CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022544Orig1s000

MEDICAL REVIEW(S)

Application Type	NDA
Application Number(s)	22-544
Priority or Standard	S
Submit Date(s)	30 March, 2010
Received Date(s)	30 March, 2010
PDUFA Goal Date	30 January, 2011
Division / Office	DAAP/ODE2
Reviewer Name(s)	Timothy T. Jiang, MD, PhD
Review Completion Date	December 7, 2010
Addendum Date	December 13, 2010
Established Name	Gabapentin Extended Release
Trade Name	Gralise
Therapeutic Class	Anti-epileptic
Applicant	Abbott
Formulation(s)	Tablet
Dosing Regimen	Once daily
Indication(s)	Post-herpetic neuralgia
Intended Population(s)	Adults with Post-herpetic neuralgia

Template Version: March 6, 2009

Correction:

The following is from page 102 of clinical review (NDA 22544):

"Open-label extension study in patients **with DPN** (Study 81-0052)
The most commonly reported AEs were URTI (5.9%), nasopharyngitis and diarrhea (each at 4.2%), and dizziness and rash (each at 3.4%). The incidence of dizziness and somnolence were both low in this study (dizziness 3.4%, somnolence 0.8%) possibly because these patients became tolerant to the adverse events since they were on the drug for an extended period of time."

It must be noted that Study 52 is the open label extension in patients with **PHN**, not DPN. The following has been revised to reflect the correction:

Open-label extension study in patients **with PHN** (Study 81-0052)
The most commonly reported AEs were URTI (5.9%), nasopharyngitis and diarrhea (each at 4.2%), and dizziness and rash (each at 3.4%). The incidence of dizziness and somnolence were both low in this study (dizziness 3.4%, somnolence 0.8%) possibly because these patients became tolerant to the adverse events since they were on the drug for an extended period of time.

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/s/

TIMOTHY T JIANG
12/13/2010

ELLEN W FIELDS
12/13/2010
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CLINICAL REVIEW

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1. Recommendations/Risk Benefit Analysis

1.1 Recommendation on Regulatory Action

I recommend approval for gabapentin-ER (G-ER) for the management of postherpetic neuralgia (PHN) in adults pending resolution of the biopharmaceutics issues. Efficacy was demonstrated at a dose of 1800 mg given once daily with the evening meal in one adequate and well-controlled clinical trial. This trial examined adult subjects with post-herpetic neuralgia. Efficacy was demonstrated by positive results for the primary endpoint, improvement of average daily pain score at the end of eight weeks of treatment compared to placebo using a conservative method of imputation for missing data acceptable to the Division.

The safety profile of G-ER was demonstrated in over 1500 treated subjects. The adverse event profile appeared acceptable and similar to that for Neurontin, (gabapentin immediate-release tablets) previously approved for the treatment of PHN.

The dosing recommendation of 1800mg once daily is acceptable based on data from the Phase 2 and 3 studies. Patients should undergo a gradual titration from 300 mg daily to 1800 mg daily with evening meal. As G-ER is excreted unchanged by the kidneys, reductions in gabapentin dose should be made in patients with compromised renal function. Dosing must be reduced in the setting of renal impairment for patients with creatinine clearance less than 60 mL/mim.

As a 505(b)(2) application, the Sponsor relied in part on the Agency's previous findings of safety and efficacy for gabapentin (Neurontin) which was approved for the same indication in 2002.

1.2 Risk Benefit Analysis

G-ER at 1800 mg given as a single daily dose with the evening meal in the treatment of patients with PHN demonstrated positive findings for the primary endpoint in one adequate and well-controlled clinical study (Study 81-0062).

In this pivotal Phase 3 study, the planned primary outcome measure was the diary based average daily pain rating at study termination compared to baseline. There was statistically significantly greater reduction in pain when the G-ER group was compared to placebo. The least squares mean difference of G-ER vs. placebo was -0.49 with p-value of 0.0125, using baseline observation carried forward (BOCF) imputation. The three key secondary outcome measures [Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), and Daily Sleep Interference (DSI)]

however, did not reach statistical significance when the G-ER group was compared to placebo using pre-specified statistical plan, although both PGIC and CGIC trended in the direction in favor of G-ER. The efficacy appears to be driven by the US sites which contributed to the majority of subjects (57.2% of ITT).

In terms of safety, the premarketing exposure to G-ER of more than 1500 subjects appears adequate. There were no deaths attributable to G-ER, and no unexpected or unusual gastrointestinal adverse events of interest that appeared to be associated with the gastric retentive formulation.

G-ER was found to have a safety profile very similar to that of gabapentin IR (Neurontin). Common adverse events included dizziness, somnolence, headache, peripheral edema and diarrhea. There were no adverse events related to laboratory findings or vital signs.

The risk/benefit analysis for G-ER is similar to that of gabapentin IR. G-ER appears to be effective in the treatment of postherpetic neuralgia in adults. Given its safety profile, the risks of G-ER appear manageable by standard pharmacovigilance approaches.

At this writing, the following issues remain unresolved:

The Chemistry, Manufacturing and Controls (CMC) team has requested the following Information:

- (b) (4) drug substance particle size distribution
- Particle size specification for drug substance
- Tightened limit for total impurities in drug product
- Dissolution specification revision

The biopharmaceutics review team has raised the following issues:

- IVIVC models not acceptable
- The designation of ER tablet is not met for the proposed gabapentin ER tablet because (b) (4) (b) (4) (b) (4) .

In the absence of approval issues from the Pharmacology/Toxicology and Clinical Pharmacology teams, and findings of efficacy and safety based on my review, I recommend approval for G-ER for the treatment of postherpetic neuralgia in adult, pending resolution of the CMC and Biopharmaceutics issues noted above.

1.3 Recommendations for Postmarketing Risk Management Activities

The Applicant submitted a Risk Evaluation and Minimization Strategy (REMS) for G-ER which includes a Medication Guide and relevant Sponsor employee training. As an antiepileptic drug, G-ER has a potential for increased risk of suicidal thought or behavior.

The Medication Guide is intended to inform and educate patients and caretakers regarding proper use of G-ER. Training is intended to inform and educate Sponsor employees who have or may have interactions with patients, caretakers, and health care providers (HCPs).

Medication Guide
Pharmacies will dispense to patients a Medication Guide with each new and refill G-ER prescription in accordance with 21 CFR 208. Each shipment of G-ER product will include the US Prescribing Information and the Medication Guide to ensure distribution with each prescription. The Medication Guide will also be publicly available on the Sponsor's web site within 10 days of approval of the Medication Guide.

Training of Relevant Sponsor Personnel
As part of routine corporate training on products, relevant Sponsor personnel will be trained on the potential for an increased risk of suicidal thoughts or behavior associated with the use of G-ER.

The Sponsor will evaluate the effectiveness of the REMS for G-ER and reporting the results to FDA. Assessments of the REMS will be provided to the FDA 18 months after approval of the REMS, with additional reports to be provided three and seven years after approval, as described in the table below. The reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. The assessments will include an evaluation of the effectiveness of the risk mitigation program and recommendations for program improvements or changes, if required.

1.4 Recommendation for other Postmarketing Study Commitments

The Applicant requested a waiver from pediatric studies based on section 505B(a)(4)(B)(i) of the Pediatric Research Equity Act. The indication studied and applied for in this New Drug Application is for the management of PHN. This is a disease that is not prevalent in the pediatric age groups of 18 years and younger, which would make recruitment of clinical studies impossible or highly impractical due to the small number of pediatric patients. Based on the available information concerning the occurrence of herpes zoster and PHN in pediatric patients, it would not be reasonable to conduct a study of the efficacy of G-ER in PHN. The waiver request was granted by the Pediatric Research Committee (PeRC) on November 3, 2010.

No additional postmarketing study commitments are recommended at this time.

2. Introduction and Regulatory Background

2.1 Product Information

G-ER is a gastric retentive formulation of gabapentin for the treatment of postherpectic neuralgia. Gabapentin is an antiepileptic drug. The mechanism of action for treatment of postherpetic neuralgia is unknown.

- Description of the product: Extended-release oral tablet; 300 and 600 mg doses
- Established name and proposed trade name: Gabapentin-ER (Gralise)
- Pharmacological class: Antiepileptic drug
- Applicant's proposed indications, dosing regimens, age groups: Treatment of postherpetic neuralgia in adults; 1800 mg given daily with evening meal

2.2 Table(s) of Currently Available Treatment(s) for Proposed Indication(s)

Multiple approved products are available for the treatment of postherpetic neuralgia including Neurontin (gabepentin), Lyrica (pregabalin), Lidoderm, and Qutenza (capsaicin patch 8%).

2.3 Availability of Proposed Active Ingredient in the United States

Gabapentin is marketed as Neurontin and generics in the United States.

2.4 Important Issues with Consideration to Related Drugs

G-ER is the gastric retentive formulation of the antiepilectic drug gapapentin (Neurontin).

It is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. In addition, this drug class is known to increase the risk of suicidal thoughts or behavior. Increased seizure frequency may occur in patients with seizure disorder if G-ER is rapidly discontinued. The most common adverse reaction is dizziness. All of these issues have been well-described in the product label.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

G-ER was developed under IND 71,439. Key milestones in the clinical development program are noted below

Initial IND, December 30, 2004
"A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Gabapentin Extended Release (G-ER) Tablets in the Treatment of Patients with Postherpetic Neuralgia."

