreases were notably larger in subjects with hepatic impairment and are noted by the sponsor as larger than changes seen in any other population studies. Mean potassium increased slightly in hepatically impaired subjects compared to healthy volunteers. The sponsor's table showing these results is duplicated below.

**Table 11.2.1.6.2-1: Mean (SD) Baseline Values and Mean (SD) Changes from Baseline for Sodium and Potassium at Each Study Visit by Group for Study 2093-111 (Safety Population)**

| Parameter (Units) | Visit | Hepatic Impairment (N=9) | | Healthy Volunteers (N=8) | |
|---|---|---|---|---|---|
| | | N | Mean (SD) | N | Mean (SD) |
| Sodium (mEq/L) | Screening | 9 | 138.7 (4.07) | 8 | 141.7 (2.94) |
| | Δ to Day 1 | 9 | -1.3 (3.50) | 8 | -1.0 (1.76) |
| | Δ to Day 4 | 9 | -5.3 (4.15) | 8 | -1.7 (1.64) |
| | Δ to Day 8 | 8 | -6.3 (4.93) | 8 | -0.6 (2.57) |
| | Δ to Follow-up | 9 | -0.8 (2.56) | 8 | -0.1 (2.64) |
| Potassium (mEq/L) | Screening | 9 | 4.07 (0.65) | 8 | 4.28 (0.39) |
| | Δ to Day 1 | 9 | 0.12 (0.48) | 8 | -0.05 (0.41) |
| | Δ to Day 4 | 9 | 0.40 (0.82) | 8 | -0.07 (0.34) |
| | Δ to Day 8 | 8 | 0.27 (0.56) | 8 | 0.00 (0.51) |
| | Δ to Follow-up | 9 | 0.09 (0.67) | 8 | 0.07 (0.52) |

Abbreviations: Δ=change from baseline; SD=standard deviation.
Note: Chloride was not assessed in this study.
Note: Sodium and potassium data are presented in conventional units (mEq/L), which are equivalent to the standard units (mmol/L) in the CSR.
Reference: Study 2093-111 CSR Section 14.1 Table 11

One subject in study 111 is reported as having an abnormal serum electrolyte value adverse event. This was a decrease in blood magnesium in a subject with hepatic impairment. The magnesium level and/or change in values is not described.

### 7.4.3 Vital Signs

Deferred.

### 7.4.4 Electrocardiograms

Study 116 was a QT study. This study is described in more detail in section 7.4.5 below.

**Study 116**
The QT study was reviewed by the FDA QT group. This review is described elsewhere. The ISS included Table 12.1-3 that shows mean time-averaged change from baseline for several EKG parameters on study day 5. PR and QRS intervals are higher in ESL groups than in placebo. The ISS states that these changes are of no clinical significance and demonstrate no effect of the active agents (ESL or moxifloxacin) on atrioventricular conduction (p. 344/582).

**Table 12.1-3: Mean (SD) Time-Averaged Change from Baseline on ECG Intervals on Day 5 for Study 2093-116 (Safety Population)**

| Parameter | Placebo (N=64) Mean (SD) | 1200 mg ESL QD (N=61) Mean (SD) | 2400 mg ESL QD (N=58) Mean (SD) | Moxifloxacin[a] (N=61) Mean (SD) |
|---|---|---|---|---|
| QTcI (ms) | -2.74 (5.829) | -5.80 (7.727) | -4.67 (9.071) | 5.49 (7.556) |
| QTcB (ms) | 0.18 (5.930) | -1.01 (7.712) | 1.80 (7.931) | 9.73 (6.512) |
| QTcF (ms) | -2.85 (5.579) | -6.30 (7.651) | -5.24 (8.208) | 5.36 (6.947) |
| Heart rate (bpm) | 3.15 (3.502) | 5.67 (5.180) | 7.46 (4.586) | 4.39 (7.308) |
| PR (ms) | 2.20 (4.668) | 4.56 (5.791) | 8.15 (6.956) | 0.25 (6.424) |
| RR (ms) | -40.31 (43.208) | -70.98 (58.754) | -91.9 (56.221) | -53.95 (73.826) |
| QRS (ms) | 0.32 (1.606) | 0.79 (2.368) | 1.05 (2.008) | -0.11 (2.003) |
| QT (ms) | -8.50 (9.0780) | -16.17 (13.044) | -18.28 (13.020) | -2.74 (16.087) |

Abbreviations: QTcI=individual-corrected QT interval; QTcB=Bazett's correction; QTcF=Fridericia's correction; ms=milliseconds; bpm=beats/minutes.
a Administered as a single dose.
Reference: Study 2093-116 CSR Section 11.4.2 Table 8

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### 7.4.5 Special Safety Studies/Clinical Trials

The QT study and a study assessing cognition are described in this section.

**Thorough QT study:** Study 116 was the sponsor's thorough QT study. This study was conducted in 67 healthy, adult males and females ages 18- 45 years and was a randomized, double-blind, placebo-controlled and open-label active-controlled (moxifloxacin), 4 period crossover trial to evaluate the effect of eslicarbazepine acetate on cardiac repolarization. Subjects were randomized to one of four treatment sequences that consisted of: eslicarbazepine acetate 1200 mg once daily x 5 days, eslicarbazepine acetate 2400 mg once daily x 5 days, a single dose of moxifloxacin 400 mg on day 5, and placebo once daily x 5 days.

The study results were reviewed by the FDA's Interdisciplinary Review Team for QT studies. The QT review states that no significant QT prolongation effect of eslicarbazepine acetate (1200 mg and 2400 mg) was detected. The following paragraphs are based on the QT review team's review dated 10-30-09.

Dose selection was acceptable. The QT review notes that "because although the mean Cmax and AUC∞ after supratherapeutic dose (2400 mg) were only 2-times higher than those at a therapeutic dose of 1200 mg as the sponsor identified maximum tolerated dose." The largest upper bounds of the 2-sided 90% CI for the mean difference between eslicarbazepine acetate and placebo were <10 ms. Moxifloxacin profile over time and the lower bound of the 90% CI for the ΔΔ QTcI for moxifloxacin was > 5ms indicated that assay sensitivity was established. The review included a summary table of findings, which is duplicated below. As noted in the legend, there was not a multiplicity adjustment.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Eslicarbazepine Acetate (1200 mg and 2400 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

| Treatment | Time (hour) | ΔΔQTcI (ms) | 90% CI (ms) |
|---|---|---|---|
| Eslicarbazepine Acetate 1200 mg | 12 | 1.5 | (-1.0, 3.9) |
| Eslicarbazepine Acetate 2400 mg | 23.5 | 1.4 | (-1.2, 4.1) |
| Moxifloxacin 400 mg* | 2 | 12.0* | (9.5, 14.5) |

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 6 timepoints is 8.3 ms.

Data for Vimpat (lacosamide), a recently approved sodium channel AED, indicates a dose-related effect in the cardiac conduction system, specifically PR and QRS intervals. Given the similar mechanism, the results of PR and QRS analyses are shown, as per the QT group's review, below.

PR analysis:

The largest upper limits of 90% CI for the PR mean difference between ESL 1200 mg and placebo was 6.5 ms and between ESL 2400 mg and placebo was 11 ms.

**Table 14: Analysis Results of ΔPR and ΔΔPR**

| | Placebo | Eslicarbazepine Acetate 1200 mg | | | Eslicarbazepine Acetate 2400 mg | | |
|---|---|---|---|---|---|---|---|
| | ΔPR | ΔPR | ΔΔPR | | ΔPR | ΔΔPR | |
| Time (hrs) | LS Mean | LS Mean | Diff LS Mean | 90% CI | LS Mean | Diff LS Mean | 90% CI |
| 0.5 | 0.9 | 3.5 | 2.6 | (0.3, 4.9) | 6.6 | 5.7 | (3.4, 8.0) |
| 1 | 2.1 | 4.2 | 2.1 | (-0.0, 4.2) | 9.2 | 7.1 | (4.9, 9.2) |
| 1.5 | 3.4 | 3.6 | 0.2 | (-2.4, 2.7) | 8.3 | 4.9 | (2.3, 7.4) |
| 2 | 2.0 | 5.1 | 3.1 | (0.8, 5.4) | 9.6 | 7.7 | (5.3, 10.0) |
| 3 | 2.2 | 5.8 | 3.6 | (1.4, 5.8) | 10.9 | 8.7 | (6.5, 11.0) |
| 4 | 2.3 | 5.9 | 3.6 | (1.2, 6.1) | 9.0 | 6.7 | (4.2, 9.2) |
| 5 | 2.2 | 6.3 | 4.1 | (1.7, 6.5) | 7.4 | 5.2 | (2.7, 7.7) |
| 6 | 2.2 | 6.2 | 4.0 | (1.8, 6.3) | 8.6 | 6.3 | (4.0, 8.6) |
| 8 | 1.9 | 5.7 | 3.9 | (1.5, 6.2) | 7.3 | 5.4 | (3.1, 7.8) |
| 12 | 3.8 | 6.9 | 3.2 | (1.1, 5.2) | 9.2 | 5.4 | (3.3, 7.4) |
| 16 | 0.8 | 3.3 | 2.5 | (-0.3, 5.3) | 4.4 | 3.6 | (0.8, 6.4) |
| 23.5 | 1.2 | 1.1 | -0.1 | (-2.5, 2.3) | 7.0 | 5.8 | (3.3, 8.2) |

Outlier:
Five subjects had a post-dose PR over 200 ms but none experienced a change from baseline > 25%. The review states there were no clinically relevant effects on PR and QRS intervals.

**Table 15: Categorical Analysis for PR**

| Treatment Group | N | PR < 200 ms | PR >=200 ms |
|---|---|---|---|
| Baseline | 67 | 65 (97.0%) | 2 (3.0%) |
| Eslicarbazepine Acetate 1200 mg | 61 | 58 (95.1%) | 3 (4.9%) |
| Eslicarbazepine Acetate 2400 mg | 58 | 55 (94.8%) | 3 (5.2%) |
| Moxifloxacin 400 mg | 61 | 58 (95.1%) | 3 (4.9%) |
| Placebo | 64 | 61 (95.3%) | 3 (4.7%) |

QRS analysis:
The largest upper limits of 90% CI for the QRS mean differences between eslicarbazepine acetate 1200 mg and placebo and between eslicarbazepine acetate 2400 mg and placebo are 2.1 ms and 2.7 ms respectively. No subject experienced an absolute QRS interval > 120 ms in either eslicarbazepine group.

**Cognition and Psychomotor effects:**

Phase 1 study- 2093-123

This was a single-blind, single-center, single and multiple dose, study of cognitive and psychomotor function in healthy volunteers. A single dose of 900 mg ESL was followed by seven consecutive days of placebo→ ESL 800mg x 7 days-→ ESL 1200 mg daily x 7 days.

46 subjects were screened. 26 were dosed in period 1, 25 in period 2, 23 in period 3, and 22 in period 4. Overall, about 65% of the 26 subjects were female. 4 subjects withdrew early; two reportedly for non-compliance, 1 withdrew consent, and one was for an adverse event (listed as placebo with a sore throat). 19 of the 26 randomized subjects took all doses of the study drug. The sponsor reports pharmacodynamic results for an evaluable population which included 22 subjects. 3 of these had missed one dose of study drug. Pharmacodynamic variables were Choice Reaction Time, Divided Attention, Sternberg Short-Term Memory Test, Digit Vigilance, Digit Symbol Substitution Test (DSST), Rey Verbal Auditory Learning Test, Controlled Oral Word Associates Test, and Trail Making Part A and Part B.

It appears there was no wash-out or time lapse between dosing of the 900 mg ESL on days -1 to 1 and placebo on day 2. The study report indicates that no drug concentration measurements were taken during the study.

The sponsor reports that ANCOVA revealed no significant difference between the ESL 900 mg dose and the placebo dose on any of the PD measures tested. The sponsor reports that with the chronic phase, the analysis of variance demonstrated a number of significant differences between placebo and the ESL 800 and ESL 1200 mg doses as well as between the ESL 800 mg and ESL 1200 mg doses.

The sponsor concludes that the administration of ESL was associated with slower motor reaction times, diminished recognition memory, and lower digit detection sensitivity when compared to placebo. At the highest dose of ESL, there was diminished reaction time as compared to placebo. At the highest dose of ESL, the sponsor reports significantly faster response times for correct responses on the Divided Attention Test and an increased ability to produce words for a given semantic category within 1 minute on Controlled Oral Word Association Test as compared to the placebo condition.

With acute dosing, the largest difference in LS means for the DSST was at 6 hours. The sponsor's contrast was at 3 hours, which, as reported, is not statistically significant (p. 153 CSR). ANOVA in the chronic phase also indicated total reaction times with motor reaction times and total reaction times significantly slower for ESL 1200 mg than for both placebo and ESL 800 mgs.

The placebo TEAES cannot be definitively attributed to placebo as there was no washout before placebo after a single dose of 900 mg ESL. The data should be viewed within the limitations of the study design.

| | Placebo n=26 | ESL 800 mg n=24 | ESL 900 mg n=26 | ESL 1200 mg n=23 |
|---|---|---|---|---|
| # with AE | 13 (50%) | 6 (25%) | 9 (34.6%) | 7 (30.4%) |
| # with serious AE | 0 | 0 | 0 | 0 |
| # discontinue due to an AE | 0 | 0 | 0 | 0 |

**Data from Table 14.3.1.1 of the CSR**

**TEAEs**: (data from Table 14.3.1.2 of the CSR for study 123):

The most common AES in placebo were in GI SOC (30.8%) versus 12.5%, 15.4%, and 4.3% of the ESL 800 mg, ESL 900, and ESL 1200 mg groups respectively. Nervous Systems Disorders were the SOC with the next most common events reported at 19.2% of placebo versus 16.7% of ESL 800 mg, 15.4% of ESL 900 mg, and 17.4% of ESL 1200 mg. Within this SOC, most of the placebo patients experienced somnolence (11.5% placebo versus 0%, 7.7%, and 8.7% of the ELS groups respectively). Within this SOC, dizziness and headache were each seen in 3.8% of placebo versus 8.3% of the ESL 800 mg group, 0% of the ESL 900 mg group, and 4.3% of the ESL 1200 mg group for dizziness and 8.3% of the ESL 800 mg group, 3.8% of the ESL 900 mg group, and 8.7 % of the ESL 1200 mg group.

The most common AES in the ESL groups in general were in the Nervous System Disorders, followed by the GI disorders, as described above. Blurred vision was reported in two ESL patients (900 mg and 1200 mg) and no placebo or ESL 800 mg patients. An event of erythema of the eyelid and an event of chest discomfort were reported in 1 ESL subject each (900 mg and 1200 mg subject respectively).

### 7.4.6 Immunogenicity

Not Applicable

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

one subject in both ESL groups. The SU notes that "A number" of treatment-emergent adverse events occurred in only one subject in the 1200 mg group or in one subject in both ESL groups. (SU p.59)

### 7.5.2 Time Dependency for Adverse Events

Deferred.

### 7.5.3 Drug-Demographic Interactions

Age: Without regard to data quality issues, due to the low number of subjects ≥ 60 years old (n=12 in the placebo group and 28 total in the ESL groups), no conclusions can be made regarding age group differences for race/ethnicity, gender, BMI, region, baseline AED use generally and specifically for CBZ, LMT, VA, and LEV.

Race/Ethnicity: There are two few Asian (0, 2, 1, and 5 in placebo, 400 mg ESL, 800 mg ESL, and 1200 mg ESL groups respectively), Black (6, 2, 6, and 9 subjects in placebo, 400 mg ESL, 800 mg ESL, and 1200 mg ESL respectively) and "Other" (sponsor's category) (7, 4, 4, and 3 subjects in the respective groups). Hispanic ethnicity is noted as inconsistently reported across regions with subjects in Spain and Portugal reporting race as Caucasian.

The sponsor reports this demographic by region as per the table excerpt below (from ISS Table 19.2.1-1).

| | | Placebo (N=289) | | Total ESL (N=760) | |
|---|---|---|---|---|---|
| Parameter | Category/Statistic | Caucasian (N=222) | Hispanic (N=54) | Caucasian (N=618) | Hispanic (N=106) |
| Region n (%) | Eastern Europe[a] | 97 (43.7) | 0 | 284 (46.0) | 0 |
| | Latin America[b] | 48 (21.6) | 54 (100) | 135 (21.8) | 106 (100) |
| | Latin America excluding Mexico | 48 (21.6) | 0 | 135 (21.8) | 1 (0.9) |
| | Western Europe/ROW[c] | 77 (34.7) | 0 | 199 (32.2) | 0 |

Caucasians had a higher incidence of at least 1 TEAE (49% and 66% for placebo and total ESL respectively) compared to Hispanics (31.5% and 48%, respectively). Caucasians had a higher incidence of severe TEAES than did Hispanics in both placebo and total ESL. Headache or nausea was reported by a large percentage of Caucasian subjects than Hispanic while Hispanic subjects reported more dizziness, somnolence, and vomiting than Caucasian subjects. The sponsor's table showing these events is reproduced below.