IND Safety Correspondence, February 23, 2005

- Three safety concerns (the potential enrollment of subjects with a history of epilepsy and two issues pertaining to withdrawal of anticonvulsant drugs) were conveyed to the Sponsor.
- The Sponsor agreed to modify the protocol to account for all three issues prior to enrolling any subjects.

Type C Meeting, December 19, 2005

- Because this is a 505(b)(2) application relying on findings of efficacy and safety for Neurontin, a single,positive, adequate and well-controlled study in PHN is sufficient.
- A two-week titration period followed by eight weeks of stable dosing followed by a seven-day taper is adequate.
- The primary outcome should be the difference in pain scores between baseline and end-of-treatment
- Conservative Imputation such as BOCF should be applied.
- Daily dose of 1800 mg is appears appropriate.
- The total safety database should be 300 to 500 subjects.

Advice Correspondence, August 18, 2006

- Performing continuous responder analyses by calculating the proportion of responders for each treatment arm using multiple cutoffs to define responders was advised. Any subjects who drop out or discontinue, regardless of the reason for drop-out, should be classified as non-responders (i.e. treatment failures).

(b) (4) -Request Denied due to protocol deficiencies, January 07, 2008

- The proposed sample size is acceptable. Of note, the division's assessment of efficacy will consider the overall risk and benefit and not just statistical outcomes.
- Although your primary analysis using BOCF is acceptable, we recommend that you also perform continuous responder analyses by calculating the proportion of responders for each treatment arm using multiple cutoffs to define responders.

Any subjects who drop out or discontinue regardless of the reason for drop-out should be classified as non-responders (i.e. treatment failures).

Pre-NDA Meeting, December 15, 2009

- The Summary of Efficacy for the indication PHN should be based on the results of the pivotal Phase 3 study 81-0062, and the Phase 2 study 81-0038 and Phase 3 study 81-0045, which should be presented as supportive evidence of efficacy. None of the studies should be pooled for efficacy analysis.

- In the Summary of Safety, the pooled datasets should be as follows:
  - All Phase 2 and 3 double-blind placebo controlled studies in PHN. Duration of treatment should not be truncated for the Phase 3 trials.
  - Safety data for study 81-0052 (open label PHN study) should not be pooled with any other study.
  - Study 81-0046 (placebo-controlled DPN) should not be pooled with any other study
  - Studies 81-0058 and 81-0059 (DB, PC, VMS) should be pooled.

2.6 Other Relevant Background Information

This product is not approved or marketed outside the United States.

3. Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission appeared to be of good quality. It was well organized and easily navigated except missing narratives of Serious Adverse Events (SAEs) for Vasomotor Symptoms (VMS) studies. A number of information requests were sent to the Applicant for exploratory analysis and clarifications.

3.2 Compliance with Good Clinical Practices

The applicant certified that all studies submitted were conducted in compliance with Good Clinical Practices. The Division of Scientific Investigations (DSI) conducted routine inspections of three study sites involved in study 81-0062. The study sites were selected based on the number of enrolled study subjects. DSI inspected the following investigators:

Figure 1 DSI Inspection Sites and Classification

Name of CI, IRB, or Sponsor & Location	Protocol # and # of Subjects screened (s)/enrolled (e)/ Completed (c)	Inspection Date	Final Classification
CI #1 Shisuka Malhotra, M.D. Neuro-Behavioral Clinical Research 4825 Higbee Ave.NW, Suite 102 Canton, OH 44718	Protocol 81-0062 s 19/e 9/c 3	October 4 to 14, 2010	VAI
CI #2 Daniel Koontz, M.D. Palmetto Institute of Clinical Research, Inc. 323 Lebby Street Pelzer, SC 29669	Protocol 81-0062/ s 35/e 22/c 19	October 19 to 26, 2010	Pending (Preliminary classification NAI)
CI#3 Alan Rauba, M.D. Jefferson City Medical Group 1241 West Stadium Boulevard Jefferson City, MO 65109	Protocol 81-0062/ s 16/e 12/c 11	October 13 to 15, 2010	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

Source: Evaluation of Clinical Inspections, DSI, September 10, 2008

One inspection site, site 052 (Dr. Malhotra), is classified as VAI (Voluntary Action Indicated) as reported by Dr. Susan Leibenhaut as follows:

An audit of the 10 randomized subjects' records was conducted and the reasons for screen failure were verified for the 9 subjects that were not randomized. Source data consisted of office records, worksheets provided by the sponsor, and copies of protocol specified test results. Source data concerning eligibility, concomitant medications, adverse events, and study drug dosing were compared to the line listings and the case report forms. During the study, subjects entered pain scores, the primary endpoint, into an electronic diary provided by the CRO, (b) (4) The primary endpoint data were verified by comparing the listings in the NDA with a CD of the electronic diary data provided by (b) (4) to the clinical site at the end of the study. There was no evidence of under-reporting of AEs.

A Form FDA 483 was issued to Dr. Malhotra for the regulatory violation of failure to adhere to the protocol in the following instances:
1. The protocol required that subjects have post herpetic neuralgia (PHN) for at least 6 months prior to study enrollment. Subject 052009 was enrolled after having only 5 months of PHN.
2. Dose tapering medications were dispensed to Subject 052007 during the randomization visits and were taken during the second week of the study instead of at the end of the treatment period.
3. The protocol required that subjects taking NSAIDs for comorbid conditions be on stable doses of these medications for at least 30 days prior to enrollment. Subjects 052001 and 052003 were not on stable doses of the NSAID prior to enrollment.

Dr. Leibenhaut concluded that the violations noted above do not appear to be systematic and are not widespread. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

Dr. Leibenhaut made the following overall assessment regarding the three inspected sites:

The primary endpoint data were verified and there was no evidence of underreporting of adverse events. Inspection of Dr. Malhotra's site noted violations that did not appear to be systemic or widespread and no significant violations were noted at the other two clinical sites. Although some regulatory violations were noted as per above, these are considered isolated occurrences and are unlikely to significantly impact the integrity of primary efficacy and safety data overall. The data are considered reliable in support of the application.

3.3 Financial Disclosures
The applicant has submitted the Financial Certification and Disclosure document as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*.

4 Significant Efficacy or Safety Findings Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

G-ER is supplied as extended release tablets containing 300 mg or 600 mg of gabapentin. Each 300 mg tablet also contains the inactive ingredients copovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene oxide, and Opadry® II white. In addition, Opadry II white contains: polyvinyl alcohol-part, (b) (4), titanium dioxide, talc, macrogol/peg 3350, and lecithin (soya). Each 600 mg tablet also contains the inactive ingredients copovidone, hypromellose, magnesium

stearate, polyethylene oxide, and Opadry® II beige. In addition, Opadry II beige contains: polyvinyl alcohol-part, (b) (4) titanium dioxide, talc, macrogol/peg 3350, iron oxide yellow, and iron oxide red.

Gabapentin is 1-(aminomethyl)cyclohexaneacetic acid; γ-amino-2-cyclohexyl-butyric acid with a molecular formula of $C_9H_{17}NO_2$ and a molecular weight of 171.24.

Gabapentin is a white to off-white crystalline solid with a pKa1 of 3.7 and a pKa2 of 10.7. It is freely soluble in water and acidic and basic solutions. The log of the partition coefficient (n-octanol/ 0.05M phosphate buffer) at pH 7.4 is -1.25.

Dr. Yong Hu, the CMC reviewer, did not report any issues related to the approvability of G-ER although the following informations requests are still pending:

(b) (4) drug substance particle size distribution
Particle size specification for drug substance
Tightened limit for total impurities in drug product
Dissolution specification revision

4.2 Clinical Microbiology (if applicable)

This section does not apply to this product.

4.3 Preclinical Pharmacology/Toxicology

The Sponsor is relying upon the Agency's prior finding of Safety and Efficacy for Neurontin® (NDA's 20-129) to support this application. The Sponsor conducted a 28-day repeat dose toxicity study in Beagle dogs (80-0014) using G-ER which were similar in formulation to those used in the clinical studies.

Acute Toxicity Studies
Doses of gabapentin up to 8000 mg/kg PO, 4000 mg/kg subcutaneously, and 2000 mg/kg IV caused no mortality in adult mice nor were there any effects on clinical chemistry or necropsy results. The main clinical findings were ataxia, cringing posture, and labored breathing at the highest doses. Three-week-old animals showed the same clinical signs plus ptosis, diarrhea, and reduced grip strength.

Adults and 3-week-old rats had similar responses to the same doses. However, in 7-day old animals there were a few deaths at 2000 (1 of 20), 3000 (2 of 20), and 5000 (1 of 20) mg/kg. Clinical signs included prostration and hypoactivity. Additionally, these animals had reduced weight gain.

Monkeys dosed up to 2000 mg/kg IV and 5000 mg/kg PO had no mortality. Clinical signs with animals dosed PO included diarrhea, ataxia and hypoactivity, while ataxia

and hypoactivity were observed in the IV group. Doses of 1250 mg/kg produced no clinical signs.

Subacute/ Chronic Toxicity Studies
Several subacute and chronic toxicity studies were conducted in mice, rats, dogs and monkeys.

Mice (10/sex/group) were administered gabapentin in their diet at doses of 0, 100, 500, 1000, 1500, and 2000 mg/kg/day for 13 weeks. There were no treatment-related clinical or pathological findings.

A decreased RBC (~ 13% for male and female received 2400 mg G-ER) and decreased hemoglobin (12% for male received 2400 mg G-ER) were recorded at the end of the dosing phase. However these changes were not seen in Neurontin groups. Gross necropsy of the dogs at the scheduled sacrifices revealed an increased absolute (38%) and relative to body weight (28%) testicular weight values for male dogs that received 2400 mg of G-ER tablets. These changes were dose dependent. However these findings were not seen in the Neurontin group. There were no treatment-related histopathology findings observed in this study. However, an increased severity of lymphocytic infiltrates in the prostates of males up to 2400 mg/day was seen. The incidence of the prostatic change was variable among treatment groups and was seen in control group therefore this it was considered to be unrelated to treatment. Due, organ weight and hematology findings a dose level of 1200 mg/day were considered to be the NOAEL. At 1200 mg/day on day 28, the exposure ($AUC_{0\ 24}$) was 492.5 and 598.4 µg.hr/mL and C_{max} was 32.8 and 41.7 µg/mL in males and females, respectively. The exposures to gabapentin after the administration of G-ER tablets at the NOAEL exceeded (by 3.9- fold for C_{max} and 4.1-fold for AUC) the exposure to humans dosed once daily with three 600 mg G-ER tablets, or 1800 mg/day, at steady state.

Genotoxic, reproductive toxicology, carcinogenicity studies
Negative studies are reported in gabapentin in Neurontin NDA and literature.

Upon referral to Janice Weiner in the Office of Regulatory Policy (ORP), the (b) (4) impurity specification (which is above the ICH3B guidance) is consistent with FDA's finding of safety and effectiveness for the listed drug relied upon and therefore additional studies are not needed to qualify the level of this impurity in the proposed specifications. However, the Sponsor conducted an Ames assay, an *in vitro* Chromosomal aberration assay and a 1 month general toxicity study in rats to qualify the impurity. Summary reports were provided but the draft report has not been submitted yet to the NDA.

Although the NDA will not be complete without the FINAL reports, these reports are not necessary now due to the ORP determination.

No issues were reported related to the approvability of G-ER, and no additional nonclinical studies were recommended by the Pharmacology/Toxicology reviewer, Dr. Armaghan Emami. Please see her review for details.

4.4 Clinical Pharmacology

For a detailed review of the clinical pharmacology aspects of this application, please see Dr. Suresh Naraharisetti's review.

4.4.1 Mechanism of Action

The mechanism of action by which gabapentin exerts its analgesic action is unknown. Gabapentin prevents allodynia and hyperalgesia in animal models of analgesia. It prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formulin test), but does not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.

4.4.2 Pharmacodynamics

No pharmacodynamic studies have been conducted with G-ER.

4.4.3 Pharmacokinetics

G-ER tablets are designed to be retained in the stomach in the fed state and release drug over approximately 8 – 10 hours to the small intestine where gabapentin is best absorbed. This release profile allows for once-daily dosing with a bioavailability similar to that of an IR formulation administered three times a day.

Absorption
Gabapentin is absorbed from the proximal small bowel by a saturable L-amino transport system.

Compared to gabapentin IR 600 mg given three times a day, a once-daily 1800 mg daily dose of G-ER has a higher C_{max} and lower AUC at steady state. Time to reach maximum plasma concentration (T_{max}) for G-ER is 8 hours, which is about 4-6 hours longer compared to gabapentin IR. When G-ER is administered with the evening meal, C_{max} and the majority of the AUC occurs at night.

Food effect
Gastro-retention of G-ER is driven by fed conditions. Administration of G-ER with food increases the rate and extent of absorption of gabapentin compared to the fasted state. C_{max} of gabapentin increases 33-84% and AUC of gabapentin increases 33-118% with food depending on the fat content of the meal. G-ER should be taken with food.

Distribution
Gabapentin is less than 3% bound to plasma proteins. After 150 mg intravenous administration, the mean ± SD volume of distribution is 58 ± 6 L. In patients with epilepsy, steady-state predose (Cmin) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Metabolism and elimination
Gabapentin is eliminated by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans. In patients with normal renal function given gabapentin IR 1200 to 3000 mg daily, the drug elimination half-life ($t_{1/2}$) was 5 to 7 hours. Elimination kinetics do not change with dose level or multiple doses.

Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. In elderly patients and patients with impaired renal function, plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

Special populations
Elderly
Since renal function decreases with age, gabapentin clearance may also decrease with age, resulting in higher exposure to the compound in older subjects. Reduction in gabapentin dose should be made in patients with age-related compromised renal function as described below.

Renal impairment
Renal excretion is the predominant elimination pathway of gabapentin. As renal function decreases, renal and plasma clearances and the apparent elimination rate constant decrease, while C_{max} and $t_{1/2}$ increase.

The table below summarized the Agency's recommended doses for subjects with different degrees of renal impairment based on creatinine clearance.

Figure 2 G-ER Dosage Based on Renal Function

Creatinine Clearance (mL/min)	Once Daily Dose (mg) with evening meal
≥ 60	1800 mg
30-60	600 mg to 1800 mg
<30	GRALISE should not be administered

In patients receiving hemodialysis	GRALISE should not be administered

Source: Clinical Pharmacology Review, NDA 22544

Hepatic Impairment
Because gabapentin is not metabolized, studies have not been conducted in patients with hepatic impairment.

Biopharmaceutical Issues:
Dr. Sandra Sharp, the Biopharmaceutical reviewer, reported the four issues related to the approvability of G-ER as outlined below:

IVIVC models not acceptable
The designation of ER tablet is not met for the proposed gabapentin ER tablet because (b) (4) . (b) (4) . (b) (4) .

For a detailed review of the Biopharmaceutical aspects of this application, please see Dr. Sharp's review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Eleven clinical trials have been completed during the development of G-ER (six Phase 1, and three Phase 2/3 double-blind studies for PHN, one open-label extension, and one randomized, double-blind trial for DPN). There are two additional Phase 3 studies (81-0058, 81-0059) for the treatment of vasomotor symptoms (VMS) in postmenopausal women. The following table describes the completed Phase 2 and 3 studies.

Table 1 Phase 2 and 3 Studies

Phase	Study Identifier	Diagnosis of Patients	Study Design	Number of Enrolled /Completed	Duration of G-ER Treatment (weeks)
2	81-0038	PHN	R, DB	158/140	4

3	81-0045	PHN	R, DB	407/319	10
3	81-0062	PHN	R, DB	452/379	10
3	81-0052	PHN	Open-Label Extension of 81-0045	119/117	14
2	81-0046	DPN	R, DB	182/147	4
3	81-0058	VMS	R, DB	541/373	24
3	81-0059	VMS	R, DB	565/446	12

5.2 Review Strategy

The Applicant identified one trial (81-0062) as contributing to evidence of efficacy for G-ER for the treatment of patients with postherpetic neuralgia. This study was reviewed thoroughly for study design and conduct, as well as assessment of the Applicant's efficacy conclusions. The Applicant's efficacy results were also reanalyzed by the statistical reviewer, Dr. Yongman Kim.

One Phase 3 study (81-0045) and one Phase 2 study (81-0038) that failed on the primary endpoints were reviewed individually but briefly.

Data from the pooled Phase 2/3 multiple-dose, double-blind safety analysis set were used to establish the safety of G-ER, augmented by the uncontrolled and long-term studies in patients with PHN, and the non-PHN studies. The data were reviewed to identify serious and common adverse effects of the drug in each treatment population. Additionally, all deaths were identified, and narratives/CRFs examined for evidence of causality.

5.3 Discussion of Individual Studies/Clinical Trials

PROTOCOL 81-0062; Phase 3

Title:
A Phase 3 Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Once-Daily Gabapentin Extended Release (G-ER) Tablets in the Treatment of Patients with Postherpetic Neuralgia

Date issued:
Original protocol was issued 02 November 2007; Amendment 1 was submitted 25 January 2008. First patient was enrolled 19 March 2008, and last patient was completed 17 August 2009.