**Table 19.2.2-1: Treatment Emergent Adverse Events by Race/ethnicity for the Pooled Phase III Epilepsy Studies (Part 1 of 2093-301, 2093-302, and 2093-303) (Safety Population)**

| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | Placebo (N=289) | | Total ESL (N=760) | |
|---|---|---|---|---|
| | Caucasian (N=222) Subjects n (%) | Hispanic (N=54) Subjects n (%) | Caucasian (N=618) Subjects n (%) | Hispanic (N=106) Subjects n (%) |
| AT LEAST 1 TEAE | 109 (49.1) | 17 (31.5) | 409 (66.2) | 51 (48.1) |
| Common TEAE | | | | |
| Diplopia | 5 (2.3) | 0 | 51 (8.3) | 2 (1.9) |
| Dizziness | 14 (6.3) | 6 (11.1) | 128 (20.7) | 24 (22.6) |
| Headache | 19 (8.6) | 5 (9.3) | 69 (11.2) | 7 (6.6) |
| Nausea | 5 (2.3) | 1 (1.9) | 48 (7.8) | 6 (5.7) |
| Somnolence | 21 (9.5) | 5 (9.3) | 80 (12.9) | 15 (14.2) |
| Vomiting | 5 (2.3) | 2 (3.7) | 34 (5.5) | 8 (7.5) |
| AT LEAST 1 POTENTIALLY RELATED TEAE | 79 (35.6) | 13 (24.1) | 346 (56.0) | 43 (40.6) |
| AT LEAST 1 SEVERE TEAE | 11 (5.0) | 2 (3.7) | 63 (10.2) | 7 (6.6) |

Gender: More female subjects than male subjects reported at least 1 TEAE (48% in placebo compared to 45% males and 69% of ESL females compared to 60% of ESL males). The same trend was seen for reporting of severe TEAEs.

**Table 19.3.1-1: Treatment Emergent Adverse Events by Gender for the Pooled Phase III Epilepsy Studies (Part 1 2093-301, 2093-302, and 2093-303) (Safety Population)**

| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | Placebo (N=289) | | Total ESL (N=760) | |
|---|---|---|---|---|
| | Male (N=143) n (%) | Female (N=146) n (%) | Male (N=360) n (%) | Female (N=400) n (%) |
| AT LEAST 1 TEAE | 64 (44.8) | 70 (47.9) | 215 (59.7) | 274 (68.5) |
| Common TEAE | | | | |
| Diplopia | 4 (2.8) | 1 (0.7) | 25 (6.9) | 32 (8.0) |
| Dizziness | 10 (7.0) | 11 (7.5) | 67 (18.6) | 99 (24.8) |
| Headache | 13 (9.1) | 12 (8.2) | 34 (9.4) | 50 (12.5) |
| Nausea | 2 (1.4) | 4 (2.7) | 15 (4.2) | 44 (11.0) |
| Somnolence | 10 (7.0) | 17 (11.6) | 33 (9.2) | 67 (16.8) |
| Vomiting | 1 (0.7) | 6 (4.1) | 9 (2.5) | 34 (8.5) |
| AT LEAST 1 POTENTIALLY-RELATED TEAE | 43 (30.1) | 56 (38.4) | 173 (48.1) | 244 (61.0) |
| AT LEAST 1 SEVERE TEAE | 6 (4.2) | 7 (4.8) | 25 (6.9) | 50 (12.5) |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; TEAE=treatment emergent adverse event.
a Reported AE terms were coded using the MedDRA version 7.0 dictionary for Study 2093-301 and version 9.0 for Studies 2093-302 and 2093-303.

*Reviewer's preliminary comment: Problems with subgroups, especially with small numbers, and also difference in way race considered in some regions. If that was not standardized in some way, data less evaluable than with normal caveats.*

### 7.5.4 Drug-Disease Interactions

Subjects with hepatic impairment are reported as more likely to have decreased sodium levels during ESL treatment when compared to healthy volunteers. Shift tables

indicated 38% of subjects with hepatic impairment shifted to low sodium on day 4 compared to 0% of healthy volunteers (ISS p. 339).

### 7.5.5 Drug-Drug Interactions

The ISS indicates the following drug interaction studies were conducted:
•AEDs: phenytoin (Studies 2093-106 and 2093-121), lamotrigine (Study 2093-119), and topiramate (Study 2093-120).
• Other drugs: digoxin (Study 2093-107), warfarin (Study 2093-108), ethinylestradiol and levonorgestrel (Study 2093-114).

The ISS reports that a study of ESL with warfarin was conducted (Study 2093-108). During this study, warfarin was initially administered. Once the INR was considered stable, warfarin was administered concurrently with ESL 1200 mg daily for 7 days. ESL was stopped and warfarin was administered alone to assess an possible impact on coagulation. The sponsor reports that based on the results of this study, it was concluded that there was no significant change in INR levels observed when ESL was administered concurrently with warfarin. There was one report of mild epistaxis. The sponsor reports that no other bleeding events were noted.

Please see the OCBP review for full discussion and conclusions of drug interactions. The following summaries are based on the ISS:

1) Study 106- phenytoin study considered by sponsor as too few subjects to allow reliable assessment. The study was terminated prematurely due to difficulties recruiting.
2) Study 121- phenytoin study-A pharmacokinetic interaction between ESL and phenytoin was observed. The ISS states this interaction did not appear to significantly or clinically impact the safety profile of the drugs. The addition of ESL as a concomitant with phenytoin increased $AUC_t$ and Cmax of phenytoin by 30-35%. The sponsor notes that the dose of eslicarbazepine may need to be increased and the dose of phenytoin decreased.
3) Study 119- lamotrigine study-The ISS states there was no statistically significant impact of ESL on the pharmacokinetic properties of lamotrigine when using a bioequivalence approach. AEs of sodium decreased all were reported during 1200 mg ESL = 150 mg lamotrigine. The ISS states that it “appears that the combination of lamotrigine and ESL are more responsible for the observations of reduced sodium than ESL alone.”
4) Study 120-Topiramate interaction study- The ISS reports that no interaction was observed on the PK of ESL when administered concomitantly with topirimate. The BA of topirimate at steady state was not BE to topirimate in the presence of ESL and was outside of the 80-125% range. Based on this information, an interaction is considered as observed for topirimate when administered with ESL.
5) Study 107-Digoxin study-The ISS reports there was no “relevant effect on the extent of systemic exposure of digoxin” as expressed by $AUC_t$. Concomitant ESL decreased the Cmax of digoxin by 15%.

6) Study 108-warfarin study- The sponsor reports there was no significant pharmacodynamic interaction between ESL and warfarin “despite a small pharmacokinetic interaction between ESL and (S)-warfarin, but not (R)-warfarin.” P. 374/ 582). The sponsor states that normal INR monitoring is sufficient when prescribing these drugs concomitantly.
7) Study 114-combined contraceptive- The results showed that concomitant administration of 1200 mg ESL with hormonal contraceptives may render these contraceptives less effective. There was a higher overall incidence of TEAEs with ESL + ethinylestradiol and levonorgestrel (100%) when compared with ethinylestradiol and leveonorgestrel alone (~28%).
8) Population studies-the Sponsor states that based on population PK analyses of the phase 3 studies in epileptic patients, subjects administered phenobarbital had a higher eslicarbazepine clearance compared to subjects administered other AEDs. The sponsor states that a higher dose of eslicarbazepine acetate may be necessary concomitantly with phenobarbital administration. The sponsor reports no clinically relevant effect of eslicarbazepine acetate on the clearance of phenobarbital was observed.
9) Population studies-the Sponsor states that based on population PK analyses of the phase 3 studies in epileptic patients, subjects administered carbamazepine had a higher eslicarbazepine clearance compared to subjects administered other AEDs. The sponsor states that a higher dose of eslicarbazepine acetate may be necessary with concomitant carbamazepine administration. The sponsor reports no clinically relevant effect of eslicarbazepine acetate on the clearance of carbamazepine was observed.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

NA

### 7.6.2 Human Reproduction and Pregnancy Data

Table 2-1 was submitted in a 9-29-09 response to a 9-11-09 FDA request for a listing of all subjects who became pregnant while exposed to active drug or placebo in the development program. The table indicates there were 12 pregnancies in the development program, of which four were not exposed to ESL. Of the 8 subjects reported as exposed to ESL, 4 pregnancies were terminated by induced abortion and 4 resulted in normal deliveries. The sponsor’s table describing the pregnancy information is duplicated below.

Table 2-1: Listing of Subjects who Became Pregnant While Exposed to Active or Placebo Study Drug during the ESL Clinical Development Program through 30 March 2009

| Study Type | Study Number/Part | Subject Number | Treatment | Treatment Start Date | Treatment Stop Date | Exposure Prior to Start of Pregnancy | Date of Pregnancy Outcome (b) (6) | Pregnancy Outcome |
|---|---|---|---|---|---|---|---|---|
| Phase I | 2093-117 | 005 | ESL 800 mg | 26 May 2007 | 26 May 2007 | 1 dose | | Induced Abortion |
| Phase II | 2093-201 | 02/040 | Placebo | Unknown | Unknown | 54 days | | Induced Abortion |
| Phase III | 2093-301 Part 1 | 111/90331 | ESL 800 mg | 12 Oct 2004 | 21 Dec 2004 | 71 days | | Induced Abortion |
| Phase III | 2093-301 Part 1 | 123/90482 | ESL 800 mg | 27 Jul 2005 | 01 Apr 2006 | 249 days | | Normal Delivery |
| Phase III | 2093-302 Part 1 | 412/80593 | None (baseline) | NA | NA | 0 days | | Induced Abortion |
| Phase III | 2093-302 Part 2 | 315/80256 | ESL 800 mg | 22 Jun 2006 | Ongoing | Ongoing | | Induced Abortion |
| | | | ESL 1200 mg | 11 Apr 2006 | 21 Jun 2006 | 72 days | | |
| | | | ESL 800 mg | 15 Mar 2006 | 10 Apr 2006 | 27 days | | |
| | | | ESL 400 mg | 07 Dec 2005 | 14 Mar 2006 | 98 days | | |
| Phase III | 2093-302 Part 2 | 334/80101 | ESL 800 mg | 09 Sep 2005 | 17 Jun 2007 | 647 days | | Normal Delivery |
| Phase III | 2093-303 Part 1 | 701/70224 | None (baseline) | NA | NA | 0 days | | Normal Delivery |
| Phase III | 2093-303 Part 1 | 709/70324 | None (baseline) | NA | NA | 0 days | | Normal Delivery |
| Phase III | 2093-303 Part 2 | 712/70062 | ESL 800 mg | 28 Jul 2006 | 28 Nov 2007 | 489 days | | Normal Delivery |
| Phase III | 2093-303 Part 2 | 712/70064 | ESL 800 mg | 31 Aug 2006 | 13 Jul 2007 | 317 days[a] | | Normal Delivery |
| | | | ESL 400 mg | 13 Aug 2006 | 30 Aug 2006 | 18 days | | |
| Phase III | 2093-304 Part 1 | 801-01 | Blinded (ESL 800 mg or 1200 mg or placebo) | 27 Jan 2009 | 20 Mar 2009 | 53 days | | Induced Abortion |

Abbreviations: ESL=eslicarbazepine acetate; mg=milligram; NA=not applicable.
a Includes 2 weeks of placebo treatment during the tapering-off period.

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### 7.6.3 Pediatrics and Assessment of Effects on Growth

Not addressed.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The primary reviewer for Controlled Substance (CSS) review was Dr. A. Lerner. Her review of 12-07-09 may be found in DARRTs. The reader is referred to this review for detailed review. The major conclusions of Dr. Lerner's review are listed below:

- the profile of ESL resembled sedative-hypnotic drugs, specifically the benzodiazepines
- the preclinical abuse studies are limited by design and do not provide enough data to fully assess the abuse potential of ESL
- there are significant problems in the methodology and conduct of the clinical studies that prevent an accurate and adequate assessment of abuse potential.

A memo from the CSS review staff dated 3-19-10 addresses a letter from Sepracor dated 2-10-20 in which the sponsor responded to CSS comments of 1-4-10 and 1-13-10. The memo is available in DARRTS and only a summary is described in this review.

The 3-19-10 memo states that although Sepracor provided additional information regarding preclinical abuse studies conducted with eslicarbazepine, the data do not provide convincing evidence of the absence of abuse potential.

The opinion of the CSS review staff is that the data submitted in preclinical studies show evidence of anxiolytic activity, sedation, and muscle relaxation resulting from eslicarbazepine administration. CSS also indicates they consider the negative results in the mouse cognition study as not able to be validated because the dose cannot be justified.

In terms of clinical memory impairment, CSS is in disagreement with Sepracor and concludes that eslicarbazepine produces memory impairment in humans. CSS notes areas of the study report from study 123 as supportive.

In terms of abnormal coordination, CSS does not believe the incidence is low and states this was the fourth most commonly reported neurological adverse event in clinical trials.

In terms of withdrawal effects, CSS indicates that the data for subjects with abrupt withdrawal from ESL presented in Table 22.1.1-1 do not allow an adequate assessment of physical dependence due to methodology and data quality issues.

CSS makes four recommendations for the sponsor in order for the sponsor to provide adequate data for the assessment of whether eslicarbazepine has abuse potential. These are listed below.

- CSS recommends the conduct of a human abuse potential study with eslicarbazepine that is well-designed.
- CSS recommends a two-week prospective evaluation of physical dependence at the conclusion of the new clinical efficacy study.
- CSS recommends updating of the reporting of adverse events in clinical studies to the most recent version of MedDRA used in the NDA (version 10) by using verbatim descriptions that occurred in clinical trials
- CSS recommends the sponsor provide an analysis of all abuse-related adverse events, using the terms provided previously by CSS.

## 7.7 Additional Submissions / Safety Issues

There were about 30 NDA submissions to the FDA EDR. Not all were clinically based.

**RASH AND HYPERSENSITIVITY:**
**RASH**
The occurrence of rash was seen in more ESL patients than in those on placebo. As per the ISS, there were no fatal or life-threatening dermatologic reactions like SJS or TEN reported in the ESL development program. There is a phase 1 subject reportedly on ESL + lamotrigine with a rash and findings consistent with SJS spectrum (119-004) and there have been medically significant rashes (or exanthema), including one considered as serious in a phase 3 epilepsy study.

- subject 119-004- The ISS narrative is in the discontinuation section and indicates the subject was on ESL 1200 mg + Lamotrigine 150 mg. The CRF indicates the subject was hospitalized for one night ( (b) (6) -CRF page 122- "transfer to hospital demanded by Dr. "). From a handwritten note on a comment page in the CRF (page 125/139), which is somewhat difficult to read due to copy quality and handwriting, it appears this subject had a macular rash, facial swelling and/or lip swelling, sore ulceration in the mucosa of the lower lip, and perhaps an increased temperature ("Clinical Event Report" - fever on (b) (6) . A "Clinical Event Report" page indicates the subject apparently complained of "sore inside mouth" a day after hospital discharge and there appears to have been exfoliation ("peeling all over the body" on (b) (6) , p.134 of CRF). On (b) (6) , subject apparently complained of "feels his tongue is swelling". ALT was increased (value 152 U/L-no reference range given). AST was increased at 62 U/L, LDH at 291 U/L, GGT increased at 146 U/L. He appears to have been treated with solumedrol on (b) (6) . Although hospitalized, the CRF does not seem to indicate this was an SAE but indicates patient withdrawn for safety reasons. As reported, the SAE is confounded by lamotrigine, which is labeled for serious skin reactions.
- In phase 3 epilepsy studies, one "serious dermatological reaction coded as exanthema was noted" (301-111-90341). This was in a 37 year-old female who developed a severe "exanthem" 14 days after randomization to ESL 1200. The rash was preceded by fever of 39.8°C six days before the rash. The subject was hospitalized due to the rash. Laboratory testing in the hospital indicated an elevated C-reactive protein, leukopenia, anemia, thrombocytopenia ($97x10^9$/L), increased LDH, AST, and GGT, and "mildly" reduced gamma globulin. Hepatitis B, C, and HIV screening were negative. CBZ level was therapeutic range. The patient was treated with steroids, an antihistamine, and an antibiotic. Study medication was discontinued.
- 2 serious cases of rash in ongoing or clinically completed but not reported studies (as per the SU, there is updated information for these studies that has not been fully reviewed). One case was in a 73 year old female receiving study drug for post-herpetic neuralgia who developed a maculo-papular rash 13 days after starting study medication. She was hospitalized and treated with steroids and anti-histamines. The second was a 4-year old female on study drug for epilepsy who developed exanthema on her face and limbs 2 weeks after receiving study treatment, which disappeared after an hour but re-appeared a week later on the body, limbs, face, neck, and genitals accompanied by fever. The study drug was discontinued and the event is reported resolved after one week.
- Study 126 was a drug-drug interaction study of glicazide with and without ESL. One subject (2093-126-007) experienced a generalized urticarial rash that led to study discontinuation. This subject also experienced a clinically significant decrease in neutrophils, a clinically significant increase in ALT (74 units with ULN at 31), and a clinically significant increase in C-reactive protein associated with the rash. CRF laboratory slip is not in English but it looks like eosinophils were

above the reference range on 11-16-07 and both AST and ALT were high on 11-15-07 (at 66 UI/L and 96 UI/L with reference range of < 32 and <31 respectively). IV steroids were given on 11-14 for the urticaria and rash. Per CRF (p. 52/58 or 59/91), these events started 11-14 and ended on 11-27. The narrative of this event (p.238/290 SU) does not contain the information about the laboratory elevations although text on page 189/290 does.