Objectives:

Primary:
To assess the efficacy of G-ER 1800 mg, given as a single dose with the evening meal, compared to placebo in reducing the average daily pain score from the baseline week to the end of the efficacy treatment period (Treatment Week 10) in patients with PHN, as evaluated from the daily pain diary

Secondary:

- To assess the overall effect of treatment, rated by Patient Global Impression of Change (PGIC), Investigator-rated Clinical Global Impression of Change (CGIC), and assessment of changes from baseline in average daily sleep interference (DSI) scores

- To evaluate changes in various patient assessments of pain, including the Short-Form McGill Pain Questionnaire (SF-MPQ), the Brief Pain Inventory-short form (BPI), and the Neuropathic Pain Scale (NPS); the percent change from baseline to endpoint in average daily pain score; and the percentage of patients with 50% reduction (responders) in average daily pain scores from baseline to endpoint

Study design:
This Phase 3 study was to have been a prospective, randomized, double-blind, multicenter trial in patients with PHN who had experienced neuropathic pain for ≥ 6 months after the healing of acute herpes zoster skin rash

Duration of Treatment:
8 weeks of stable dose after two weeks of titration plus one week of tapering

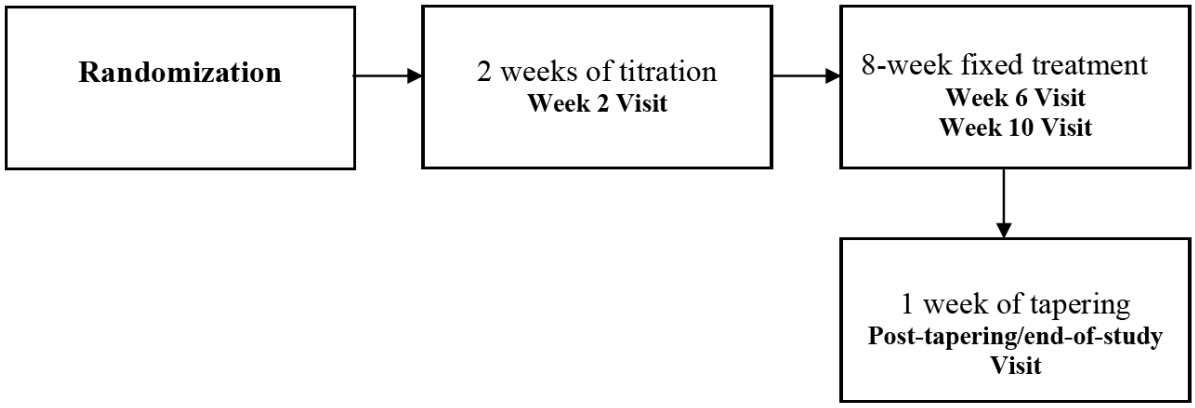
Treatment groups (N = 450):

- Placebo
- G-ER 1800 mg daily after titration

Study conduct:
After tapering and/or washout of any medications to be discontinued, patient's baseline pain and sleep interference scores were to have been established during a 1-week baseline. At the end of the Baseline Week, patients continuing to meet the pain score eligibility requirement of an average daily pain score of ≥ 4 on the 11-point NRS5 (0 = no pain;10 = worst possible pain) were to have been randomized to treatment with G-ER 1800 mg or placebo dosed once daily with the evening meal.

As show in Figure 3, the study treatment for all patients was to have been comprised of a 10-week treatment period followed by one week of gabapentin dose tapering. Double-blind treatment was to have began with titration starting at 300 mg/day and going up to a total daily dose of 1800 mg over two weeks, followed by stable dosing at 1800 mg daily for an additional eight weeks, and then one week of dose tapering.

Figure 3 Study Flow Chart



Source: Applicant's submission (PN-81-0062 Clinical Study Report, page 22)

Patients were to have used an electronic diary each morning from the beginning of the Baseline Week through the end of the efficacy treatment period (Treatment Week 10) to record pain intensity experienced during the preceding 24 hours and the degree to which pain caused sleep interference during the previous night on the 11-point NRS.

The Short-Form-McGill Pain Questionnaire (SF-MPQ), the Brief Pain Inventory-Short Form (BPI) and the Neuropathic Pain Scale (NPS) were to have been completed at the end of the Baseline Week (Randomization Visit) and at the Treatment Week 2 and Treatment Week 10 (end of efficacy treatment period) visits. A brief visit was to have occurred at Week 6 to upload diaries and assess compliance, AEs and concomitant medication use. At the Treatment Week 10 (end of efficacy treatment period or at the time of early termination) visit, investigator and patient global assessments were to have been conducted as follows:

- Investigator-rated CGIC: Investigators were to have been asked to complete the following assessment: "Please rate the patient's overall PHN symptoms as compared to symptoms upon entry in the study" as (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, and (7) Very much worse.

- PGIC: Patients were to have been asked to complete the following assessment: "Compared to your condition at admission to the project how much have you changed?" as same rated as in CGIC. A neurological examination was to have been completed at the last efficacy study visit (Treatment Week 10 or early termination visit). At the end of the Dose Tapering Week (Week 11 visit), physical and neurological examinations were to have been performed, samples were to have been collected for clinical laboratory tests. Vital signs were to have been

measured and adverse events and use of concomitant medications were to have been assessed.

Inclusion/Exclusion criteria

Inclusion criteria

1. Men or women 18 years or older who had experienced pain for six months to five years, after the healing of a herpes zoster skin rash

2. Pain intensity **≥** 4 on the 11-point NRS at screening

3. Women of childbearing potential must have had a negative serum β-hCG pregnancy test at screening and a negative follow-up urine pregnancy test at randomization, and must have used medically acceptable methods of birth control, which included oral or transdermal contraceptives, condom, spermicidal foam, IUD, progestin implant or injection, abstinence, vaginal ring, or sterilization of partner.

4. Pain intensity **≥** 4 on the 11-point NRS at screening at the end of a 1-week baseline period and had completed at least 4 days of daily pain diary entries during the Baseline Week.

5. A minimum washout period of greater than five times the half-life of the drug of any of the following medications: benzodiazepines, skeletal muscle relaxants, orally administered steroids, capsaicin, mexilitene, centrally acting analgesics (dextromethorphan, tramadol), opiates, topical lidocaine, anticonvulsants, and SNRIs. Orally administered steroids, anticonvulsants, SNRIs, opiates and benzodiazepines should have been tapered appropriately, using product label instructions as a guide.

6. Currently treated with gabapentin or pregabalin at screening were eligible for the study after a tapering period wherein the dose of gabapentin or pregabalin was reduced gradually over a period of five days followed by a 2-day washout prior before starting the Baseline Week

Exclusion criteria

1. Patients who had previously not responded to treatment for PHN with gabapentin at doses of ≥1200 mg daily or pregabalin at doses ≥300 mg daily.

2. Patients who previously experienced dose-limiting adverse effects that prevented titration of gabapentin to an effective dose.

3. A nursing mother

4. Hypersensitivity to gabapentin

5. History of neurolytic or neurosurgical treatment for PHN

6. Severe pain from causes other than PHN

7. History of using injected anesthetics or steroids within 30 days of baseline

8. History of skin conditions in the area affected by the neuropathy that could alter sensation

9. Patient was in an immunocompromised state.

10. History of renal insufficiency as an estimated creatinine clearance of <50 ml/min

11. History of malignancy within the past two years, other than basal cell carcinoma

12. History of gastric reduction surgery

13. History of severe chronic diarrhea, chronic constipation, uncontrolled irritable bowel syndrome (IBS) or unexplained weight loss

14. History of any abnormal chemistry or hematology results that were deemed by the investigator to be clinically significant

15. History of substance abuse within the past year

16. History of seizure (except for infantile febrile seizure) or was at risk of seizure due to head trauma

17. History of chronic hepatitis B or C, hepatitis within the past three months, or HIV infection

18. History of any other clinically significant medical or psychological condition that, in the opinion of the Investigator would have jeopardized the safety of the patient or affected the validity of the study results

19. Continuing use of any concomitant medication excluded by Inclusion Criterion 5

20. Participated in a clinical trial of an investigational drug or device within 30 days of the screening visit

Procedures

Randomization and blinding

After the one-week baseline period, patients who still met the eligibility requirements of an average pain intensity score of at least 4 on the 11-point NRS were to have been

randomized equally into one of two treatment groups. A computer-generated randomization schedule was to have been used to package and label the study medication with sequential patient number. Patients who met screening requirements were have to been randomized and assigned a unique number corresponding to the patient number on the study drug label.

Patients were to have been randomized appropriately at a 1:1 ratio to receive either G-ER or placebo.

Treatments

All study medications were to have been provided in blister packs containing the appropriate number of tablets for each day of the study for treatment weeks 1 though 10, and week 11 (dose tapering). Patients were to have been instructed to take the designated medication by mouth (p.o) in the evening with dinner. The dosing schedule (Table 2) was to have been as follows:

Table 2 Dose Schedule

Study Day (Dose)	number of tablets
Day 1 (300 mg)	1x300 mg
Day 2 (600 mg)	1x600 mg
Days 3-6 (900 mg)	1x300 mg, 1x600 mg
Days 7-10 (1200 mg)	2x600 mg
Days 11-14 (1500 mg)	1x300 mg, 2x600 mg
Days 15-70 (1800 mg)	3x 600 mg
Dose Tapering	
Days 71-73 (1200 mg)	2x600 mg
Days 74-77 (600 mg)	1x600 mg

Source: Modified from Applicant's submission (PN-81-0062 Clinical Study Report, page 25)

Prior medications

Medications taken for co-morbid conditions prior to study start and taken at stable doses for 30 days or more, with the exception of medications listed in the inclusion/exclusion criteria were to have been continued. For these medications taken for co-morbid conditions, as needed (PRN) dosing was to have been considered stable.

Patients taking stable doses (i.e., taken 30 or more days prior to screening and continuing without change in daily dose/dosing regimen throughout the study) of the following medications that might have mitigated the pain of PHN were to have been allowed to continue the medications without dose change during the study:

- Tricyclic or SSRI antidepressants (SNRIs were not permitted)
- Acetaminophen up to 4 g/day or NSAIDs including COX-2 inhibitors

- Aspirin up to 325 mg/day for myocardial infarction or transient ischemic attack prophylaxis

Since rescue medication was not specifically permitted in the study, the protocol stated "it was to have been preferable that the analgesic medications were not used on a PRN basis for the indication of PHN."

Concomitant therapy
All prescription and over-the-counter concomitant medications used currently or during 30 days prior to study screening were documented on the appropriate page of the CRF. The use of concomitant medications during the study was to have been documented through completion of the last study visit. During the Dose Tapering Week, patients may have taken additional pain medications or other medications that were disallowed from baseline through the Treatment Week 10 Visit, at the discretion of the investigator.

Rescue medication
Rescue medications were not to have been specifically provided for patients in this trial. If a patient was having unacceptable PHN pain, the protocol stated "the investigator was to have considered discontinuation of the patient from the trial." Any use of acetaminophen or any other analgesic a patient may have taken on his/her own to treat unmanaged PHN pain should have been recorded on the Concomitant Medications CRF for the indication of PHN, so that use of any apparent rescue medications could have been captured for data analysis.

Reviewer's comments: It is not clear whether the subjects who took rescue medications were required to be discontinued from the trial or was discontinuation at the discretion of the investigator. The Applicant provided the following response:

The protocol states that in the event of a subject having unacceptable PHN pain the investigator should consider withdrawing the subject from the study. At the investigators meetings it was emphasized that as the nature of the analysis was BOCF with MBIR (maximum baseline pain score imputation for the use of rescue medication) keeping the subject in the study with rescue medication would have resulted in the same net data being used in analysis as withdrawing the subject and as such the subject should be withdrawn. This encouragement to withdraw subjects still with unacceptable pain was communicated at the investigators meetings in US, Russia and Argentina. However, the investigator ultimately had the final decision on whether to discontinue the subject. Overall, the large majority of the investigators followed this direction and only 5 subjects had prohibited rescue medication administered.

The Applicant also listed the five subjects with a short description in response. Three of patients (Subjects 007008, 013012, 024003) were randomized to placebo, while two patients were randomized to G-ER.

The reviewer agrees that since only five subjects received prohibited rescue medications, this discrepancy is unlikely to affect the efficacy analysis. A sensitivity analysis (considering subjects using rescue medication as treatment failures) was performed by the Agency.

Procedure schedule

The time and events schedule below (Table 3) summarizes the frequency and timing of the efficacy, safety, tolerability, PK and other measurements during the study.

Table 3 Schedule of Procedure and Assessments

Procedures	Screening	Tapering/ Washout+	Baseline Week*	Randomization ** (end of baseline Wk 0)	Treatment Wk 2	Treatment Wk 6	Treatment Wk 10 (end of efficacy treatment)	Treatment Wk 11 Dose Tapering Week/Early Termination
Visit Window				+2 days	±2 days	±2 days	-2, +1 days	+2 days
Patient consent	x							
Medical history	x							
Physical Exam	x							x
Neurological Exam	x						x	x
Vital signs	x			x				x
Hgt/Wgt++	x							x
ECG	x							
Safety labs	x							x
serum β-hCG pregnancy test	x							x
UPT				x				
Study-Site Pain Assessment	x			x				
Tapering/Washout of prohibited meds as required		x						
Diary Dispensed to patient			x	x	x	x		
Study meds dispensed				x	x		x	
Used blister packs returned/ compliance checked					x	x	x	x
Diary Upload at site				x	x	x	x	
SF-MPQ				x	x		x	
NPS				x	x		x	
CGIC/PGIC							x	
BPI				x	x		x	
Adverse events			x	x	x	x	x	x
Concomitant meds	x		x	x	x	x	x	x

Source: Applicant's submission (PN-81-0062 Clinical Study Report, page 30 and 31)

Procedures and Assessments per visit
After providing informed consent, a medical history including a physical and a neurological examination, a 12-lead electrocardiogram (ECG), and a review of inclusion/exclusion criteria including concomitant medication use were to have been performed to assess a patient's eligibility for the study.

Vital signs, including body temperature (°F), respiratory rate, sitting radial pulse rates, and sitting systolic and diastolic blood pressures were to have been collected, and height and weight were to have been measured.

The patient was to have been asked to rate his/her neuropathic pain on the 11-point NRS, where 0 = no pain and 10 = worst possible pain. The screening pain intensity score was to have been marked on a paper scale by the patient and the result was to have been recorded on the appropriate CRF page.

If all study criteria were met, blood samples were to have been drawn for chemistry and hematology, and a urine pregnancy test was to have been performed as appropriate.
.
Patients requiring a washout of medications specified in Inclusion Criteria were to have been given instructions regarding washout procedures. If a patient was required washout, the baseline visit could have been combined with the screening visit.

Outcome measures
Efficacy
- Average Daily Pain (ADP) Scale (A 0-10 scale from 0 = "no pain" to 10 = "worst pain") rated daily
- Patient global impression of change (PGIC), Clinical Global Impression of Change (CGIC) measured once at Treatment Week 10, and daily DSI score.
- SF-MPQ, NPS and BPI at Randomization, Treatment Weeks 2 and 10

Safety laboratory tests
- ECGs, vital signs, physical exam (including neurological), serology, urine drug screens
- Pregnancy tests

Efficacy Endpoints
Primary endpoint
Mean change in average daily pain score from the baseline week to the final week of the efficacy treatment period, evaluated from the daily pain electronic diary, for patients treated with G-ER 1800 mg dosed once daily compared to placebo

Secondary endpoints

1. The proportion of patients who were categorized as “very much” or “much improved” in Patient Global Impression of Change (PGIC)

2. The proportion of patients who were categorized as “very much” or “much improved” in Clinical Global Impression of Change (CGIC)

3. The mean change in BOCF average daily sleep interference (DSI) score from baseline to the final week of the efficacy treatment period, evaluated from the daily sleep entry in the electronic diaries, assessed on an 11-point numeric rating scale ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep)

Additional endpoints

1. Mean change in LOCF average daily pain score from the baseline week to the final week of the efficacy treatment period

2. Proportion of responders according to multiple cutoffs of 10% increments based on the percent change in average daily pain score from baseline to BOCF and LOCF endpoint. Any subjects who dropout or discontinue regardless of the reason for dropout was classified as non-responders (i.e., treatment failures)

3. Proportion of responders at endpoint. Responders are those patients who had a 50% or greater reduction in average daily pain score from baseline to BOCF or LOCF endpoint.

4. Mean change in average daily pain score from baseline to follow-up weeks

5. Percent change in average daily pain score from baseline to follow-up weeks and the final week of the efficacy treatment period

6. Mean change in average daily sleep interference score from baseline to BOCF and LOCF follow-up weeks and the final week of the efficacy treatment period, evaluated from the daily sleep diaries assessed on an 11-point numeric rating scale, ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep)

7. Percent change in average daily sleep interference score from baseline to BOCF and LOCF follow-up weeks and the final week of the efficacy treatment period

8. Mean change in Pain Rating Index (Sensory) (PRIS) evaluated from SF-MPQ from baseline to LOCF endpoint in the ITT population. The PRIS is the total score of items 1 to 11 on SF-MPQ (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, and splitting)

9. Mean change in Pain Rating Index (Affective) (PRIA) evaluated from SF-MPQ from baseline LOCF to endpoint in the ITT population. The PRIA is the total score of items 12 to 15 on SF-MPQ (tiring-exhausting, sickening, fearful, and punishing-cruel)

10. Mean change in total Pain Rating Index (PRIT) evaluated from SF-MPQ from baseline to LOCF endpoint in the ITT population. The PRIT is the total score of all 15 items on SF-MPQ

11. Mean change in pain intensity in visual analogue scale (VAS) evaluated from the SFMPQ from baseline to LOCF endpoint in the ITT population

12. Mean change in present pain intensity evaluated from the SF-MPQ from baseline to LOCF endpoint in the ITT population

13. Mean change in average of all 10 items evaluated from the NPS (NPS10) from baseline to LOCF endpoint in the ITT population. The NPS10 is the average of 10 pain domains (intense, sharp, hot, dull, cold, sensitive, itchy, unpleasant, and intensity of deep and surface pain)

14. Mean change in average of 8 descriptors evaluated from the NPS (NPS8) from baseline to LOCF endpoint in the ITT population. The NPS8 is the average of six specific pain qualities (sharp, hot, dull, cold, sensitive, and itchy) and two pain locations (deep and surface) on NPS

15. Mean change in average of non-allodynia items evaluated from the NPS (NPSNA) from baseline to LOCF endpoint in the ITT population. The NPSNA is the average of eight non-allodynia items on NPS (intense, sharp, hot, dull, cold, itchy, unpleasant, intensity of deep pain)

16. Mean change in average of four peripheral pain items evaluated from the NPS (NPS4) from baseline to LOCF endpoint in the ITT population. The NPS4 is the average of four items on NPS thought to reflect peripheral pain mechanisms (sharp, hot, dull, and intensity of deep pain)

17. Mean change in BPI pain severity scores evaluated from the BPI from baseline to LOCF endpoint in the ITT population. BPI pain severity scores include the worst and least pain in the last 24 hours, average pain, and pain right now measured on the 11- point numeric pain rating scale, ranging from 0 (no pain) to 10 (worst pain possible)

18. Mean change in BPI interference scores evaluated from the BPI from baseline to LOCF endpoint in the ITT population. BPI interference scores include seven

items which are: general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life measured on the 11-point numeric pain rating scale, ranging from 0 (does not interfere) to 10 (completely interferes)

19. Mean change in average of seven BPI interference items evaluated from the BPI (BPI7) from baseline to LOCF endpoint in the ITT population

20. Proportion of patients who used rescue medication

Discontinuation and Replacement of Patients
Patients were to have been informed that they were free to withdraw from the study at any time. The Investigator, the Investigator in consultation with the Medical Monitor, or the Medical Monitor could exercise his or her medical judgment to terminate a patient's participation in the study due to clinically significant changes in any clinical or laboratory parameter.