**Phase 1**: In the summary sections about rash in the ISS and SU, there is no discussion of phase 1 data. FDA inquired as to the location of comprehensive listings of death, SAEs, and discontinuations. Listing 6.3 (all treatment emergent adverse events in subjects discontinued due to adverse event) was included in a 9-29-09 information amendment and included listings. In this listing, it is not always clear which event led to discontinuation as there is no event marked as leading to discontinuation (126-000-7). It also is not always clear as to whether the person was on ESL alone or with another drug in study 119. With this said, from this listing, it appears there were at least 12 discontinuations in phase 1 studies in which one adverse event listed was rash, urticaria, pruritus, or "hypersensitivity" (see appendix of this document for patient numbers). Most seem to have been on an ESL dose. In two cases, the treatment at the time is noted to be placebo (116-001-23 with localized rash) and 123-000-9013 with rash, although 2 days earlier was on ESL 900 mg). At least one seems to have been an SAE and suggest a serious event (119-004 described below) although the event itself is confounded by concomitant lamotrigine.

In these rashes, some were treated with antihistamines, at least one was treated with a steroid (16-001-023 -1200 mg ESL). There was a rash in study 119 that appears to have been an SAE (subject 119-004). This was discussed above.

**SUBJECTS IN PHASE 1 with discontinuations and rash in listing 6.3:**

| | | |
|---|---|---|
| 110-000-0001 | ESL 900 mg | urticaria and diffuse macular rash |
| 114-000-00014 | ESL 1200 mg | generalized erythematous rash (with pruritus) |
| 116-001-20 | ESL 2400 mg | pruritus |
| 116-001-23 | ESL 1200 mg | rash and pruritus same day (also localized rash with placebo) |
| 116-001-34 | ESL 2400 mg | rash (had fever and headache same day) |
| 116-001-66 | ESL 2400 mg | headache as discontinuation but facial rash same day (mild) |
| 119-000-04 | ESL 1200 mg | hypersensitivity |
| 119-000-23 | ESL 1200 mg | hypersensitivity |
| 120-000-15 | ESL 1200 mg | generalized rash and itchiness arms and legs |
| 121-000-28 | ESL 1200 mg | hypersensitivity syndrome |
| 121-000-9013 | placebo | withdrawn secondary to sore throat, also with rash 4 days earlier, seems first treatment may have been ESL 90 mg on 9-16, had nausea, then started placebo |
| 126-000-7 | ESL 1200 mg | generalized urticariform rash |

**Data from Listing 6.3 of 9-29-09 information amendment. In some cases, it is not clear which event led to discontinuation and these are not all events listed for these patients.**

**HYPERSENSITIVITY:** Drug hypersensitivity can include localized and systemic symptoms and signs and range from benign to life-threatening/fatal. The sponsor performed an analysis of adverse events with MedDRA higher level terms of "Angioedema", "Uriticaria", and "Allergic Conditions NEC" on the data from the pooled phase 3 trials, study 301-part 2, study 201, and studies 203-205. These data were presented in the ISS.

The sponsor states there were no serious events or cases of anaphylaxis or multi-organ hypersensitivity in the pooled phase 3 studies, part 2 of study 301, study 201, or studies 203-205 (ISS page 167). There was a case with facial edema as the preferred term (303-506-70094) which resulted in discontinuation (subject 2093-303-4506-70094). Facial edema can be consistent with angioedema.

**Seizures (Absence and Partial Complex Seizures Increased are both described in the ISS section of special events, but are described separately and separated by discussion of depression, suicidality, hypothyroidism, and nausea and vomiting. The two seizure types are discussed in this section for simplicity.)**

Absence: The CSS submitted with the SU states that there were no reports of petit mal seizures in the pooled phase 3 studies (parts 1 and 2) and no events of absence seizures from study 201.

Other seizure: As per the ISS, overall treatment-emergent complex partial seizures were comparable between placebo and active treatment groups (0.7% of the placebo group, 1.5% of the ESL 400 mg group, 0.4% of the ESL 800 mg group, and 1.1% of the ESL 1200 mg group experienced partial complex seizures as a treatment-emergent AE. Convulsions were reported (pooled phase 3) in 6 placebo subjects (2.1%), 3 ESL 400 mg subjects (1.4%), 3 ESL 800 mg subjects (1.1%), and 2 ESL 1200 mg subjects (0.7%). Epilepsy was reported in 2 (0.7%) subjects on placebo and 1 (0.4%) subject on ESL 1200 mg. No subjects in either of the 400 mg or 800 mg treatment groups experienced "epilepsy" (p. 195/582). The ISS reports that concomitant administration of 2 or 3 AEDs did not increase the incidence of convulsions. The ISS reports that the incidence of convulsions was not increased with concomitant ELS and carbamazepine, lamotrigine, valproic acid, or levetiracetam. The sponsor concludes there is no indication for potential exacerbation of seizures during treatment with ESL.

Seizure SAEs**:** Two ESL subjects experienced serious events. One subject in the ESL 400 mg group had complex partial seizures reported as serious and another subject in the 400 mg group had a serious event of "grand mal convulsion".

As a reason for discontinuation in part 1 of study 301, 302, or 303: "Convulsion", Complex Partial Seizures" 0.7% of placebo (2/289), compared to 0.5% (1/196) of the ESL 400 mg group, 0% of the ESL 800 mg group, 0.75 (2/280) of the ESL 1200 mg group. (based on Table 7.7.1 of the ISS). Using the dataset ADAE2.xpt from the SU submission (safety population, part 1 data, action taken = patient withdrawn), 5 subjects experienced seizure events resulting in discontinuation (subjects 301-193-90148 and 302-338-80236 on 1200 mg ESL, subject 302-306-80607 on 400 mg ESL, and subjects 303-517-70106 and 303-613-70131 on placebo).

Data from phase 1 or other indications are not described in this section of the ISS or specifically described in the SU.

T**HYROID**
The development program does not allow for conclusions about thyroid functioning as TSH was not measured. Free T3 and T4 were examined for the pooled phase 3 studies 301-302. Thyroid function was not assessed in study 303.

Adverse events: In part 1, SU table 4.1.4.4-1 indicates there was one event of hypothyroidism (1200 mg ESL) in the pooled part 1 population of studies 301 and 302 and one of "Tri-iodothyronine free decreased" (400 mg ESL). None are reported in study 303. The ISS reports that no cases of hypothyroidism or decreases in thyroid were reported in study 201.

Exploration of the integrated safety dataset ( in the 8-28-09 submission) indicates there were six subjects in the phase 3 epilepsy studies with an AE related to thyroid function based on search string searching for AETERMs containing "hyp" or "tri" or "low" or "thy".

| Subject Number | Treatment assigned | AETERM | AEPERIOD |
|---|---|---|---|
| 2093302-338-80172 | PLACEBO | HYPOTIREODISM | OPEN LABEL |
| 2093302-307-80624 | ESL 400 mg | HYPOTHIROIDISM | OPEN LABEL |
| 2093302-385-80426 | ESL 400 mg | HYPOTHYROIDISM | OPEN LABEL |
| 2093302-307-80642 | ESL 800 mg | HYPOTHIROIDISM | OPEN LABEL |
| 2093302-331-80151 | ESL 1200 mg | HYPOTHYROIDISM | MAINTENANCE |
| 2093302-382-80444 | ESL 400 mg | LOW T3 LEVEL | MAINTENANCE |
| 2093302-382-80444 | ESL 400 mg | LOW T3 LEVEL (LAB RESULT) | OPEN LABEL |

**ADAE2.xpt search strings containing "hyp" or "tri" or "low" or thy"**

**Phase 1:**
STUDY 118: (Information from ISS) This study was conducted in the U.S.

This was a randomized, double-blind, placebo-controlled sequential, multiple ascending dose study in healthy volunteers performed for safety and pharmacokinetic data. The

primary objective was to determine a maximum-tolerated supratherapeutic ESL dose that could be safely administered in a thorough QT study. There were 4 treatment groups of 8 subjects each. These subjects were to receive single doses of ESL or placebo daily for 5 days. Originally, the doses were to be 3600 mg, 4800 mg, 6000 mg, and 7200 mg ESL. After the 3600 mg group, dosing was reduced to 3000 mg.

16 subjects were enrolled and treated. The first cohort received 3600 mg ESL with 5 subjects receiving 2 of the 5 planned daily doses and 1 receiving one of the doses. In the 2nd cohort, 5 subjects received 2 daily doses of 3000 mg ESL and one subject received one dose. Placebo was received by 4 subjects (2 doses). Vomiting was reported in 50% of subjects in the 3600 mg cohort and 66% in the 3000 mg cohort. No placebo subjects vomited. Nausea was reported by 16.7% in the ESL group and ¼ of the placebo group. No serious or severe events are reported. In ESL-treated subjects, 50% of the subjects discontinued secondary to vomiting. The sponsor reports that the intensity of AES did suggest a dose-related trend. The sponsor stopped dosing in each cohort secondary to vomiting.

**MYOCARDIAL INFARCTION AND STROKE-** please see section 7.3.5

# 8 Postmarket Experience

Not Applicable.

# 9 Appendices

## 9.1 Tables and Figures not included in the review text

Table xx- Sponsor's Table 9-4 (from 1-25-10 submission) referenced in Quality section of review

**Table 9-4: Serious Adverse Events Excluded from Table 3 in the 74-day Response**

| Subject Number | Treatment Group | Treatment Start Date | Last Dose Date | SAE Start Date (b) (6) | Reported Term | Preferred Term |
|---|---|---|---|---|---|---|
| 2093-203-335-203087 | ESL 800 mg | 7 Apr 06 | 19 Apr 06 | | Manic episode | Mania |
| 2093-204-471-204110 | ESL 1800 mg | 1 Aug 06 | 4 Aug 06 | | Manic episode | Mania |
| 2093-204-488-204211 | Placebo | 19 Sep 06 | 20 Sep 06 | | Worsening of manic symptoms | Mania |
| 2093-205-543-203144 | ESL 900 mg | 31 Mar 06 | 28 Aug 06 | | Inferior esofagian stenosis | Oesophageal stenosis |
| 2093-205-548-203064 | ESL 300 mg | 16 Jun 06 | 3 Jul 06 | | Mania | Mania |
| 2093-301-111-90341 | ESL 1200 mg | 3 Feb 05 | 15 Feb 05 | | Exanthema | Exanthem |
| 2093-301-124-90357 | Placebo | 10 Jan 05 | 12 Jun 05 | | Intoxication | Drug toxicity |
| 2093-301-161-90069 | ESL 800 mg | 22 Sep 04 | 25 Jan 06 | | Status epilepticus | Convulsion |
| 2093-301-182-90023 | Placebo | 28 Mar 05 | 20 Jun 05 | | Paraesthesia of left arm and leg and right leg | Paraesthesia |
| 2093-301-192-90259 | ESL 800 mg | 12 May 05 | 25 May 05 | | Stomach ulcer | Gastric ulcer |
| 2093-301-214-90041 | ESL 400 mg | 22 Dec 04 | 28 Jan 06 | | Psychogenic paranoid psychosis | Delusional disorder, persecutory type |
| 2093-301-214-90215 | ESL 1200 mg | 2 Feb 05 | 4 Oct 06 | | Acute lymphadenitis | Lymphadenitis |
| 2093-302-334-80097 | ESL 400 mg | 11 Mar 05 | 12 Jun 05 | | Worsening depression | Depression |
| 2093-302-334-80097 | ESL 400 mg | 11 Mar 05 | 12 Jun 05 | | Vomiting | Vomiting |
| 2093-302-336-80067 | ESL 1200 mg | 5 Jan 05 | 30 May 07 | | Atoxia | Coordination abnormal |
| 2093-302-395-80742 | ESL 400 mg | 30 Mar 06 | 27 Jun 07 | | Seizures | Convulsion |
| 2093-303-601-70156 | ESL 800 mg | 28 Jun 05 | 11 Nov 05 | | Hyponatremia | Hyponatraemia |
| 2093-303-601-70156 | ESL 800 mg | 28 Jun 05 | 11 Nov 05 | | Infection urinary | Urinary tract infection |

Reference: Data on file at Sepracor.

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Table xx (sponsor table 1.4.5-2)

**Table 1.4.5-2: Major Entry Criteria and Primary Endpoint of Last Five New AEDs Approved in US Compared with ESL Pivotal Study Entry Criteria**

| Drug | Study # | Age (years) | Diagnosis | Baseline Seizure Criteria | Primary Endpoint |
|---|---|---|---|---|---|
| Vimpat® (lacosamide) | SP667<br>SP754<br>SP755 | 18-65<br>16-70<br>16-70 | All studies: simple (with motor signs) and/or complex partial seizures with or without secondary generalization, per ICES | All studies: At least 4 partial-onset seizures per 28 days with seizure-free phases no longer than 21 days during the 8 week baseline period. | Percent change in seizure frequency per 28 days |
| Lyrica® (pregabalin) | 009<br>011<br>034 | ≥18<br>≥18<br>12-70[c] | 009: Partial seizures per ICES<br>011: Partial seizures: simple, complex or secondarily generalized tonic clonic, per ICES[a]<br>034: Partial seizures, per ICES | All studies: 6 seizures during the 8 week baseline period with no 4-week seizure-free period. | Responder ratio= [(treatment – baseline)/ (treatment + baseline)] x 100 |
| Zonegran® (zonisamide) | 912-US<br>912-EUR<br>922 | 18-65<br>18-65<br>≥12 | 912-US and 912-EUR: Complex partial seizures, per ICES<br>922: Complex or simple partial seizures (with motor signs) with or without secondary generalization, per ICES | 912-US and 912-EUR: At least 4 complex partial seizures per month<br>922: At least 4 seizures per month and not seizure-free for more than 30 consecutive days | Percent change in seizure frequency per 28 days |
| Trileptal® (oxcarbazepine) | OT/PE1 | 15-65 | Simple or complex partial seizures with or without secondary generalization | At least 4 per 28 days during the 8 week baseline period. | Percent change in seizure frequency per 28 days |
| Keppra® (levetiracetam) | N051<br>N132 | 16-65<br>16-70 | N051: Partial-onset seizures, per ICES<br>N132: Simple and/or complex partial seizures with or without secondary generalization | N051: At least 4 seizures in each 4 week period of the baseline period<br>N132: At least 12 partial-onset seizures in 12 weeks, with at least 2 seizures per 4 week period | Standardized seizure frequency per 1 week |
| ESL | 2093-301<br>2093-302 | ≥18<br>≥18 | Both studies: Simple or complex partial seizures with or without secondary generalization, per ILAE (ICES) | Both studies: At least 4 partial seizures in each 4-week period during the 8-week baseline period with no seizure-free interval more than 21 consecutive days. | Standardized seizure frequency per 4 weeks |

Abbreviations: ESL=eslicarbazepine acetate; ICES=International Classification of Epilepsy Seizures; ILAE=International League Against Epilepsy
Reference: NDA NDA SBAs for Vimpat™ (22-253), Lyrica® (21-724), Zonegran® (20-789), Trileptal® (21-014) and Keppra® (21-035) except where noted:
[a]Arroyo 2004[8]

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Table xx (sponsor table 3.3.2.5-2)

**Table 3.3.2.5-2: Baseline Concomitant Use of AEDs for the Last Five New AEDs Approved in US Compared with ESL**

| Drug | Study # (Region) % Subjects using AED | | |
|---|---|---|---|
| Vimpat™ (lacosamide) | Study SP667 (US/EUR)<br>Carbamazepine 21-41%<br>Levetiracetam 26-38%<br>Lamotrigine 23-32%<br>Topiramate 16-26%<br>Oxcarbazepine 15-21% | Study SP754 (US)<br>Levetiracetam 40%<br>Lamotrigine 36%<br>Carbamazepine 25%<br>Oxcarbazepine 21%<br>Phenytoin 19% | Study SP755 (EUR/AUS)<br>Carbamazepine 48%<br>Valproate 33%<br>Lamotrigine 31%<br>Topiramate 28%<br>Levetiracetam 20% |
| Lyrica® (pregabalin) | Study 009 (US/CAN)<br>Carbamazepine 58%<br>Lamotrigine 33%<br>Phenytoin 22%<br>Topiramate 22%<br>Valproate 11% | Study 011 (EUR)<br>Carbamazepine 61%<br>Lamotrigine 33%<br>Topiramate 19%<br>Clobazam 17%<br>Phenytoin 14% | Study 034 (US/CAN)<br>Carbamazepine 52%<br>Phenytoin 29%<br>Lamotrigine 22%<br>Valproate 19%<br>Topiramate 17% |
| Zonegran® (zonisamide) | Study 912-US (US)<br>Carbamazepine<br>Phenytoin<br>Primidone<br>Phenobarbital | Study 912-EUR (EUR)<br>Carbamazepine<br>Phenytoin<br>Primidone<br>Phenobarbital<br>Valproate | Study 922 (US)<br>Carbamazepine<br>Phenytoin<br>Valproate<br>Phenobarbital<br>Primidone |
| Trileptal® (oxcarbazepine) | Study OT/PE1 (Ex-US)[a]<br>Carbamazepine 71-78%<br>Valproic acid 20-29%<br>Phenytoin 18-26%<br>Phenobarbital 14-16%<br>Vigabatrin 12-16% | NA | NA |
| Keppra® (levetiracetam) | Study N051 (EUR)<br>Carbamazepine 71-75%<br>Phenytoin 20-27%<br>Valproic Acid 19-24%<br>Lamotrigine 10-13%<br>Clobazam 8-11% | Study N132 (US)<br>Carbamazepine 53-62%<br>Phenytoin 30-38%<br>Valproic Acid 24-29%<br>Gabapentin 24-36%<br>Phenobarbital 7-10% | NA |
| ESL | Study 301 (EUR)<br>Carbamazepine 58%<br>Lamotrigine 26%<br>Valproic acid 26%<br>Topiramate 14%<br>Levetiracetam 8% | Study 302 (Ex-US)<br>Carbamazepine 60%<br>Valproic acid 22%<br>Lamotrigine 21%<br>Clobazam 17%<br>Levetiracetam 16% | NA |

Abbreviations: AUS=Australia; CAN=Canada; EUR=Europe; ESL=eslicarbazepine acetate; NA=not applicable; US=United States

Reference: NDA SBAs for Vimpat™ (22-253), Lyrica® (21-724), Zonegran® (20-789), Trileptal® (21-014) and Keppra® (21-035) except where noted: [a]Barcs 2000[12].