Patients were to have been instructed to not cease taking study medication abruptly. If a patient elected to terminate the study prematurely during study drug treatment, he/she was to have been instructed to return to the clinic for end of efficacy evaluations and was given the blister pack for gabapentin tapering.

Tapering medication was not to have been given to a patient who withdrew from the study during Treatment Week 1 or who had discontinued from the study and stopped taking study medication for two or more days. The Investigator was to have determined the appropriateness of giving the tapering medication to a patient who withdrew from the study due to a drug-related AE, based on the specifics of the AE.

The Sponsor was to have been notified immediately if the withdrawal was due to a serious adverse event. Ongoing serious adverse events at the time of withdrawal were to have been followed until resolved or medically stable. The investigator in collaboration with the medical monitor could have concluded the study due to serious adverse events, and the sponsor could terminate the study at any time for clinical or administrative reasons. Patients who discontinued from the study were not to have been replaced.

Statistical Methods
Sample size determination
A sample size of approximately 450 patients (225 patients per treatment group) was planned for this study to ensure at least 382 patients (191 patients per treatment group) would complete the efficacy treatment period and have available primary efficacy data at the final week of efficacy treatment period for data analysis.

A sample size of 382 patients (191 patients in both the G-ER treatment group and in the placebo group) provided 90% power to detect at least a 0.4 point difference between

two treatment groups in the mean change of average daily pain score from baseline week to the final week of the efficacy treatment period. This calculation was based on a two-sided, two-sample t-test with one to one ratio of sample size allocation, a standard deviation of 1.2 points, and significance level of $\alpha = 0.05$.

Subject information analyses
Demographic and baseline characteristics were to have been summarized by treatment group for all randomized patients. Baseline disease characteristics related to PHN and electrocardiogram (ECG) data were to have been summarized by treatment group for all randomized patients, the ITT population, Completers, and the safety population.

Primary efficacy analyses
The primary efficacy parameter was the mean change in BOCF average daily pain score from the Baseline Week to Treatment Week 10, evaluated from the daily pain electronic diary. Pain score were measured on the 11-point numerical rating scale, ranging from 0 (no pain) to 10 (worst possible pain).

Secondary efficacy analyses

- Proportion of patients who were categorized as “very much” or “much improved” in Patient Global Impression of Change (PGIC)
- Proportion of patients who were categorized as “very much” or “much improved” in Clinical Global Impression of Change (CGIC)
- Mean change in BOCF average daily sleep interference score from baseline to final week of the efficacy treatment period, evaluated from the daily sleep electronic diaries assessed on an 11-point numeric rating scale, ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep)

Protocol amendments
Original protocol was issued 02 November 2007. Amendment 1 was submitted 25 January 2008 before any patients were enrolled (The study started from 19 March 2008). These changes are briefly described below.
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Amendment 1

1. Protocol Title: The dosing regimen was specified.

2. Both the end of efficacy treatment and the length of the tapering week were updated throughout the whole document.

3. Synopsis: wording describing specific countries of investigation was modified and clarified.

4. Primary Objectives: wording was clarified.

5. Study Overview: pre-baseline week was removed; treatment duration and associated procedures were modified and clarified; option to titrate to 2400 mg at week 3 was removed; anchors on the Numerating Rating Scale were specified; wording for use of the PGIC and CGIC was clarified.

6. Study Medication Dosing: the table was modified for clarification.

7. Discussion of Study Design: wording was removed for clarification.

8. Duration of Study: modification and clarification of the original text reflecting removal of the pre-baseline week, change in stable dose period, and change in estimated study duration.

9. Inclusion Criteria were revised to reflect the following updates: use of NRS in IC # 2, requirement for a negative β-hCG pregnancy test at screening in IC #2, addition of steroids to list of drugs requiring prior washout in IC # 5, and tapering period and process for gabapentin or pregabalin at screening in IC # 6.

10. Treatment Administration: wording was modified for clarification.

11. Potential Toxicity, Dose Modification, and Management: wording was modified to specify that dose modification was not permitted.

12. Prior Medication: the use of analgesic medications was clarified.

13. Screening Visit: type of screening pregnancy test, maximum duration between screening and beginning of washout, and use of NRS were specified.

14. Baseline Week Visit: section title was changed to reflect elimination of the pre-baseline week; reinforcement of a full 7-day baseline week and Diary PRO questions about pain and sleep interference were added for clarification.

15. Randomization Visit: wording was added to emphasize the need for a full 7-day baseline period.

16. Treatment Week 2 Visit: wording was added to reflect a change in schedule for study drug dispensing.

17. Treatment Week 3 Visit: this visit was removed from the study.

18. Treatment Week 6 Visit: wording was removed to emphasize that the pain questionnaires would not be completed at this visit.

19. End of Efficacy Treatment Period (Week 10) Visit: change in visit week and wording for the PGIC and CGIC were clarified.

20. Tapering Visit: change in visit week and use of serum β-hCG pregnancy test were specified.

21. Appropriateness of Measures: wording was added to clarify the anchors used in the NRS wording.

22. Primary Efficacy Variable: wording was deleted to reflect dosing update.

23. Physical Examination / Vital Signs: wording describing conduct of neurological examination was clarified.

24. Laboratory Parameters: wording was modified to specify pregnancy test process.

25. Wording describing statistical analysis was added in the Efficacy Parameters section and modified in the Analysis of Responder and Percent Change Data section for clarification. Definition of completers was clarified.

Reviewer's comment: The above protocol amendment would not be expected to have an important effect on the conduct of the study or the analyses related to efficacy of the study drug. The protocol amendment was issued before the first subject was screened.

Results
The study was conducted from 19 March 2008 – 17 August 2009 at 57 sites in the United States, 24 in Russia and 9 in Argentina.

Subject Disposition
A total of 512 patients were assessed for eligibility. Of those, 60 were excluded. Four hundred and fifty two patients were randomized, but only 451 completed the baseline period (patient # 052-005 who had no baseline data was randomized to the G-ER group). Patient # 052-005 was thus excluded from the ITT population but was included in the safety population. In addition, one patient entered the study twice, at 2 different sites, with 2 different ID numbers (# 028-002 and #013-009). As # 028-002, this patient was randomized on 03 October 2008 into the G-ER group and her data was analyzed. As # 013-009, this same patient had a later randomization date of 01 May 2009 and was randomized to the placebo group. Patient 013-009 was then excluded from the ITT analysis set for placebo, because she entered the study for the second time, but included in the safety population for placebo.

Summaries of patient disposition are provided in Figure 4 and Table 4.