**Table below from CSE page 77/175**

**Table 3.3.2.5-2: Baseline Concomitant Use of AEDs for the Last Five New AEDs Approved in US Compared with ESL**

| Drug | Study # (Region) % Subjects using AED | | |
|---|---|---|---|
| Vimpat™ (lacosamide) | Study SP667 (US/EUR)<br>Carbamazepine 21-41%<br>Levetiracetam 26-38%<br>Lamotrigine 23-32%<br>Topiramate 16-26%<br>Oxcarbazepine 15-21% | Study SP754 (US)<br>Levetiracetam 40%<br>Lamotrigine 36%<br>Carbamazepine 25%<br>Oxcarbazepine 21%<br>Phenytoin 19% | Study SP755 (EUR/AUS)<br>Carbamazepine 48%<br>Valproate 33%<br>Lamotrigine 31%<br>Topiramate 28%<br>Levetiracetam 20% |
| Lyrica® (pregabalin) | Study 009 (US/CAN)<br>Carbamazepine 58%<br>Lamotrigine 33%<br>Phenytoin 22%<br>Topiramate 22%<br>Valproate 11% | Study 011 (EUR)<br>Carbamazepine 61%<br>Lamotrigine 33%<br>Topiramate 19%<br>Clobazam 17%<br>Phenytoin 14% | Study 034 (US/CAN)<br>Carbamazepine 52%<br>Phenytoin 29%<br>Lamotrigine 22%<br>Valproate 19%<br>Topiramate 17% |
| Zonegran® (zonisamide) | Study 912-US (US)<br>Carbamazepine<br>Phenytoin<br>Primidone<br>Phenobarbital | Study 912-EUR (EUR)<br>Carbamazepine<br>Phenytoin<br>Primidone<br>Phenobarbital<br>Valproate | Study 922 (US)<br>Carbamazepine<br>Phenytoin<br>Valproate<br>Phenobarbital<br>Primidone |
| Trileptal® (oxcarbazepine) | Study OT/PE1 (Ex-US)[a]<br>Carbamazepine 71-78%<br>Valproic acid 20-29%<br>Phenytoin 18-26%<br>Phenobarbital 14-16%<br>Vigabatrin 12-16% | NA | NA |
| Keppra® (levetiracetam) | Study N051 (EUR)<br>Carbamazepine 71-75%<br>Phenytoin 20-27%<br>Valproic Acid 19-24%<br>Lamotrigine 10-13%<br>Clobazam 8-11% | Study N132 (US)<br>Carbamazepine 53-62%<br>Phenytoin 30-38%<br>Valproic Acid 24-29%<br>Gabapentin 24-36%<br>Phenobarbital 7-10% | NA |
| ESL | Study 301 (EUR)<br>Carbamazepine 58%<br>Lamotrigine 26%<br>Valproic acid 26%<br>Topiramate 14%<br>Levetiracetam 8% | Study 302 (Ex-US)<br>Carbamazepine 60%<br>Valproic acid 22%<br>Lamotrigine 21%<br>Clobazam 17%<br>Levetiracetam 16% | NA |

Abbreviations: AUS=Australia; CAN=Canada; EUR=Europe; ESL=eslicarbazepine acetate; NA=not applicable; US=United States

Reference: NDA SBAs for Vimpat™ (22-253), Lyrica® (21-724), Zonegran® (20-789), Trileptal® (21-014) and Keppra® (21-035) except where noted: [a]Barcs 2000[12].

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**CRF excerpts**

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**Table 4.1.4.2-1**

Table 4.1.4.2-1: Serious Treatment-Emergent Adverse Events by Overall Treatment Group for Part 1 of the Phase III Studies (2093-301 and 2093-302 Pooled vs 2093-303) (Safety Population)

| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | Studies 2093-301 and 2093-302 Pooled | | | | Study 2093-303 | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo (N=202) | | Total ESL (N=595) | | Placebo (N=87) | | Total ESL (N=165) | |
| | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n |
| AT LEAST 1 SAE | 4 (2.0) | 4 | 27 (4.5) | 45 | 0 | 0 | 1 (0.6) | 1 |
| NERVOUS SYSTEM DISORDERS | 1 (0.5) | 1 | 12 (2.0) | 13 | 0 | 0 | 1 (0.6) | 1 |
| Abnormal coordination | 0 | 0 | 4 (0.7) | 5 | 0 | 0 | 0 | 0 |
| Convulsion | 0 | 0 | 2 (0.3) | 2 | 0 | 0 | 0 | 0 |
| Dizziness | 0 | 0 | 2 (0.3) | 2 | 0 | 0 | 0 | 0 |
| Ataxia | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Complex partial seizures | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Grand mal convulsion | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Vasculitis cerebral | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Paresthesia | 1 (0.5) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cerebellar syndrome | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.6) | 1 |
| GASTROINTESTINAL DISORDERS | 0 | 0 | 8 (1.3) | 9 | 0 | 0 | 0 | 0 |
| Vomiting | 0 | 0 | 4 (0.7) | 5 | 0 | 0 | 0 | 0 |
| Constipation | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Gastric disorder | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Gastric ulcer | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Nausea | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| INJURY, POISONING, & PROCEDURAL COMPLICATIONS | 0 | 0 | 4 (0.7) | 5 | 0 | 0 | 0 | 0 |
| Drug toxicity | 0 | 0 | 3 (0.5) | 3 | 0 | 0 | 0 | 0 |
| Brain contusion | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Traumatic brain injury | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| EAR & LABYRINTH DISORDERS | 0 | 0 | 3 (0.5) | 3 | 0 | 0 | 0 | 0 |
| Vertigo | 0 | 0 | 3 (0.5) | 3 | 0 | 0 | 0 | 0 |
| EYE DISORDERS | 0 | 0 | 3 (0.5) | 3 | 0 | 0 | 0 | 0 |
| Diplopia | 0 | 0 | 3 (0.5) | 3 | 0 | 0 | 0 | 0 |
| PSYCHIATRIC DISORDERS | 0 | 0 | 2 (0.3) | 3 | 0 | 0 | 0 | 0 |
| Depression | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Nervousness | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Psychotic disorder | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| CARDIAC DISORDERS | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Angina pectoris | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| INFECTIONS & INFESTATIONS | 1 (0.5) | 1 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Gastroenteritis | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Pneumonia primary atypical | 1 (0.5) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | Studies 2093-301 and 2093-302 Pooled | | | | Study 2093-303 | | | |
|---|---|---|---|---|---|---|---|---|
| | Placebo (N=202) | | Total ESL (N=595) | | Placebo (N=87) | | Total ESL (N=165) | |
| | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n |
| METABOLISM & NUTRITION DISORDERS | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Hyponatremia | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| NEOPLASMS BENIGN, MALIGNANT & UNSPECIFIED (INCL CYSTS & POLYPS) | 1 (0.5) | 1 | 1 (0.2) | 2 | 0 | 0 | 0 | 0 |
| Follicle center lymphoma, follicular Grade I, II, III | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Lymphoma | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Fibroadenoma of breast | 1 (0.5) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| RENAL & URINARY DISORDERS | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Acute renal failure | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| REPRODUCTIVE SYSTEM & BREAST DISORDERS | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Endometriosis | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| SKIN & SUBCUTANEOUS TISSUE DISORDERS | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Exanthem | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| VASCULAR DISORDERS | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| Hypertensive crisis | 0 | 0 | 1 (0.2) | 1 | 0 | 0 | 0 | 0 |
| GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS | 1 (0.5) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Death (hypothermia) | 1 (0.5) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; SAE=serious adverse event; SU=120-day safety update.

a Reported AE terms were coded using the MedDRA version 7.0 dictionary for Study 2093-301 and version 9.0 for Studies 2093-302 and 2093-303.

Note: The titration, maintenance, and tapering-off periods were combined. Study 2093-302 did not have a tapering-off period. Treatment-emergent adverse events are those that occurred on or after the date of first dose, or the date of randomization if the date of the first dose was missing. Adverse events with missing or incomplete onset dates were considered to be treatment emergent unless it could be determined that the event began before the treatment period.

Note: Subjects were counted at most once within each system organ class and preferred term.

Reference: SU EOT Tables 5.6.1.1 and 5.6.1.2

**SAE narratives controlled phase of phase 3 epilepsy studies:**

***Reviewer's note: contents not fully verified for accuracy of data or any conclusions***

**Drug toxicity:**

**Two serious events are stated to be related to carbamazepine or AEDs:**

2093302-421-80778 CARBAMAZEPINE TOXICITY- ESL 800 mg **Dizziness, Nausea, Vomiting, and Drug Toxicity-**38 year old female, 53 days after starting SM, dizziness, nausea, vomiting, and drug toxicity, reportedly related to carbamazepine. Treatment not required but stopped

SM about a week later. Narrative reports events resolved 5 days before stopping SM. Concomitant medications at time of event onset were CBZ, VPA, and diazepam.

2093301-142-90178 INTOXICATION WITH CARBAMAZEPINE- **drug toxicity as per the narrative**--1200 mg- 31 year old white female with no significant medical history other than epilepsy, hospitalized 7 days after randomization (on (b) (6)) to ESL 1200 mg for nausea, vertigo, gait difficulties, and equilibrium disturbance. Carbamazepine level was high at 14. Carbamazepine dose decreased. Carbamazepine level was 11.2. Drug toxicity reportedly resolved on (b) (6)

2093301-146-90192- **ataxia, vertigo**-400 mg- hospitalized 2 days after randomization to 400 mg ESL with ataxia and vertigo. Vertigo started about 3 hours after receiving study drug and he presented with vertigo, unstable gait with tendency to fall, nausea, and relapsing vomiting (confounded with cohabitants also reporting nausea and vomiting so question of food poisoning but not confirmed). Concomitant medications included valproic acid, lamotrigine, and clobazepam. Based on local labs results and reference ranges the subject's lamotrigine level was out of range at 21 (reported toxic at 15). 5 days after presenting, the subject was discharged from the hospital with events of ataxia and vertigo considered resolved 11 days after starting (b) (6) CRF indicates study medication stopped on (b) (6) due to vertigo and ataxia.

301-122-90387- **vertigo, "insecurity in space", loss of memory, intermittent vision loss, headache, and appetite loss**- 1200 mg-Narrative indicates 17 days after randomization to 1200 mg ESL. CRF data clarification indicates diplopia and nausea led to discontinuation of study medication and withdrawal from study.

301-113-90333-**vertigo**-800 mg- 71 year old male with history of epilepsy and arterial hypertension, randomized to 800 mg ESL on (b) (6) Eight days later the subject was hospitalized with vertigo. Vertigo occurred about 3 hours and 20 minutes after his last study medication intake and had occurred for about 2 hours the previous day that was associated with nausea and gait disturbance. Labs are reported as normal as are CT and MRI. Study drug administration was not changed according to the narrative (or CRF).

302-401-80348-**Dizziness** 1200 mg- 69 year old female with history of epilepsy, gait abnormality due to left-sided paresis, right cerebral hemorrhage, right frontal lobe resection, depression, and vagus nerve stimulation experienced dizziness 15 days after first dose of ESL 1200 mg. The narrative reports no treatment was given. The event did not resolve for about 6 weeks. Dataset notes the dizziness was intermittent and she continued to part 2. CRF was reviewed. Not all of diary is translated into English. AE (page 114/330) indicates also with ongoing hypertension since 11-23-2005.

302-334-80094-**Coordination abnormal, vomiting**- 1200 mg ESL- 41 year old female with medical history of epilepsy and skull fracture requiring surgery, randomized to ESL 1200 on (b) (6) who experienced vomiting and abnormal coordination thirteen and 36 days later. At the first episode, study drug was held for one day and metaclopramide was given. Events were considered resolved on 4-7-2005. Study medication reportedly ended on 4-09-2005 although the patient reportedly was hospitalized a 2nd time (b) (6). Vomiting and abnormal coordination were resolved on 5-3-2005 and 5-10-2005 respectively. CRF (page 118/177) indicates the patient was withdrawn after (b) (6) secondary to ataxia and vomiting.

302-334/80097 **Coordination Abnormal, Diplopia, Vomiting, Depression- ESL 400 mg.** 29-year-old female with a history of epilepsy and depression randomized to 400 mg ESL group. She received the first dose of study drug on (b) (6). On (b) (6), 90 days after receiving the first dose of ESL, the subject was hospitalized with coordination abnormal and diplopia. Treatment medication included metoclopramide.

Concomitant medication included carbamazepine, and clobazam. The subject's investigational product was lost during hospitalization and study medication was discontinued on (b) (6). The last dose of study drug was received on (b) (6). The subject reported as asymptomatic on (b) (6) and discharged from the hospital on (b) (6). On (b) (6), 104 days after receiving the first dose of study drug, and 10 days after receiving the last dose of study drug, she was hospitalized with vomiting and depression. The subject was given sertraline for depression. Concomitant medication included carbamazepine and clobazam. The dose of carbamazepine was reduced on (b) (6). The events of vomiting and depression were reported as having resolved (b) (6) and; the subject discharged from the hospital that same day. CRF seems messy, one whole AE page is in as data clarification entries [looks like the AEs were entered on another AE page in the CRF that apparently was not the right location.] AEs of vomiting and ataxia are recorded on (b) (6) and ending on (b) (6) A handwritten comment on page 129/187 indicates the patient discontinued dosage of 400 mg of carbamazepine due to side effects and that carbamazepine dose was resumed on 3-7 as five divided doses.

301-182-90032-**gastric disorder-**1200 mg- 20 year old female with epilepsy and otherwise medical history reported as non-significant who presented with weakness, nausea, vomiting, and diplopia 16 days after being randomized to ESL 1200 mg. EEG revealed spike activity, other workout of labs and EKG are reported as without pathological findings. Abdominal ultrasound reported as no clinically relevant abnormalities. Study medication was interrupted for 1 day, then re-started. The event is reported as resolved about a month after starting. Unable to locate a CRF for this patient.

301-124-90485- 1200 mg -**hypertensive crisis-**49 year old female with history of hypertension, hospitalized 28 days (b) (6) after receiving first dose of study drug with symptoms of diplopia, nausea, seated and standing vertigo, and inability to stand on admission. Symptoms began on (b) (6) and included chest pressure, dyspnea, and intermittent blood pressure elevations. Blood pressure was 210/110, pulse 70, ophthalmologic examination was positive for nystagmus and hypertensive angiosclerosis grade II. The patient was discharged on (b) (6).

302-312-80299-**gastroenteritis**-800 mg-38 year old male with history of epilepsy, acute renal failure, and systemic lupus erythematosus. 35 days after receiving first dose of ESL 800 mg, the subject was hospitalized (b) (6) with gastroenteritis and **acute renal failure.** The SAE narrative reports the renal failure as secondary to gastroenteritis. He was treated for vomiting and dehydration. The event is reported as resolved 2 days after hospitalization. The narrative for the SAE of gastroenteritis does not comment on whether medication was stopped and does not include the history of chronic renal failure that is seen in the narrative for this subject that is in the discontinuation section. The CRF indicates this subject had a fistula placed in the left cubital fossa on (b) (6) for acute on chronic renal failure. This narrative in the discontinuation section indicates he was discontinued from the study on 6-06-06 due to intermittent blurred vision that started on 5-11-06.

301-92-90259-**gastric ulcer**-800 mg- 40 year old male with epilepsy and reported medical history otherwise as non-significant, presented with epigastric pain about 40 days after randomization to the ESL 800 mg group. Subject was hospitalized the next day with a gastric ulcer. Upper GI endoscopy and showed stomach ulcer in the curvature of his stomach. The event is reported as resolved about a month after starting.

301-201-90094-**constipation**- 1200 mg ESL-44 year old male with history of epilepsy and otherwise non-significant medical history was hospitalized 131 days after randomization to ESL 1200 mg with constant abdominal pain. Abdominal film showed intestinal air but no free intra-abdominal air. The subject was treated with laxatives.

301-145-90194-**angina pectoris**-800 mg-35 year old male with reported non-significant medical history other than simple or complex partial seizures, 74 days after randomization to ESL 800 mg, subject hospitalized with thoracic pressure complaints. Troponin and EKG reported without

pathologic findings and sinus rhythm, respectively. Transthoracic echo is reported as revealing no pathology. X ray is reported to have revealed “Beckwith-Wiedemann syndrome with moderate scoliosis”. He was treated with acetylsalicylic acid. His event “angina pectoris” was considered resolved about 4 days.

## TABLE 5.5.2-1 of the SU-Treatment Emergent SAES for phase 3 extensions, (part 2 of studies 301,302, and 303)

**Table 5.5.2-1: Treatment-Emergent Serious Adverse Events for the Phase III Extensions (Part 2 of 2093-301, 2093-302, and 2093-303) (Safety Population)**

| MedDRA* SYSTEM ORGAN CLASS Preferred term | 400-1200 mg ESL QD | | | | | |
|---|---|---|---|---|---|---|
| | Studies 2093-301, 2093-302, and 2093-303 Pooled (N=835) | | Studies 2093-301 and 2093-302 Pooled (N=639) | | Study 2093-303 (N=196) | |
| | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n |
| ANY TREATMENT-EMERGENT SAE | 58 (6.9) | 76 | 47 (7.4) | 63 | 11 (5.6) | 13 |
| NERVOUS SYSTEM DISORDERS | 21 (2.5) | 22 | 18 (2.8) | 19 | 3 (1.5) | 3 |
| Convulsion | 4 (0.5) | 4 | 4 (0.6) | 4 | 0 | 0 |
| Grand mal convulsion | 4 (0.5) | 4 | 4 (0.6) | 4 | 0 | 0 |
| Status epilepticus | 4 (0.5) | 4 | 3 (0.5) | 3 | 1 (0.5) | 1 |
| Somnolence | 2 (0.2) | 2 | 2 (0.3) | 2 | 0 | 0 |
| Cerebellar syndrome | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| Complex partial seizures | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Coordination abnormal | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Hemiparesis | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Nervous system disorder | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Postictal state | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Psychomotor hyperactivity | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Transient ischemic attack | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| INJURY, POISONING, & PROCEDURAL COMPLICATIONS | 15 (1.8) | 16 | 11 (1.7) | 11 | 4 (2.0) | 5 |
| Drug toxicity | 3 (0.4) | 3 | 3 (0.5) | 3 | 0 | 0 |
| Head injury | 2 (0.2) | 2 | 2 (0.3) | 2 | 0 | 0 |
| Multiple injuries | 2 (0.2) | 2 | 0 | 0 | 2 (1.0) | 2 |
| Skull fracture | 2 (0.2) | 2 | 1 (0.2) | 1 | 1 (0.5) | 1 |
| Burns third degree | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| Hepatic rupture | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Post procedural hematoma | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| Skin laceration | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Spinal fracture | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Thermal burn | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Traumatic brain injury | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| PSYCHIATRIC DISORDERS | 7 (0.8) | 8 | 7 (1.1) | 8 | 0 | 0 |
| Psychotic disorder | 2 (0.2) | 2 | 2 (0.3) | 2 | 0 | 0 |
| Acute psychosis | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Aggression | 1 (0.1) | 2 | 1 (0.2) | 2 | 0 | 0 |
| Delusion | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Delusional disorder, persecutory type | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Schizoaffective disorder | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS | 5 (0.6) | 5 | 5 (0.8) | 5 | 0 | 0 |
| Drowning | 2 (0.2) | 2 | 2 (0.3) | 2 | 0 | 0 |
| Asthenia | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Death (drowning) | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Sudden death (severe coronary atherosclerosis) | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |

| MedDRA* SYSTEM ORGAN CLASS Preferred term | 400-1200 mg ESL QD | | | | | |
|---|---|---|---|---|---|---|
| | Studies 2093-301, 2093-302, and 2093-303 Pooled (N=835) | | Studies 2093-301 and 2093-302 Pooled (N=639) | | Study 2093-303 (N=196) | |
| | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n |
| INFECTIONS & INFESTATIONS | 4 (0.5) | 4 | 3 (0.5) | 3 | 1 (0.5) | 1 |
| Otitis media acute | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Pneumonia | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Pyelonephritis | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Urinary tract infection | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| GASTROINTESTINAL DISORDERS | 3 (0.4) | 3 | 3 (0.5) | 3 | 0 | 0 |
| Appendix disorder | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Dyskinesia esophageal | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Nausea | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| NEOPLASMS BENIGN, MALIGNANT & UNSPECIFIED (INCL CYSTS & POLYPS) | 3 (0.4) | 3 | 2 (0.3) | 2 | 1 (0.5) | 1 |
| Colorectal cancer | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Insulinoma | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Neoplasm recurrence | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| CARDIAC DISORDERS | 2 (0.2) | 2 | 2 (0.3) | 2 | 0 | 0 |
| Arteriosclerosis coronary artery | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Atrial flutter | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS | 2 (0.2) | 2 | 1 (0.2) | 1 | 1 (0.5) | 1 |
| Mobility decreased | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Rheumatoid nodule | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| BLOOD & LYMPHATIC SYSTEM DISORDERS | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Lymphadenitis | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| EAR & LABYRINTH DISORDERS | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Vertigo | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| HEPATOBILIARY DISORDERS | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| Hepatitis | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| INVESTIGATIONS | 1 (0.1) | 4 | 1 (0.2) | 4 | 0 | 0 |
| Lymphocyte count decreased | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Monocyte count decreased | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Neutrophil count decreased | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| White blood cell count decreased | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| METABOLISM & NUTRITION DISORDERS | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| Hyponatremia | 1 (0.1) | 1 | 0 | 0 | 1 (0.5) | 1 |
| PREGNANCY, PUERPERIUM & PERINATAL CONDITIONS | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Pregnancy | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |

| MedDRA[a] SYSTEM ORGAN CLASS Preferred term | 400-1200 mg ESL QD | | | | | |
|---|---|---|---|---|---|---|
| | Studies 2093-301, 2093-302, and 2093-303 Pooled (N=835) | | Studies 2093-301 and 2093-302 Pooled (N=639) | | Study 2093-303 (N=196) | |
| | Subjects n (%) | Events n | Subjects n (%) | Events n | Subjects n (%) | Events n |
| REPRODUCTIVE SYSTEM & BREAST DISORDERS | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Ovarian mass | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |
| Pneumonia Aspiration | 1 (0.1) | 1 | 1 (0.2) | 1 | 0 | 0 |

Abbreviations: EOT=end of text; ESL=eslicarbazepine acetate; QD=once daily; SAE=serious adverse event.
a Reported AE terms were coded using the MedDRA version 9.0 dictionary for Part 2 of Study 2093-301 and version 10.0 for Part 2 of Studies 2093-302 and 2093-303.
Note: Treatment-emergent adverse events are those that occurred after the date and time of the first dose of open-label study medication.
Note: Subjects were counted at most once within each system organ class and preferred term.
Reference: SU EOT Tables 16.8, 16.8.1, and 16.8.2

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**Table 4.5-1: Brief Summary of Subject Disposition for the Phase I Healthy Volunteer Studies (Safety Population)**

| Study Number | Subjects Dosed | Completed n (%) | Most Common Reason(s) for Discontinuation: n (%) | Discontinuation Due to an AE: n (%) [Treatment Group] |
|---|---|---|---|---|
| 2093-101 | 64 | 64 (100.0) | NA | 0 |
| 2093-102 | 32 | 32 (100.0) | NA | 0 |
| 2093-103 | 12 | 12 (100.0) | NA | 0 |
| 2093-104 | 13 | 12 (92.3) | Withdrawal of consent: 1 (7.7) | 0 |
| 2093-106 | 4 | 4 (100.0) | NA | 0 |
| 2093-107 | 13 | 12 (92.3) | AE: 1 (7.7) | AE: 1 (7.7) [digoxin+placebo] |
| 2093-108 | 15 | 13 (86.7) | Withdrawal of consent: 1 (6.7)<br>Unstable INR during warfarin dose-finding phase: 1 (6.7) | 0 |
| 2093-109 | 18 | 18 (100.0) | NA | 0 |
| 2093-110 | 12 | 10 (83.3) | AE: 2 (16.7) | AE: 2 (16.7) [450 mg ESL BID, 450 mg BID oxcarbazepine] |
| 2093-113 | 18 | 18 (100.0) | NA | 0 |
| 2093-114 | 20 | 17 (85.0) | AE: 2 (10.0) | AE: 2 (10.0) [both 1200 mg ESL+ ethinylestradiol and levonorgestrel] |
| 2093-115 | 32 | 28 (87.5) | AE: 2 (6.3)<br>Noncompliance: 2 (6.3) | AE: 2 (6.3) [450 mg S-licarbazepine, 450 mg R-licarbazepine] |
| 2093-116 | 67 | 55 (82.1) | AE: 10 (14.9) | AE: 10 (14.9) [1 ABCD, 3 BDAC, 5 CADB, 1 DCBA][a] |
| 2093-117 | 18 | 17 (94.4) | Positive pregnancy test: 1 (5.6) | 0 |
| 2093-118 | 16 | 0 | Sponsor's request[b]: 10 (62.5)<br>AE: 6 (37.5) | AE: 6 (37.5) [3-3600 mg ESL QD, 3-3000 mg ESL QD] |
| 2093-119 | 32 | 28 (87.5) | AE: 2 (6.3) | AE: 2 (6.3) [1200 mg ESL+150 mg lamotrigine (1 each from Group A and B)] |
| 2093-120 | 32 | 27 (84.4) | Withdrawal of consent: 3 (9.4)<br>AE: 2 (6.3) | AE: 2 (6.3) [2x600 mg ESL+100 mg topiramate, 600 mg ESL+200 mg topiramate ] |
| 2093-121 | 32 | 28 (87.5) | AE: 2 (6.3) | AE: 2 (6.3) [1200 mg ESL+300 mg phenytoin] |
| 2093-122 | 60 | 59 (98.3) | Pharmacokinetic: 1 (1.7) | 0 |

Abbreviations: AE=adverse event; ESL=eslicarbazepine acetate; INR=International Normalized Ratio; NA=not applicable.

a The 4 treatments were A=1200 mg ESL QD x 5 days, B=2400 mg ESL QD x 5 days, C=400 mg moxifloxacin x 1 day, D=placebo QD x 5 days.

b In Study 2093-118, supratherapeutic doses of ESL (3000 mg and 3600 mg) were administered to determine the maximum tolerated supratherapeutic dose that could be safely administered in the thorough QT study. The sponsor terminated the study early in accordance with stopping criteria provided in the protocol (Study 2093-118 CSR Sections 8 and 9.1).

Table 8.6.16-6: CPK Elevations in Phase I Studies

| Study No. | Number of Subjects with 1 or More Adverse Events of CPK Elevation | CPK Collected | CPK Details, If Available |
|---|---|---|---|
| 2093-101 | 0 | Yes | Placebo Subject 54 had a result of 1432 IU/L at follow-up (normal range: 2-407 IU/L). |
| 2093-102 | 0 | Yes | All CPK results <3xULN based on data listings. |
| 2093-103 | 0 | Yes | All CPK values <3xULN based on data listing. |
| 2093-104 | 1 | Yes | Subject 104-008 had a result of 1037 IU/L at follow-up. All other CPK values <3xULN based on data listing. |
| 2093-105 | 0 | Yes | At least one subject was discharged from Phase B with a value of 213 IU/L (normal ranges: Male 0-80 IU/L, Female 0-70 IU/L) based on CSR. One subject had a follow-up value of 247 IU/L. |
| 2093-106 | 0 | Yes | No abnormal CPK values noted. |
| 2093-107 | 0 | Yes | Five high CPK values, all were not clinically significant. |
| 2093-108 | 0 | Yes | All CPK values <3xULN based on data listing. |
| 2093-109 | 1 | Yes | Subject 109-007 had a result of 724 IU/L at follow-up. |
| 2093-110 | 0 | Yes | All CPK values <3xULN based on data listing. |
| 2093-111 | 0[a] | No | Per protocol, CPK not collected. |
| 2093-112 | 0[b] | No | Per protocol, CPK not collected. |
| 2093-113 | 0 | Yes | All CPK results <3xULN based on data listings. |
| 2093-114 | 1 | Yes | Subject 114-007 had a result of 624 IU/L at follow-up. All other CPK values <3xULN based on data listing. |
| 2093-115 | 0 | Yes | Subject 115-026 had a result of 1069 IU/L at screening. All other CPK values <3xULN based on data listing. |
| 2093-116 | 0[a] | No | Per protocol, CPK not collected. |
| 2093-117 | 2 | Yes | Subject 117-005 had a result of 657 IU/L at discharge from 1st treatment.<br>Subject 117-015 had a result of 1447 IU/L at discharge from 1st treatment. |
| 2093-118 | 0[a] | No | Per protocol, CPK not collected. |
| 2093-119 | 0[a] | No | Per protocol, CPK not collected. |
| 2093-120 | 0[a] | No | Per protocol, CPK not collected. |
| 2093-121 | 0[a] | No | Per protocol, CPK not collected. |
| 2093-122 | 0[a] | No | Per protocol, CPK not collected. |

a No adverse events for elevated CPK were found. However, per the protocol, CPK values were not collected.
b No adverse events for elevated CPK were found. However, no information could be found in the protocol or report indicating that it was collected.

## 9.2 Literature Review/References

ISS: The initial literature discusses oxcarbazepine, licarbazepine (not marketed in any country), and eslicarbazepine acetate (not marketed at that time, although Bial (original sponsor and non-US sponsor) had received a positive opinion by the Committee for Medicinal Products for Human Use as brand name Zebinix for adjunctive use in adults with partial-onset seizures with or without secondary generalization).

For oxcarbazepine, the sponsor conclusions include that review and analysis of the published literature demonstrated several adverse events that are notable with regards to frequency or severity. The events referenced to for frequency are hyponatremia, diplopia, and CNS-related events (e.g. impaired cognition, somnolence, fatigue, and coordination abnormalities). The sponsor notes that these should be monitored for during the post-marketing period of SEP-0002093. The sponsor states that, "Additionally, rare but potentially serious adverse events such as anaphylaxis, angioedema, multi-organ hypersensitivity, serious dermatological reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis), and hematological events have been identified following oxcarbazepine administration and will be carefully monitored for during SEP-0002093 administration" (p. 50/104 of literature-review-pdf).

There were 15 published reports for licarbazepine, which the sponsor says only three of these had any clinically relevant safety findings. One publication included 7 cases of fatigue and one of somnolence in the 24 subjects exposed for up to six days in a pharmacokinetic trial. Somnolence was noted as the most frequent adverse event in another publication. In the third publication, there were three reports of ataxia and disturbance of equilibrium in an open-label trial of up to six months duration in eleven trigeminal neuralgia patients.

The sponsor reports that 62 published references with SEP-0002093 were retrieved. For the review and analysis of eslicarbazepine acetate published literature, the sponsor reports that five cases of hyponatremia (sodium < 125 mmol/L) were reported in the literature and that four of these were concomitantly treated with ≥ 1000 mg carbamazepine. There are two cases reported of impaired concentration in a study, reports of somnolence and fatigue, reports of circumoral, lip, or tongue paresthesia

The sponsor states there were no literature reports indicative of anaphylactic reactions or angioedema following SEP-0002093 administration and no instances of hypersensitivity or serious dermatological reactions. There are no reported hematologic events.

The sponsor also reports there were no reports of abuse, no instances of overdose, no reports of depression, no reports of suicidality, including self-injury, suicide ideation, suicidal thoughts, or attempted suicide, and no literature reports indicative of tolerance to administration or withdrawal after administration.

The sponsor states the only significant drug-drug interaction was a decrease in hormonal oral contraceptives containing ethinylestradiol and levonorgestrel where the author concluded that concomitant administration with SEP-000293 could reduce the effectiveness of the contraceptive.

120-day SU: The literature review submitted with the 120-day SU was basically a list of references. The sponsor was asked to discuss the literature, summarize any findings,

and state whether they believed any of the literature changed the overall safety profile of the product or presented new or unusual findings. The response came 9-29-09.

The literature review describes oxcarbazepine, licarbazepine, and eslicarbazepine acetate.

The sponsor states that review and analysis of oxcarbazepine published literature indicated that several adverse events stand out with regard to frequency or severity (e.g., impaired cognition, somnolence, fatigue, and coordination abnormalities-frequency, and anaphylaxis, angioedema, multi-organ hypersensitivity, serious dermatological reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, teratogenicity and hematologic events as rare but potentially serious events).

The sponsor reports there are no references for licarbazepine in the literature (reported as not marketed in any country).

The sponsor states that literature search identified 11 published clinical references for eslicarbazepine acetate in the period 1-2-09 to 3-30-09. Of the 11 references, only one (Elger, et al, Epilepsia, 2009, 50 (3): 454-463) is reported as having safety information and as a summary of study 301. This article describes the incidence of rash as low (1% and states oxcarbazepine as 10% and carbamazepine as 11%) and of psychiatric disorders as very low. This article seems to reference an add-on study with oxcarbazepine that was a placebo-controlled, dose ranging trial published by Barcs, et al in 2000 in Epilepsia.