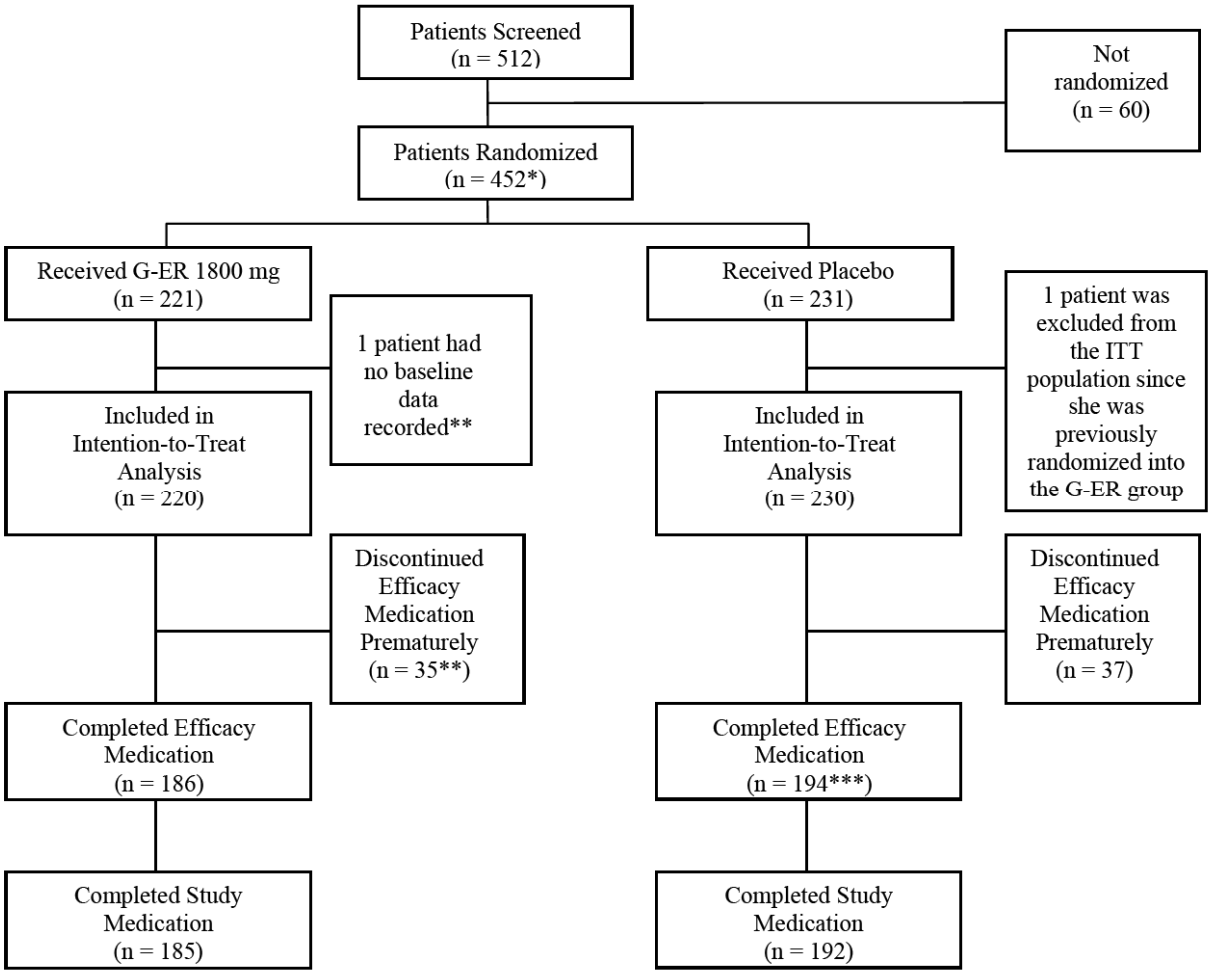


Figure 4 Subject Disposition

Source: Applicant's submission (PN 81 0062 Clinical Study Report, page 55)

Table 4 Subject Disposition

	G-ER 1800 mg Daily n (%)	Placebo	Total
Randomized	221 (100)	231 (100)	452 (100)
ITT	220 (100)	230 (100)	450 (100)
Completed	185 (84)	192 (83)	377 (83)
Dropout	36 (16)	39 (17)	75 (16)

Table 5 Reasons for Dropout of Study Medication

	G-ER 1800 mg Daily N=221(%)	Placebo N=231 (%)	Total N=452 (%)
Dropout	36 (16)	39 (17)	75 (17)
AE	19 (53)	8 (21)	27 (36)
Lack of efficacy	7 (19)	12 (31)	19 (25)
Protocol violation	2 (6)	2 (5)	4 (5)
Lost to follow-up	0	1 (3)	1 (1)
Death	0	1 (3)	1 (1)
W/D of consent	4 (11)	9 (23)	13 (17)
Others	4 (11)	6 (15)	10 (13)

Source: Modified from Applicant's submission (PN-81-0062 Clinical Study Report, page 56)

Seventy-five (17%) patients prematurely discontinued the study medication, 36 (16 %) in the G-ER group and 39 (17%) in the placebo group (

Table 5). Seventy-two patients discontinued during the efficacy treatment period and three during the study drug tapering period. The three most common reasons for discontinuation of study medication were adverse events, lack of efficacy, and withdrawal of consent. Among the patients who prematurely discontinued G-ER, 19 (53 %) did so because of an adverse event, 7 (19 %) because of lack of efficacy, and 4 (11 %) withdrew their consent. Among the patients who prematurely discontinued placebo, 8 (21 %) did so because of an adverse event, 12 (31 %) because of lack of efficacy, and 9 (23 %) withdrew their consent. In the placebo group, one patient died and one was lost to follow-up.

Reviewer's comment #1: Regarding the disposition of patients, the Applicant was asked to readjudicate those patients who discontinued due to the reasons "withdrew consent" or "other reasons" by reviewing the CRFs to determine whether any of these subjects actually discontinued due to adverse events or lack of efficacy. The applicant was also asked to submit the CRFs to the NDA. The following response was provided:

During the conduct of study 81-0062 there were 13 patients who withdrew consent (4 receiving G-ER 1800 mg and 9 receiving placebo) and 10 patients who withdrew citing other reasons (4 receiving G-ER 1800 mg and 6 receiving placebo). These patients are discussed in their respective groups. For each of these patients, narratives were written describing the adverse events and for assessment of efficacy, the change from baseline for the Daily Pain Diary (LOCF) and the patient's self-rating on the PGIC.

The applicant concluded that of the 8 subjects randomized to G-ER who discontinued due to either withdrawal of consent or other reasons five subjects also had coincidental mild adverse events including an episode of dizziness and an episode of pedal edema that were both reported as associated with gabapentin therapy. In both cases the investigator confirmed on the study completion form that these were not the primary reasons for discontinuations. The other adverse events were exacerbation of overactive bladder, back pain secondary to injury/fall and dental pain not felt to be related to therapy by the investigator or medical monitor. In the case of the 15 subjects who were randomized to placebo who discontinued due to either withdrawal of consent or other reasons four subjects experienced mild adverse events at the time of discontinuation. These were deemed unrelated to therapy by the investigator and included cystitis, abdominal pain, vomiting plus abdominal tenderness and nausea/vomiting/diarrhea.

The reviewer agrees that the reasons for discontinuation reflected in the 81-0062 datasets are acceptable except there was one case of dizziness (Subject 077003) and one case of pedal edema (subject 025006) for which withdrawal could be deemed due to AEs.

Reviewer's comment #2: The Applicant was asked to provide the disposition of study subjects by country for study 81-0062. The following response was provided:

In the US, 259 patients were randomized, in Russia 161 patients were randomized and 32 patients were randomized in Argentina.

Overall, seventy-five (16.6%) patients prematurely discontinued the study medication, 36 (16.3%) in the G-ER group and 39 (16.9%) in the placebo group. In the US, 58 patients discontinued prematurely (26 or 20.5% in the G-ER group and 32 or 24.2% in the placebo group), in Russia 14 patients discontinued prematurely (9 or 11% in the G-ER group and 5 or 6.3% in the placebo group) and in Argentina three patients discontinued prematurely (one or 7.7% patient in the G-ER group and two or 10.5% patients in the placebo group).

The Reviewer acknowledges that the overall rates of premature discontinuation in both G-ER group and placebo group are higher in US than in non-US subjects. The difference in drop out rate in US and non-US may not be able to explain the marked difference in efficacy findings in three countries.

Demographic and Baseline Characteristics

There was no statistical adjustment for multiplicity; thus, all analyses in this section should be considered descriptive.

A summary of demographics and baseline characteristics for the randomized population is presented in Table 6. The mean age for all randomized patients was 65.6 years, with

a range of 21 to 89 years. Overall, 62.6% of patients were female and 37.4% were male. There was not a significant difference in gender distribution between the G-ER (61.1% female, and 38.9% male) and the placebo (64.1% female, and 35.9% male) groups. A majority (88.9%) of patients were Caucasian. Mean (SD) weight was 80.8 (19.0) kg, mean (SD) height was 166.7 (10.2) cm, and mean (SD) body mass index (BMI) was 29.0 (5.9) kg/m2. There were no significant differences between the G-ER group and the placebo group at baseline in mean weight, height, or BMI.

Table 6 Demographics and Baseline Characteristics

	Gabapentin ER 1800 mg (n = 221)	Placebo (n = 231)	Total (n = 452)	p-value[1]
Age (years): n (%)				
< 65	81 (36.7%)	90 (39.0%)	171 (37.8%)	0.811
65-74	82 (37.1%)	86 (37.2%)	168 (37.2%)	
≥ 75	58 (26.2%)	55 (23.8%)	113 (25.0%)	
Mean (SD)	65.3 (13.3)	65.9 (11.1)	65.6 (12.2)	0.609
Sex: n (%)				
Female	135 (61.1%)	148 (64.1%)	283 (62.6%)	0.560
Male	86 (38.9%)	83 (35.9%)	169 (37.4%)	
Race: n (%)				
Caucasian	197 (89.1%)	205 (88.7%)	402 (88.9%)	0.619
Black	10 (4.5%)	6 (2.6%)	16 (3.5%)	
Asian	1 (0.5%)	2 (0.9%)	3 (0.7%)	
Other	13 (5.9%)	18 (7.8%)	31 (6.9%)	
Weight (kg): n (%)				
Mean (SD)	81.9 (20.2)	79.7 (17.7)	80.8 (19.0)	0.210
Height (cm): n (%)				
Mean (SD)	166.8 (10.1)	166.7 (10.4)	166.7 (10.2)	0.927
Body Mass Index (kg/m^2): n (%)				
< 30	138 (62.4%)	150 (64.9%)	288 (63.7%)	0.625
≥ 30	83 (37.6%)	81 (35.1%)	164 (36.3%)	
Mean (SD)	29.3 (5.8)	28.7 (6.0)	29.0 (5.9)	0.277

Source: Post-text Table 14.1.6.
[1] The p-value for the comparison between treatment groups is based on the two-sample t-test for continuous data and a two-sided Fisher's Exact test for categorical data.
Source: Applicant's submission (PN 81 0062 Clinical Study Report, page 60)

There were no significant differences between the G-ER group (6.6) and the placebo (6.5) group at baseline in mean baseline average daily pain score.