## 9.3 Labeling Recommendations

Deferred.

## 9.4 Advisory Committee Meeting

Not planned.

## 9.5 Other efficacy studies

### Phase 3, Study 303-"Efficacy and Safety of BIA-2-093 as Adjunctive Therapy for Refractory Partial Seizures in a Double-blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Clinical Trial"

This study was conducted from 12-14-2004 to 1-19-2007 at 39 sites in Western Europe and Latin America with Bial-Portela & C, SA as the sponsor.

Study 2093-303 was a multi-center, randomized, double-blind, placebo-controlled, parallel group study designed to assess the efficacy and safety of 2 dose levels of ESL as adjunctive therapy for subjects with refractory partial-onset seizures. Subjects were randomized on a 1:1:1 basis to receive ESL 800 mg, ESL 1200 mg, or placebo. There were many similarities in design to the pivotal studies 301 and 302. The design was similar to the pivotal study 302 in that the baseline was observational (301 was single-blind placebo). There was a baseline of 8 weeks followed by randomization, a titration period of 2 weeks, a maintenance period of 12 weeks, and a taper period of 4 weeks.

The primary and secondary efficacy endpoints were the same as those in study 301 (statistical review).

Inclusion Criteria: included documented diagnosis of simple partial or complex partial seizures with or without secondary generalization for at least 12 months prior to screening, at least 4 partial seizures in each 4-week period during the last 8 weeks prior to screening, current use of 1-2 AEDs (except oxcarbazepine or felbamate) in stable dose regimen for at least 2 months before screening (vigabatrin acceptable if on for at least a year and no visual field deficit), and VNS considered an AED.

Exclusion Criteria: included the following: only simple partial seizures with no motor symptoms that were not video-EEG documented, primary generalized epilepsy, history of status epilepticus or seizure clusters within 3 months of screening, history of psychogenic seizures within the last 2 years, use of benzodiazepines on more than occasional basis (except as AED chronic use), and inadequate compliance with concomitant AEDs during the 8-week baseline period.

Demographics: The mean age was 38 years in the ITT placebo group, 36.8 years in the ITT ESL 800 mg group, and 35.4 years in the ITT ESL 1200 mg group. The minimum age was 17 years and the maximum age was 77 years in the placebo group and 64 years in the ESL 800 mg and 68 years in the 1200 mg group. 50% of the placebo group was female compare to about 58% of the ESL 800 mg group and about 56% of the ESL 1200 mg group. 35.1% to 39.3 % were Caucasian and about 62% were “other” ethnicities (not defined but non- Asian-there was one Asian person in the entire trial).

Neurologic Demographics: Of the ITT population, the mean time since diagnosis was about 22 – 24 years with standard deviation of about 12 to 13. Etiologically, most in each group were considered “idiopathic” (about 38% to 42%). About 23% to 33% had an etiology classified as “other/unknown”.

The average number of seizures in the ITT population during the 8-week baseline period was:

- Weeks -8 to -5: Placebo= 12 ± 17.6 , ESL 800 =12.2 ± 23.12, and ESL 1200= 11.2 ± 12.44. The range was from 0 to 200 when combining all groups.
- Weeks -4 to -1: Placebo= 11.4 ± 18.73 , ESL 800 =11.7 ± 22.24, and ESL 1200= 11.5 ± 10.39. The range was from 0 to 200 when combining all groups.

Concomitant AED use in the ITT population: All patients were on concomitant AEDS. 69-79% of patients were on 2 concomitant AEDs, 14 – 25% were on one concomitant AED, and about 5-6.5% were on three concomitant AEDS. One patient was on 4 other concomitant AEDs.

Carbamazepine was the most commonly used concomitant AED (69% placebo, 50% ESL 800 mg, 46.8% ESL 1200 mg). Valproic acid was used in 27.4 to 35.1% of patients and levetiracetam was used in 18.2% to 25%. Clobazam (not available in the US) was used in 7-9% of the patients and vigabatrin was used in 0 to 2.6% of patients.

Disposition/Population: 330 patients were screened, 253 were randomized (88 placebo, 85 ELS 800 mg, 80 ESL 1200 mg). Seven of the either 252 or 253 randomized (different numbers in the CSR) were treated but had no post-baseline seizure frequency assessment and were not included in the ITT population. The ITT population was comprised of 245 patients (84 placebo, 84 ESL 800 mg, and 77 ESL 1200 mg).

The table below is excerpted from the Clinical Summary of Efficacy and shows disposition, as per the Sponsor.

**Table 2.3.1-1: Subject Disposition (Study 2093-303)**

| Disposition | Placebo | Eslicarbazepine Acetate Dose Group | | Total |
|---|---|---|---|---|
| | | 800 mg | 1200 mg | |
| Randomized | 88 | 85 | 80 | 253 |
| Completed the Study | 66 (75.0) | 70 (82.4) | 59 (73.8) | 195 (77.1) |
| Withdrew Prematurely | 22 (25.0) | 15 (17.6) | 21 (26.3) | 58 (22.9) |
| Withdrew during/end of Baseline | 2 (2.3)[a] | 0 | 0 | 2 (0.8) |
| Withdrew during/end of Titration | 2 (2.3) | 3 (3.5) | 4 (5.0) | 9 (3.6) |
| Withdrew during/end of Maintenance | 11 (12.5) | 9 (10.6) | 15 (18.8) | 35 (13.8) |
| Withdrew during/end of Taper | 7 (8.0)[b] | 3 (3.5) | 2 (2.5) | 12 (4.7)[b] |
| Reasons for Withdrawal[c] | | | | |
| Unacceptable Adverse Event | 7 (8.0) | 8 (9.4) | 9 (11.3) | 24 (9.5) |
| Subject Non-compliance | 2 (2.3) | 3 (3.5) | 5 (6.3) | 10 (4.0) |
| Withdrawal of Consent | 4 (4.5) | 2 (2.4) | 2 (2.5) | 8 (3.2) |
| Lack of Efficacy | 2 (2.3) | 1 (1.2) | 1 (1.3) | 4 (1.6) |
| Protocol violation | 2 (2.3) | 0 | 0 | 2 (0.8) |
| Other | 9 (10.2) | 5 (5.9) | 4 (5.0) | 18 (7.1) |

a One subject was not dosed and the other received a single dose prior to discontinuation for non-compliance.
b Includes 3 subjects who completed the tapering-off period but who did not continue into Part 2 of the study.
c A subject may have more than 1 reason for discontinuation.
Reference: CSR 2093-303, Section 16.2.1, Listing 16.2.1-1 and Listing 16.2.1-2

Protocol violations: The study report defined major protocol violations as protocol deviations that could have affected the primary efficacy variable. The study report states these were identified at the blinded data review meeting before database lock. 85 patients from the ITT population (about 26%) are reported in the clinical study report as having major protocol violations (26/84 placebo, 30/85 ESL 800 mg, and 29/80 ESL 1200 mg).

Of these 85 patients, 39 (about 16%) had a baseline seizure frequency per 4 weeks of < 4 (13 patients per group), 23 patients (9.4%) had study drug compliance either ≤ 80% or ≥ 120% during the double-blind (9.5% placebo, 7.1% 800mg, and 11.7% 1200 mg), 18 patients (7.4%) had a baseline period of only 2 weeks (6% placebo, 7.1% 800mg, 9.1% 1200mg), and the blind was broken at the end of the double-blind for 5 patients (2%).

Sponsor's table of protocol violations:

**Table 10-1. Major Protocol Violations Affecting > 5 Patients Overall (ITT Population)**

| | Placebo (N=84) n (%) | ESL 800 mg (N=84) n (%) | ESL 1200 mg (N=77) n (%) | Total (N=245) n (%) |
|---|---|---|---|---|
| **Any Protocol Violation** | 26 ( 31.0) | 30 ( 35.7) | 29 ( 37.7) | 85 ( 34.7) |
| Baseline period was only two weeks. | 5 ( 6.0) | 6 ( 7.1) | 7 ( 9.1) | 18 ( 7.4) |
| Baseline seizure frequency per 4 weeks is less than 4. | 13 ( 15.5) | 13 ( 15.5) | 13 ( 16.9) | 39 ( 15.9) |
| Blinded codes broken at completion of double-blind assessment period. | 1 ( 1.2) | 2 ( 2.4) | 2 ( 2.6) | 5 ( 2.0) |
| Non-compliance with dosage regimen. | 2 ( 2.4) | 3 ( 3.6) | 0 ( 0.0) | 5 ( 2.0) |
| Study drug compliance during the double-blind assessment period ≤ 80% or > 120% | 8 ( 9.5) | 6 ( 7.1) | 9 ( 11.7) | 23 ( 9.4) |

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Sponsor's Results:

**Table 11-5. ANCOVA Analysis for Seizure Frequency per 4 Weeks over the 12-week Maintenance Period (ITT Population)**

| Parameter | Placebo (N=84) | ESL 800 mg (N=84) | ESL 1200 mg (N=77) |
|---|---|---|---|
| Seizure Frequency per 4 weeks | | | |
| N | 79 | 80 | 69 |
| LS Mean | 7.3 | 5.7 | 5.5 |
| 95% CI for Mean | (6.3, 8.5) | (4.9, 6.7) | (4.6, 6.5) |
| LS Mean Difference to Placebo | | -1.6 | -1.9 |
| P-value | | 0.048 | 0.021 |

ANCOVA model: treatment as factor and log-transformed baseline seizure frequency as covariate. Model was based on log-transformed seizure frequencies. Estimates from the ANCOVA model were back transformed using the exponential function. Dunnett's multiple comparison procedure was used for the comparison of the active treatment means to the placebo mean.
Cross-reference: Table 14.2-2.2.1

**Table 11-8. Distribution of Seizure Reduction per 4 Weeks over the 12-week Maintenance Period (ITT Population)**

| | Placebo (N=84) n (%) | ESL 800 mg (N=84) n (%) | ESL 1200 mg (N=77) n (%) | Total (N=245) n (%) |
|---|---|---|---|---|
| **Seizure Reduction per 4 Weeks** | | | | |
| <50% | 59 (70.2) | 51 (60.7) | 39 (50.6) | 149 (60.8) |
| 50% to 75% | 14 (16.7) | 17 (20.2) | 15 (19.5) | 46 (18.8) |
| >75% | 5 ( 6.0) | 12 (14.3) | 14 (18.2) | 31 (12.7) |
| p-value♦ | | 0.059 | 0.008 | |

♦ p-value for comparison with placebo based on CMH test stratified by region using the ANOVA statistic for ordinal data
Cross-reference: Table 14.2-3.1.1

Best Available Copy

**Table 11-9. Proportion of Responders, Seizure-free Patients and Patients with a 25% or Greater Exacerbation in Seizure Frequency over the 12-week Maintenance Period (ITT Population)**

| | Placebo (N=84) n (%) | ESL 800 mg (N=84) n (%) | ESL 1200 mg (N=77) n (%) | Total (N=245) n (%) |
|---|---|---|---|---|
| Responder (Seizure Reduction ≥ 50%) | 19 (22.6) | 29 (34.5) | 29 (37.7) | 77 (31.4) |
| p-value♦ | | 0.106 | 0.020 | |
| Seizure-free (Seizure Reduction = 100%) | 1 ( 1.2) | 4 ( 4.8) | 3 ( 3.9) | 8 ( 3.3) |
| p-value♦ | | 0.185 | 0.263 | |
| Exacerbation ≥ 25% | 19 (22.6) | 14 (16.7) | 10 (13.0) | 43 (17.6) |
| p-value♦ | | 0.292 | 0.141 | |

♦ p-value for comparison with placebo based on CMH test stratified by region using the ANOVA statistic for ordinal data
Cross-reference: Table 14.2-3.2.1

FDA reviewer:

The FDA's statistical review of the primary endpoint is copied from the draft review below. Based on this analysis, the 1200 mg group separated from placebo statistically although the 800 mg group did not.

**Table 5. Study 303: FDA Analysis Results for the Primary Endpoint**

| | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg |
| **Completers (with maintenance assessment)** | | | | |
| N | 79 | | 80 | 70 |
| LSmean (SE) | 6.7 ( 0.59) | | 5.2 ( 0.47) | 4.9 ( 0.48) |
| 95% CI | 5.6, 8.0 | | 4.4, 6.2 | 4.0, 5.9 |
| Log Difference in LSMean (SE) | | | -0.21 ( 0.107) | -0.27 ( 0.111) |
| 95% CI for Difference in LSMean | | | -0.45, 0.03 | -0.51, -0.02 |
| p-value | | | 0.0882 | 0.0322 |
| **ITT population (Conservative Imputation)** | | | | |
| N | 84 | | 84 | 77 |
| LSmean (SE) | 7.0 ( 0.59) | | 5.4 ( 0.47) | 5.3 ( 0.48) |
| 95% CI | 5.9, 8.3 | | 4.6, 6.4 | 4.4, 6.3 |

| | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg |
| Log Difference in LSMean (SE) | | | -0.22 ( 0.104) | -0.25 ( 0.106) |
| 95% CI for Difference in LSMean | | | -0.45, 0.01 | -0.49, -0.01 |
| p-value | | | 0.0594 | 0.0363 |
| **ITT population (Non-conservative Imputation)** | | | | |
| N | 84 | | 84 | 77 |
| LSmean (SE) | 6.8 ( 0.58) | | 5.3 ( 0.47) | 5.0 ( 0.47) |
| 95% CI | 5.7, 8.0 | | 4.4, 6.3 | 4.1, 6.0 |
| Log Difference in LSMean (SE) | | | -0.21 ( 0.106) | -0.26 ( 0.108) |
| 95% CI for Difference in LSMean | | | -0.45, 0.03 | -0.50, -0.02 |
| p-value | | | 0.0887 | 0.0335 |

Source: FDA

FDA analysis of secondary endpoints supported FDA's analysis of the primary endpoint (table below duplicated from statistical review).

**Table 6. Study 303: FDA Analysis Results for the Responder Analysis**

| Responder | Placebo | Eslicarbazepine Acetate Dose Group | | |
|---|---|---|---|---|
| | | 400 mg | 800 mg | 1200 mg |
| **I. Subjects w/o maintenance data as non-responder** | | | | |
| n/N (%)a | 19/ 84 ( 22.6 ) | | 28/ 84 ( 33.3 ) | 31/ 77 ( 40.3 ) |
| CMH p-valueb | | | 0.1230 | 0.0160 |
| Chi-square p-valueb | | | 0.1691 | 0.0247 |
| Odds Ratio | | | 1.71 | 2.31 |
| 95% CI | | | 0.86, 3.39 | 1.16, 4.57 |
| **II. Impute Using Titration** | | | | |
| n/N (%)a | 21/ 84 ( 25.0 ) | | 29/ 84 ( 34.5 ) | 34/ 77 ( 44.2 ) |
| CMH p-valueb | | | 0.1783 | 0.0107 |
| Chi-square p-valueb | | | 0.2375 | 0.0167 |
| Odds Ratio | | | 1.58 | 2.37 |
| 95% CI | | | 0.81, 3.09 | 1.22, 4.63 |

a. n/N=number of responders/number of subjects with seizure data in the maintenance period.
b. Unadjusted p-value from pairwise test of each active treatment group compared to placebo.
Source: FDA.

FDA analysis of percent change from baseline in seizure frequency indicated that the difference between ESL groups and placebo are not statistically significant (0.32 and 0.35 for the 800 mg and 1200 mg group respectively).

## Phase 2, Study 201-

"A Placebo-Controlled Study to Investigate Safety and Efficacy of BIA 2-093 In Controlling Refractory Partial Seizures When Added to Ongoing Therapy"

This was a randomized, double-blind, placebo controlled, add-on, exploratory study to evaluate the efficacy of the compound in the treatment of adult epileptic patients with refractory simple or complex partial seizures with or without secondary generalization. Safety evaluation was the secondary objective.

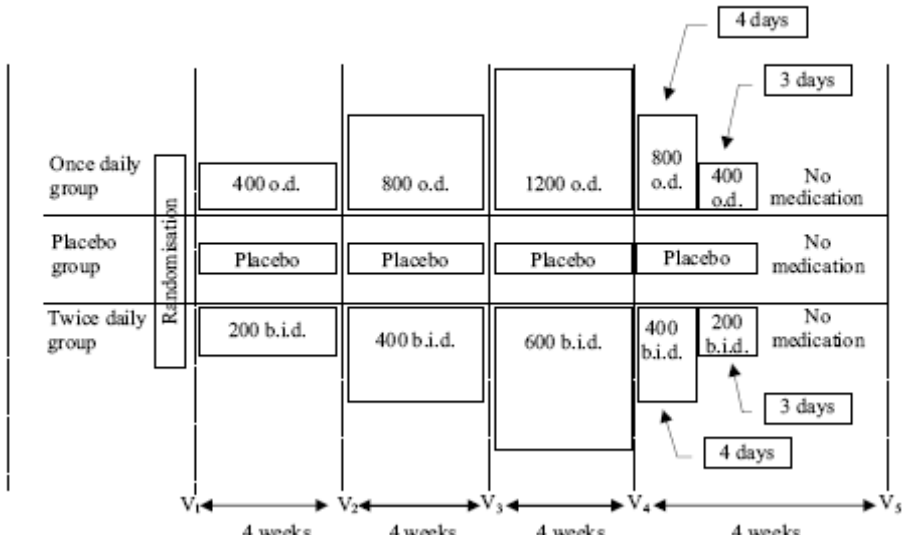
The study was conducted from 4-15-02 (admission 1st patient) to 11-11-02 (follow-up visit of last patient) at 19 sites in Eastern and Western Europe with Bial-Portela & C, SA as the sponsor.

144 patients were randomized to either the investigational product once-daily dosing, the investigational product twice-daily dosing, or placebo (50 to ODG, 47 to TDG, 47 to PLG-see the figure below for design). The double-blind phase was 12 weeks long and there was a scheduled 1-week taper. The daily dose was titrated from 400 mg to 800 mg to 1200 mg at 4-week intervals. Each dosage regimen (daily or twice daily and placebo) was tested during the 4 weeks.

Subjects were to have 4 seizures per month within the last 2 months before randomization, be on a stable AED dose of up to 2 AEDs during the 2 months before randomization, and have no EEG findings contradicting the epilepsy diagnosis (for example, primary generalized epilepsy). Exclusion criteria included that subjects could not have VNS, could not have primary generalized epilepsy, could not have a history of status epilepticus within 3 months, could not have seizures of non-epileptic origin, and could not use MAO inhibitors, calcium channel blockers, oxcarbazepine, or carbamazepine. Investigators had to withdraw patients for several reasons including meeting exclusion criterion or use of an excluded co-medication, non-compliance, or seizure exacerbation of > than 50% of the appearance of new and severe seizure types. Allowed concomitant AEDs were phenytoin, valproate, primidone, phenobarbital, lamotrigine, gabapentin, topirimate, and clonazepam (constant for 2 months prior to the study).

The figure below is from the study report and shows the design of the study.

Figure 1: Study design diagram




Primary efficacy variable: The primary efficacy variable was the proportion of responders (patients with ≥ 50% reduction in seizure frequency compared to baseline) and was evaluated at every visit. The week 12 visit (visit 4) data were used for the primary analysis.

Demographic data: All patients were Caucasian, most were female, and the general age was 40 years ±11.

Female: 57.4 % PLG, 56 % ODG, 65.2 % TDG, Age: mean is about 40 years old ± 11-12 years per group.

Seizure history and types- The ODG's epilepsy history mean time was shorter than that of the other two groups (mean 16.73 vs. 19.49 for TDG and 19.96 for PLG). Seizure types are shown in the table below, duplicated from the CSR.

Table xx Seizure Type

Table 6: Seizure type frequency per treatment group (ITT population, 143 patients)

| Seizure type | ODG (n=50) | TDG (n=46) | PLG (n=47) | Total (n=143) |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) |
| IA simple partial | 17 (34.0) | 17 (37.0) | 13 (27.7) | 47 (32.9) |
| IB complex partial | 36 (72.0) | 33 (71.7) | 38 (80.9) | 107 (74.8) |
| IC partial evolving to secondary generalized | 40 (80.0) | 37 (80.4) | 34 (72.3) | 111 (77.6) |

Source: Statistical Output Table B05

Concomitant AED Therapy: Of the ITT population, about 68% of the PLG, 70% of the ODG, and 61% of the TDG was using 2AEDs. The rest were using 1 AED. Valproate

was the most commonly used concomitant AED with reported use of 61 to 68% of patients in each treatment group. Second and third most used concomitant AEDs were topirimate and lamotrigine.

Disposition: 144 patients were randomized at visit 1 (50 to ODG, 47 to TDG, 47 to PLG). 1 patient withdrew consent without taking any study medication. The ITT is made of 143 patients (50 ODG, 46 TDG, 47 PLG).

Table xx –Patient discontinuation (up to and including visit 4)

| | **PLG n=47** | **ODG n=50** | **TDG n=46** |
|---|---|---|---|
| **Consent withdrawal** | 1 | 3 | 3 |
| **exclusion criteria** | 5 | 2 | 2 |
| **adverse event** | 4 | 3 | 4 |
| **Seizure exacerbation** | 1 | -- | 2 |

Data from Figure 2 of the CSR

Primary Analysis: Exploratory evaluation of the primary endpoint was performed on the ITT population using the one-sided t-test and an α of 10% (0.1). Power was 0.8. Patients who discontinued early were not replaced and their data was handled using "last observation carried forward" (LOCF).

Results:

As presented by the sponsor, on-face, the analysis of the primary variable in the ITT population was as follows- The n is about 34-50 for each group (ODB, TDG, and PLG at each dose of 400 mg, 800 mg, and 1200 mg).

- statistically significantly different between ODG and PLG at 1200 mg dosing (54% responders versus 28% responder, p=0.008). The difference between TDG and PLG did not reach statistical significance (41% versus 28%, p=0.12).
- At doses of 800 mg/day, ODG versus PLG was statistically significant (58% versus 38%, p=0.04). More PLG patients than TDG patients were responders although this was not statistically significant (33% TDG versus 38% PLG, p 0.36).
- At doses of 400 mg, neither ODG or TDG separated statistically from PLG (p=0.28 and 0.5 respectively). The % of responders was 34% for the PLG, 42% for the ODG, and 35% for the TDG.

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| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22416 | ORIG-1 | SEPRACOR INC | SEP-0002093 ESLICARBAZEPINE ACETATE |

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/s/

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TERESA A PODRUCHNY
04/30/2010

NORMAN HERSHKOWITZ
04/30/2010

**MEMORANDUM**

DATE: April 29, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-416

SUBJECT: Recommendation for action on NDA 22-416, for the use of Stedesa (eslicarbazepine acetate) Tablets for adjunctive treatment of partial seizures in adults

NDA 22-416, for the use of Stedesa (eslicarbazepine acetate) Tablets for adjunctive treatment of partial seizures in adults, was submitted by Sepracor, Inc., on 3/29/09. The sponsor has submitted the results of two controlled trials (Studies 301 and 302) that they believe establish the effectiveness for this product for the proposed indication. A third controlled trial (Study 303) was performed, but because of deficiencies in the conduct of the study, the sponsor determined that the study could not be used in support of the application. The sponsor believes that the data submitted establishes the drug's safety. The application also contains what the sponsor believes is all the other requisite information to support approval of the application (e.g., toxicology, chemistry and manufacturing, clinical pharmacology, etc.). Eslicarbazepine was approved in Europe for the same indication about one year ago. All of the studies were performed outside the United States by the previous sponsor, Bial.

The application has been reviewed by Dr. Teresa Podruchny, medical reviewer, the Interdisciplinary Review Team for QT Studies, Alicja Lerner, Controlled Substances Staff (CSS), Barbara Fuller, Division of Risk Management, Drs. Antoine El-Hage and John Kadavil , Division of Scientific Investigations (DSI), Dr. Xiang Ling, statistician, Drs. Vaneeta Tandon, Kofi Kumi, and Joo-Yeon Lee, Office of Clinical Pharmacology, Dr. Steve Thomson, statistician for the carcinogenicity studies, Dr. Christopher Toscano, pharmacologist, Dr. Charles Jewell, Office of New Drug Quality Assessment (ONDQA), and Dr. Norman Hershkowitz.

The clinical team recommends that this application not be approved, not because the drug has not been shown to be effective or safe, but because of profound and extensive deficiencies in the conduct and documentation of the study, as well in the presentation of the data in the application. Because of these deficiencies, the team does not consider the data sufficiently reliable to support the sponsor's conclusions, or, critically, to be able to perform an adequate independent analysis of the data. This is true for both the effectiveness as well as the safety data. I will provide a very brief description of these deficiencies. Because of the extensive nature of these problems, I will present only a very

truncated description of the effectiveness and safety data. A more detailed review will have to await a more reliable and coherent submission by the sponsor.

The deficiencies can be considered to fall into two main categories: 1) inadequate study conduct and documentation, as identified by DSI inspectors, and 2) inadequate presentation of the data in the application, as determined by medical review.

Deficiencies related to study conduct and documentation

A total of four sites were inspected by the Agency, 2 for Study 301 and 2 for Study 302. Inspections of two of the four (one in each study) revealed no significant findings. However, there were significant findings in the two other sites. A brief description of the findings at each site is given below.

Dr. Danilo Hodoba, Zagreb, Croatia: Study 301

The records for all 17 patients randomized at this center were inspected. There was no documentation available that would permit identification of which drug was assigned to which patient. In addition, there was a lack of documentation of the amount of drug dispensed. All drug and labeling had been destroyed; therefore, it was impossible to verify returned drug, and records document that for numerous patients, more drug was destroyed than was returned by those patients. In at least one case, a blister pack of study drug assigned to one patient was dispensed to a different patient.

For several patients, seizures documented in the seizure diaries for several intervals of time were not recorded in the data listings. For at least one patient, an adverse event that led to discontinuation (leucopenia) was not referred to as such in the data listings.

Dr. Carmen Diaz-Obregon, Madrid, Spain: Study 302

The records of 15/16 screened patients were inspected.

At least four patients did not meet inclusion criteria related to the number of required seizures in a given time period in the baseline phase. Waivers for these patients were obtained, but after patients had been enrolled. In addition, source documents did not exist for the dates on which patients had seizures during this period. There was no source documentation for other inclusion/exclusion criteria (e.g., the number of concomitant anti-epilepsy drugs [AEDs]). There was a discrepancy in the number of seizures recorded in the diaries and in the CRF for at least one patient. Source documentation was apparently missing for seizure counts in some patients.

Of considerable importance, the records were generally difficult to verify. Medical charts and source documents were typed, not signed, and included handwritten and sticky notes. The records were out of sequence. Some of the (typed) progress notes had handwritten entries that were not signed, and contained no explanation for the changes.

Sepracor submitted audit reports for 34/84 sites in Studies 301 and 302, and for 10/35 sites in Study 303. These audits revealed numerous deficiencies, including frequent and significant discrepancies in the number of adverse events recorded in source documents and CRFs and inadequate drug accountability documentation. These deficiencies were noted in all three studies. Although the sponsor, as noted above, concluded that Study 303 could not be considered to provide reliable effectiveness data (though they do propose that the safety data should be considered), they did not conclude that the data from Studies 301 and 302 were unreliable. DSI inspectors have reviewed these findings and have concluded that these results are consistent with their own inspections, and suggest widespread problems in the conduct and documentation of all three studies.

Deficiencies related to presentation of the data

Numerous adverse events (N=59) were missing from the initial integrated summary of safety (ISS). These were reported in the 120 day Safety Update (SU), because the sponsor stated that, although they occurred during the controlled trials, they were not noted until they were evaluating the open, uncontrolled extension studies. The 120 day SU was missing 31 serious adverse events (SAEs). This was only determined when the medical reviewer asked for clarification of a table of SAEs (because it was difficult to read). For at least two patients, adverse events that should have been categorized as SAEs were not, and in one case the narrative was clearly inadequate (the patient was hospitalized, had mucosal ulcer, peeling skin and increased liver enzymes and was taking concomitant lamotrigine, though the “heading” for the case stated that the patient was not on concomitant medications). In the other case (purulent tonsillitis), there was no narrative. Other adverse event descriptions tended to minimize the significance of the events, and adverse events were not consistently included in data tables. There were discrepancies between rates of discontinuations among tables that presumably should have had the same numbers. Some CRFs and data clarification forms were impossible to interpret, due to sections that appeared to be “whited out”, lined out, etc. Withdrawals related to adverse events were not consistently noted as such.

Although the data are questionably reliable, for the reasons explained, I will give a brief outline of the effectiveness and safety data.

Effectiveness

As noted above, the sponsor has submitted the results of two controlled studies in support of the effectiveness of eslicarbazepine. They share a similar protocol.

Study 301

This was a randomized, parallel group, placebo controlled study in which patients with partial seizures were randomized to receive either placebo or eslicarbazepine 400, 800, or 1200 mg once a day. Patients were first entered into an 8 week baseline during which they received placebo. There was then a two week titration phase, followed by a 12 week maintenance phase, and a 4 week taper period. The primary outcome was seizure frequency standardized per 4 weeks.

A total of 402 patients were randomized in 40 centers in Austria, Germany, Switzerland, Croatia, Czech Republic, Hungary, Poland, Lithuania, Romania, Russia, and Ukraine. The following chart displays the disposition of patients.

| | Plac | 400 mg | 800 mg | 1200 mg |
|---|---|---|---|---|
| Randomized | 102 | 100 | 98 | 102 |
| Completed | 84 (82%) | 90 (90%) | 85 (87%) | 71 (70%) |
| W/D due to AE | 3 (3%) | 4 (4%) | 8 (8%) | 18 (18%) |

The sponsor's analysis only included patients who had seizure data during the maintenance period. Dr. Ling performed analyses of patients with maintenance data, the ITT population using the maximum seizure frequency during either the baseline or titration period (conservative imputation), and carrying forward seizure frequency during the titration period (non-conservative imputation). The following chart (taken from her Table 9, page 21 of her review) displays the results of these analyses for these three approaches:

| | Pla | 400 | 800 | 1200 |
|---|---|---|---|---|
| Maintenance | | | | |
| N | 99 | 97 | 93 | 92 |
| LS Mean | 6.8 | 6.1 | 5.1 | 4.6 |
| P-value | | 0.55 | 0.013 | 0.0004 |
| Conservative | | | | |
| N | 102 | 98 | 98 | 97 |
| LS Mean | 7.0 | 6.2 | 5.3 | 4.8 |
| P-value | | 0.47 | 0.018 | 0.001 |
| Non-conservative | | | | |
| N | 102 | 98 | 98 | 97 |
| LS Mean | 6.9 | 6.2 | 5.2 | 4.8 |
| P-value | | 0.51 | 0.013 | 00007 |

Percent change from baseline in seizure frequency

| | Pla | 400 | 800 | 1200 |
|---|---|---|---|---|
| N | 102 | 98 | 98 | 97 |
| LS Mean | -7.7 | -15.9 | -28.4 | -29.6 |
| P-value | | 0.64 | 0.04 | 0.03 |

Study 302

This was of similar design to Study 301.

A total of 395 patients were randomized in Belgium, Denmark, Germany, the Netherlands, Portugal, Romania, Spain, Sweden, United Kingdom, Argentina, Brazil, Australia, and South Africa. The following chart displays subject disposition.

| | Plac | 400 mg | 800 mg | 1200 mg |
|---|---|---|---|---|
| Randomized | 100 | 96 | 101 | 98 |
| Completed | 94 (94%) | 84 (88%) | 81 (80%) | 68 (69%) |
| W/D due to AE | 3 (3%) | 12 (12.5%) | 20 (20%) | 25 (25.5%) |

The following tables present the results of the primary outcome and a key secondary outcome:

| | Pla | 400 | 800 | 1200 |
|---|---|---|---|---|
| Maintenance | | | | |
| N | 99 | 94 | 87 | 81 |
| LS Mean | 9.0 | 8.3 | 6.6 | 7.0 |
| P-value | | 0.80 | 0.006 | 0.04 |
| Conservative | | | | |
| N | 100 | 96 | 98 | 94 |
| LS Mean | 9.2 | 8.5 | 7.2 | 7.9 |
| P-value | | 0.72 | 0.028 | 0.25 |
| Non-conservative | | | | |
| N | 100 | 96 | 98 | 94 |
| LS Mean | 9.2 | 8.2 | 6.8 | 7.5 |
| P-value | | 0.54 | 0.007 | 0.11 |

Percent change from baseline in seizure frequency

| | Pla | 400 | 800 | 1200 |
|---|---|---|---|---|
| N | 100 | 96 | 98 | 94 |
| LS Mean | 3.6 | -10.8 | -17.9 | -5.3 |
| P-value | | 0.28 | 0.05 | 0.66 |

In both of these studies, there were unorthodox data collection practices.

Specifically, in typical AED studies, patients are instructed to record seizure counts for every day of the study. That is, if a patient has no seizures on a day, they are supposed to record a 0. However, in these studies, patients were instructed to record data only for those days in which a seizure occurred. Therefore, if no seizure data were recorded, this was assumed to represent a day without seizures. For this reason, unreturned cards and unfilled-out cards were assumed to represent time without seizures.

The sponsor performed worst-case analyses to examine the effect of unreturned diary cards, given this rule. The results were generally unchanged. An Agency requested worst-case analysis could not be performed (see Dr. Ling's review, pages 16-18).

Also, as noted by Dr. Ling, the sponsor utilized "hardcodes" to change the values of the variables; that is, to correct errors in the data. In Dr. Ling's view, the number of changes made suggested that the study was not well conducted. Sensitivity analyses performed with the hardcodes removed did not affect the outcomes.

Safety

Although, as noted above, the safety data submitted by the sponsor are considered unreliable, I will give a very brief summary of some of the pertinent facts, as they are presented as of this writing.

A total of 1889 unique subjects received at least one dose of eslicarbazepine. A total of 1610 unique subjects received a dose of greater than 600 mg/day. In particular, 166 patients received a dose of at least 600 mg/day for between 6 months and 1 year, and 583 patients received a dose of at least 600 mg/day for greater than one year. In this latter group, the mean daily dose was 858 mg/day and the median daily dose was 800 mg. Essentially all of the experience for greater than 6 months was in the 600-900 mg/day range.

Deaths

There were a total of 16 deaths during pre-market development, but only 15 are reported in the NDA (one was an IND report that occurred after the NDA cut-off date). Two deaths were reported in placebo patients. One death was reported in the epilepsy controlled trials, in a placebo patient. One death was in a healthy volunteer in a Phase 1 study (65 year old man with a history of cardiac disease died 1 day after a single dose of 600 mg, preceded 4 days earlier by a single dose of 600 mg; autopsy revealed acute coronary artery occlusion), and 5 were in controlled trials of other indications (bipolar disorder, diabetic neuropathy, post-herpetic neuralgia).

Five patients died from cancer, 3 from drowning, two from "cardiac" causes, one from suicide, and three were presumably related to seizures/status epilepticus. None of the deaths had an obvious relationship to drug, and, as Dr. Hershkowitz points out, the rate of SUDEP (Sudden Unexplained Death in Epilepsy) seems to be consistent with that seen with other AEDs.

Serious Adverse Events (SAEs)

In controlled epilepsy studies 301 and 302, 4.5% of eslicarbazepine and 1.4% of placebo patients reported at least one SAE; there was no dose response. A total of 7% of epilepsy patients reported at least one SAE in open-label treatment.

In controlled epilepsy studies, Abnormal Coordination and Seizures were most commonly reported in the eslicarbazepine group (N=4 each). A total of 8 eslicarbazepine-treated patients experienced Vomiting as an SAE. The combined number of patients with dizziness or vertigo was 8.

Dr. Podruchny's review of a single case of rash suggests that the event was of greater severity than the company recognized.

The case of rash was in a patient who had received drug for 13 days and developed a generalized macular rash, fever of 103.6, leucopenia, anemia, thrombocytopenia, and increased LDA, AST, and GGT (ALP and bili were normal). The patient had achieved a dose of at least 800 mg/day, and perhaps1200 mg.

As Dr. Podruchny notes, several cases of ataxia were severe enough so that patients could neither walk nor stand.

In open-label extensions of the controlled epilepsy studies, there was one case of severe esophageal dyskinesia (so-called nutcracker syndrome) in a 27 year old woman who had been on drug for about one year. Apparently, the patient recovered (presumably pain-free). It should be noted that there were several cases in the database reported as esophageal stenosis (at least two in controlled

trials). Presumably, this does not represent a structural change, although in at least one case, the event was noted to have continued despite treatment (in that case with omeprazole).

There were 5 cases reported as psychosis, at least one of which, in a 65 year old man, resolved while on treatment.

Discontinuations

In Studies 301 and 302 combined, 4%, 8.7%, 14.6%, and 23% of placebo, esli 400, 800, and 1200 mg/day patients discontinued treatment secondary to an adverse event. The following table presents the most common reasons for discontinuation:

| | 301 & 302 | |
|---|---|---|
| | Placebo (N=202) | Eslicarbazepine (N=595) |
| Event | | |
| Dizziness | 0.5% | 5.5% |
| Vomiting | 0.5% | 3.7% |
| Nausea | 0.5% | 2.7% |
| Diplopia | 0 | 2.7% |
| Abnormal coordination | 0 | 2.5% |
| Somnolence | 0 | 1.7% |
| Blurred vision | 0 | 1.3% |
| Fatigue | 0 | 0.8% |

Dizziness, vomiting, diplopia, and somnolence were dose related.

There was at least one case of a rash accompanied by elevations of liver function tests. There were a total of 5 cases of rash, all on eslicarbazepine, at least two of which occurred in the setting of other symptoms (in one case, dizziness, somnolence, vomiting; in another, headache, dysarthria, and asthenia). There appears also to be a possible case of angioedema in a different controlled trial, although this is not at all clear (described by Dr. Podruchny as bilateral paresthesia in the hands after the first dose, then mild facial edema). There were rare cases of hypertension (and hypotension).

There were a few cases of disturbances in attention and psychotic disorder.

In open-label extensions, there was a case of pancreatitis, poorly documented, that apparently resolved, although Dr. Podruchny reports that it is difficult to tell if the drug was discontinued prior to the resolution of the event.

Controlled Substance Comments

The CSS found numerous deficiencies in the sponsor's abuse liability and dependence data. These deficiencies were communicated to the sponsor during the review period, and the sponsor responded. The CSS continues to find the data inadequate, and has several additional comments for the sponsor. They want the sponsor to conduct a human abuse potential study, a study evaluating any potential physical dependence (withdrawal data), and an adequate analysis of abuse related adverse events (many of CSS's concerns relate to the previously described deficiencies in the presentation of the data).

QT

The QT team has evaluated a thorough QT study (using doses of 1200 and 2400 mg/day) and finds the study adequate, and also finds that there is no signal for concern.

Toxicology

The sponsor has performed the appropriate toxicology studies. However, the team has concluded that the sponsor has not shown that eslicarbazepine was adequately tested in the in vitro chromosomal aberration assays in mammalian cells or the in vitro mouse lymphoma tk assay. It is particularly important to adequately assess the genotoxic potential of eslicarbazepine because an in vivo carcinogenicity study was performed only in the mouse (because metabolism in the rat is different than in the human), and in this mouse study, there was an increase in hepatic tumors (increase in adenomas and carcinomas in mid-dose males, and high dose males and females).

Clinical Pharmacology

Eslicarbazepine acetate is a voltage gated sodium channel blocker. It is an ester of eslicarbazepine, and is rapidly metabolized (via hydrolytic metabolism in the presence of hydrolase) to S-licarbazepine, with R-licarbazepine (about 4% with a 21:1 ratio of S to R) and oxcarbazepine (<1%) as very minor metabolites. When oxcarbazepine (an approved AED) is administered, it results in an S-licarbazepine to R-licarbazepine ratio of 4:1.

Parent levels are undetectable in the plasma. S-licarbazepine represents about 95% of the circulating species. It is primarily eliminated through the kidney either unchanged (about 67%) or as the glucuronide conjugate (about 33%). The apparent half-life varies from about 10-20 hours.

Eslicarbazepine is not a CYP 450 substrate. It is an inhibitor of CYP 2C19.

There are no pending CMC issues.

Comments

The sponsor has submitted the results of two controlled trials that they believe establish substantial evidence of effectiveness for eslicarbazepine as adjunctive treatment for partial seizures in adults. In addition, they have exposed sufficient numbers of patients to assess the safety of the drug.

As described above, however, serious deficiencies in the conduct and documentation of Studies 301 and 302 at 2 out of 4 study sites have been noted by FDA inspectors. Although numerous deficiencies were noted, among the most important were discrepancies between the number of seizures noted in patient diaries and reported in the data sets and similar discrepancies in the reporting of adverse events. The disarray in the medical records/source documents in many cases contributed to a lack of confidence in the integrity of the data, and poor/absent drug accountability records made it difficult if not impossible for inspectors to adequately reconstruct the conduct of the study. Additionally, we are still not confident that all adverse events have been reported in the application, or that they have been adequately described, based on Dr. Podruchny's review. In addition, the sponsor's own audits of additional sites have revealed similar problems at sites not investigated by the FDA. These findings, taken as a whole, raise serious, and as yet unrefuted, questions about the reliability of the data.

On face, as the data are presented by the sponsor, it appears that eslicarbazepine is effective and that there are no adverse events that would preclude approval. However, because we cannot be confident that the data are reliable, we cannot independently reach this (or any) definitive conclusion. For these reasons, we recommend that the sponsor be sent a Complete Response letter, outlining these concerns and deficiencies.

DSI has asked the sponsor for much additional information, including asking them to conduct additional audits. I agree that we should ask the sponsor for additional audits, and that we probably should perform additional inspections of our own. Whether the sponsor can adequately "resurrect" the data remains to be seen. If they cannot, it is possible, and that additional studies may need to be performed.

Russell Katz, M.D.

Appears This Way On Original

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22416 | ORIG-1 | SEPRACOR INC | SEP-0002093 ESLICARBAZEPINE ACETATE |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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RUSSELL G KATZ
04/29/2010

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 22416** **Applicant: Sepracor** **Stamp Date: 3-29-2009**

**Drug Name: Eslicarbazepine Acetate** **NDA/BLA Type:**

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **FORMAT/ORGANIZATION/LEGIBILITY** | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | x | | | |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | x | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | | x | | Doesn't seem to be unless cover letter ectd location is considered TOC |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)? | x | | | |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | x | | | Seem to be |
| 6. | Is the clinical section legible so that substantive review can begin? | x | | | Seems to be |
| **LABELING** | | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | x | | | |
| **SUMMARIES** | | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)? | x | | | |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | x | | | |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | x | | | |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | x | | | |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? | | | | 505b1 |
| **DOSE** | | | | | |
| 13. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?<br>Study Number:<br>Study Title: A placebo-controlled study to investigate safety and efficacy of BIA 2-093 in controlling refractory partial seizures when added to ongoing therapy<br>Sample Size: 144 enrolled, 110 completed<br>Arms: once daily at 400 or 800 or 1200 mg, twice daily dosing at 200 bid or 400 bid or 600 mg bid, or placebo<br>Location in submission: module 5 | | | | This does not appear optimal for dose finding |
| **EFFICACY** | | | | | |
| 14. | Do there appear to be the requisite number of adequate and | X | | | On-face |

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | well-controlled studies in the application?<br><br>**Pivotal Study #1**<br>2093-301<br>Indication: partial sz (simple or complex with/without 2nd gen)<br>Part 1- 26 week with 8 week placebo run-in, 2 wks dose titration, 12 wks maintenance, and 4 weeks tapering-off.<br>Part 2 OLE<br><br>**Pivotal Study #2**<br>2093-302 Indication: same as 301<br>(simple or complex with/without 2nd gen)<br><br>n=400 randomized 1:1:1:1 400mg, 800mg, 1200m, pl<br>Part 1-22 wk w/8 wk baseline, 2 wk DB titration, 12 wk maintenance<br>Part 2-1 year OLE | | | | Study 302 with observational baseline. 301 with single blind |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | x | | | on-face, they seem acceptable-review issue |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | | | x | Studies conducted outside IND |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | x | | | Somewhat in ISE |
| **SAFETY** | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | | | | ISS not able to locate mean change and outlier for bipolar |
| 19. | Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)? | | | | Review issue-a study was done |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | | | | There are ongoing trials and these and other data are expected in 120 day update |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious? | | x | | Not for 1200 mg and exposure presented in 600-800 mg dosing, usual dose to be 800 (label). May be inadequate upon |

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| | | | | | review of only 800 mg or greater (my numbers from preliminary from ex dataset, 249 unique exposures all trials ≥ 800mg and ≥ 180 days) Also, adequacy phase 3 study 303 review issue[2] |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | x | |
| 23. | Has the applicant submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms? | x | | | Includes dataset comparing Medra dictionaries |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | | | | Review issue-there is section about this |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | x | | | Appear to be present |
| **OTHER STUDIES** | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | x | | | Seems to have |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)? | | | x | |
| **PEDIATRIC USE** | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | x | | | Req waiver 0-1mo<br>Req def 1mo-17yrs<br>Insuff geriatric (24) |
| **ABUSE LIABILITY** | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | x | | | |
| **FOREIGN STUDIES** | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | x | | | |

[2] Footnote from Dr Hershkowitz: These numbers are borderline, but it was agreed by Dr Temple, Dr Bastings and myself that they were adequate for filling. It should be noted that there is additional patient exposure in studies on other medical conditions and there is substantial >1 year exposure (222 patients). Additional long term exposure is expected on safety update. Therefore, the adequacy is being considered a review issue.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|---|---|---|---|---|---|
| **DATASETS** | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | | x | | Missing treatment grp in some datasets. |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | | | | Details not seem specified in minutes but may have been in submission to NDA for preNDA mtg |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | | x | | See below |
| 34. | Are all datasets to support the critical safety analyses available and complete? | | x | | Missing treatment group assignments in some |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | | | | Deferred to statistics |
| **CASE REPORT FORMS** | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | x | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | X | |
| **FINANCIAL DISCLOSURE** | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | x | | | 1 PI for study 302 missing, 10 Sis missing disclosure This PI **not** listed in Appendix 1 list of inv |
| **GOOD CLINICAL PRACTICE** | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | x | | | Only epilepsy phase 2 and 3 trials and bipolar 203, 204, 205 checked- Statement of GCP, Helsinki, local ethics Committee or ICHE6 or language seems to indicate compliance Study 303 has this type of language also |



**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

The exposure data is marginal[4] in terms of ICH numbers.

Table 1.2-2 contains data from all studies and categorizes exposure as >600 mg- 900 mg.

- The proposed labeling indicates 800 mg is expected to be the usual maintenance

[4] Note from Dr. Hershkowitz: It was agreed by Dr Temple, Bastings and myself at the filling meeting that marginal exposures can be considered a review issue.

dose. Using the sponsor's table 1.2-2, the number exposed for >24 weeks at doses higher than >600mg is 307.

- The proposed label indicates that 1200 mg is the maximum daily dose. Table 1.2-2 presentation is by 1100-1300 mg, 1500-2400 mg, and ≥ 3000 mg. The stratum ≥ 3000 mg does not contribute to this duration. Combining the other two other strata, the number exposed for >24 weeks is 16.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. *(Reviewer's note: Given the consensus at the filing meeting, I have included a statement about the exposure in this section.)*

Your table 3.1-2 in the ISS provides exposure in strata for dose and duration. Based on our preliminary review, exposure to support the expected usual dose of 800 mg appears borderline, in terms of 6 month ICH numbers. Whether this will be adequate will be a matter of detailed review of your data. An additional issue will be the acceptability of the exposure from study 303. On-face, the numbers exposed to 1200 mg are not adequate to support safety.

- Provide the total number of non-fatal SAEs in the entire development program of Eslicarbazepine Acetate. Then provide the number by phase (phase 1, 2, 3) and per study. Please provide a similar list for the discontinuations secondary to an adverse event.
- Datasets for some of the safety data do not contain a variable that identifies what treatment the subject was on at the time. If there is another dataset with this information, other than an ISS dataset, please reference this. Otherwise, please submit new datasets with a variable that allows for identification of the treatment the patient was taking at the time of the event. Specific identified deficiencies are included in the bulleted item below. You should, however, reexamine your datasets and provide this informtion for any datasets that we may have missed.
    - ●For study 301 part 1, the datasets adversed.xpt, adverse.xpt, and sae.xpt and the lab and EKG datasets do not appear to allow one to identify the treatment group.
    - ●For study 301 part2 , the study started at 800 mg but patients could titrate up or down in 400 mg intervals to dose between 400 mg and 1200 mg. The datasets of adverse events, labs, and EKG findings do not have treatment group information.
    - ● The datasets of adverse events, laboratory data, and EKG data for studies 201, 202, and 203 do not have a variable to allow for identification of the treatment group the patient was on at the time of the data collection.
- The clinical overview document states that Sepracor's view is that study 303 is not "sufficiently compliant" to be formally relied upon for a conclusion of safety and efficacy, but that the study can be supportive. We need to see the details. Please send the CRO site initiation and monitoring reports as well as the Sponsor audit reports. We would like both Bial and your audit reports. Additionally, summarize the inspection findings to highlight the findings that were considered severe enough to lead to the conclusion that the data were not sufficient to be relied upon formally and reference where we may find the information in the original inspection reports. If it is the case that it was the totality of the findings that led to your conclusions, describe

this in detail. If you believe this information is in the NDA submission, please indicate exactly where we may find it.

- Given the concerns for the compliance in study 303, please show a comparison of laboratory and EKG mean change and outlier data and adverse event data between study 303 and the combined study data for studies 301 and 302. If this is already in the submission, please reference where we may find it.
- Study reports 301 and 302 have sections (for example, the investigators' curriculum vitae) that are not searchable. Please note for each study report and for the ISS and ISE the page numbers of sections that are not searchable. If all pages in a study report or ISS/ISE are searchable, please state this.
- Table 2 of the financial disclosure document (financial-cert.pdf) indicates you were unable to obtain disclosure information for a PI and a sub-investigator of this PI in study 302 (Prof. Dr. Perju-Dumbrava Lacramioara (Principal Investigator) (b) (6) (sub-investigator for Dr. Perju-Dumbrava Lacramioara). Please explain why you were not able to obtain this information. Also, through comparison of the lists of investigators found in the document, tabular-listing.pdf, with the information in the document, financial-cert.pdf, there appear to be other investigators missing information: Study 301, site 102 Dr. Korner, site 125, Dr. Waberzinek (replaced by Dr. Hojdikova, did Dr. Waberzinek contribute to randomized patients?), site 151, Prof. Dr. Halasz (replaced by Dr. Barcs, did Prof. Dr. Halasz contribute to randomized patients?), site 174, Prof. Kazibutowska-Zaranska; Study 302, site 351, Dr. Hufnagel (replaced by Dr. Diener-did Dr. Hufnagel contribute to randomized patients?), site 373, Dr. Pimentel; Study 303, site 711, Dr. Hoyos-Gomez. Please address this.

Reviewing Medical Officer Date

Clinical Team Leader Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/
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Teresa Podruchny
6/5/2009 04:07:37 PM
MEDICAL OFFICER

Norman Hershkowitz
6/7/2009 05:01:33 PM
MEDICAL OFFICER