The two most common locations for neuropathic pain at baseline were the posterior torso (42.3%) and the anterior torso (41.6%). There were no clinically relevant differences between the G-ER and placebo groups in percentage of patients reporting a specific neuropathic pain location.

There were no clinically relevant differences between the G-ER and placebo groups for time from resolution of last herpes zoster skin rash to study entry. A majority of patients (58.0% in the ITT population) had not used gabapentin/pregabalin prior to study entry.

Treatment Compliance

There were no clinically relevant differences between the G-ER 1800 mg and placebo groups for study medication compliance during the entire study, during the efficacy treatment period, or during the tapering period. The mean (SD) tablet compliance rate was 97.2% (8.2%) for the entire study, 99.1% (4.3%) during the efficacy treatment period, and 99.9% (1.6%) during the tapering period.

Protocol Deviations

There were a total of six protocol deviations:

One patient was suspected of having stomach cancer, and this resulted in “baseline failure” (The subject 082910 was not randomized).

In the placebo group, one patient received improper dosing, and one patient took a prohibited medication. One patient was randomized twice at two different clinical sites, and the second enrollment in the placebo group was considered a violation.

In the G-ER 1800 mg group, one patient took a disallowed concomitant medication, and one patient failed inclusion criteria # 4 (patient needed to have a mean baseline week pain intensity score of at least 4 on the 11-point NRS at the end of a 1-week baseline period and to have had completed at least 4 days of daily pain diary entries during the Baseline Week).

Reviewer’s comment: The above protocol deviations would not be expected to have an important effect on the conduct of the study or the analyses related to efficacy of the study drug. Based on the Patient Data Listing 16.2.5., the “baseline failure” suggests that the patient who was suspected of having stomach cancer (082910) was not randomized to the study.

Efficacy Results

Primary Efficacy Analysis

The primary efficacy parameter was the mean change in BOCF average daily pain scores from the baseline week to the final week of the efficacy treatment period for patients treated with G-ER 1800 mg compared to placebo.

The Applicant's analysis of BOCF average daily pain score for the ITT population is presented in Table 7.

All 450 patients in the ITT population were included in the primary analysis of average daily pain score. The mean (SD) BOCF average daily pain scores at baseline were 6.6 (1.4), and 6.5 (1.4) for the G-ER and placebo groups, respectively. Gabapentin ER (-2.12 ± 0.17) was superior to placebo (-1.63 ± 0.16) in reducing the LS mean ± SEM average daily pain score from baseline to BOCF endpoint, with a difference of -0.49 ± 0.20 (p = 0.0125).

Table 7 Analysis of Average Daily Pain Score (Primary Analysis)

ADP	G-ER 1800 mg Daily (n=220)	Placebo N=230)
LS Means (SE)	-2.1 (0.21)	-1.6 (2.0)
Difference from placebo (SE) 95% CI	-0.49 (0.20) (-0.88, -0.11)	
P-value*	**0.0125**	

*P-value calculated from ANCOVA

Source: Modified from Applicant's submission (PN-81-0062 Clinical Study Report, page 66)

The Applicant's analysis of the primary efficacy endpoint, using BOCF imputation, has been confirmed by the Agency's statistical reviewer, Yongman Kim, PhD..

As presented by Dr. Kim, even considering subjects using rescue medication as treatment failures, this study still reached statistical significance in primary analysis as shown in the table below.

Table 8 Sensitivity Analysis of Primary Endpoint

Average Daily Pain ADP	G-ER 1800mg QD (N 220)	Placebo (N 230)

LS Means (SE)	-2.0 (0.17)	-1.6 (0.16)
Difference from placebo (SE) 95% CI	-0.4 (0.19) (-0.8, -0.0)	
P-value*	**0.030**	

Note: Rescue medication takers were treated as treatment failures.
P-value calculated from ANCOVA model with terms for treatment, center, and baseline score as covariate.
Source: Dr. Youngman Kim

Three Key Secondary Efficacy Analyses

A statistical hierarchy was employed for three key secondary endpoints with the alpha being divided between the PGIC and CGIC (0.025 per point) and only if one of these endpoints were met was the sleep interference scores performed at $\alpha = 0.05$.

Patient Global Impression of Change (PGIC)

The Applicant's analysis of PGIC is presented in Table 9. The proportion of patients who were rated as very much improved or much improved at endpoint was 42.7% in the G-ER group and 33.5% in the placebo group. The difference (9.0%) between the two groups did trend in the positive direction, but was not statistically significant ($p = 0.0434$) based on the hierarchical requirements. Overall, 71.5% of patients in the G-ER group reported some improvement compared to 58.6% in the placebo group.

Table 9 Analysis of Patient Global Impression of Change

Patient Global Impression of Change	Gabapentin ER 1800 mg (n = 220)	Placebo (n = 230)
PGIC at Endpoint: n (%)		
Very much improved	36 (16.4%)	29 (12.6%)
Much improved	58 (26.4%)	48 (20.9%)
Minimally improved	62 (28.2%)	61 (26.5%)
No change	46 (20.9%)	69 (30.0%)
Minimally worse	8 (3.6%)	8 (3.5%)
Much worse	4 (1.8%)	4 (1.7%)
Very much worse	2 (0.9%)	1 (0.4%)
Not evaluated	4 (1.8%)	10 (4.3%)
Very Much or Much Improved at Endpoint: n (%)		
Yes	94 (42.7%)	77 (33.5%)
No	126 (57.3%)	153 (66.5%)
Gabapentin ER minus Placebo		
Difference in P(Yes)	0.09	
95% CI of DP	(0.00, 0.18)	
p-value (vs. Placebo)[1]	0.0434	

Source: Applicant's submission (PN 81 0062 Clinical Study Report, page 67)

Clinical Global Impression of Change (CGIC)

The Applicant's analysis of the CGIC is presented in Table 10. The proportion of patients who were rated as very much improved or much improved at endpoint was 44.1% in the G-ER group and 33.9% in the placebo group. The difference (10.0%) between the two groups was marginally not statistically significant (p = 0.0268), based on the hierarchical requirements of p < 0.025. Overall, 68.7% of patients in the G-ER group reported some improvement compared to 59.4% in the placebo group.

Table 10 Analysis of Clinical Global Impression of Change

Clinical Global Impression of Change at Baseline	Gabapentin ER 1800 mg (n = 220)	Placebo (n = 230)
CGIC at Endpoint: n (%)		
Very much improved	33 (15.0%)	33 (14.3%)
Much improved	64 (29.1%)	45 (19.6%)
Minimally improved	51 (23.2%)	60 (26.1%)
No change	54 (24.5%)	73 (31.7%)
Minimally worse	7 (3.2%)	9 (3.9%)
Much worse	5 (2.3%)	0 (0.0%)
Very much worse	0 (0%)	1 (0.4%)
Not evaluated	6 (2.7%)	9 (3.9%)
Very Much or Much Improved at Endpoint: n (%)		
Yes	97 (44.1%)	78 (33.9%)
No	123 (55.9%)	152 (66.1%)
Gabapentin ER minus Placebo		
Difference in P(Yes)	0.10	
95% CI of DP	(0.01, 0.19)	
p-value (vs. Placebo)[1]	0.0268	

Source: Applicant's submission (PN 81 0062 Clinical Study Report, page 68)

BOCF Average Daily Sleep Interference (DSI) Score

Neither PGIC nor CGIC reached the required alpha of 0.025 for statistical difference versus placebo; as a result, the analysis of change in BOCF average daily sleep interference score was performed on an exploratory basis only. The Applicant's analysis is presented in Table 11.

The mean (SD) BOCF average daily sleep interference scores at baseline were 5.3 (2.2), and 5.2 (2.2) for the G-ER and placebo groups, respectively. Gabapentin ER (-2.30 ± 0.16) was superior to placebo (-1.59 ± 0.15) in reducing the LS mean ± SEM average daily sleep interference score from baseline to BOCF endpoint (p-value = 0.0001)

Table 11 Analysis of Average Daily Sleep Interference Score

Average Daily Sleep Interference Score	Gabapentin ER 1800 mg (n = 220)	Placebo (n = 230)	G-ER vs. Placebo p-value
Baseline:			
Mean (SD)	5.3 (2.2)	5.2 (2.2)	
95% CI	(5.04, 5.61)	(4.88, 5.46)	
p-value (vs. Placebo)[1]			0.441
BOCF Endpoint:			
Mean (SD)	3.1 (2.6)	3.6 (2.6)	
Change from Baseline to Endpoint:			
Mean (SD)	-2.3 (2.2)	-1.6 (2.0)	
LS Mean (SEM)	-2.30 (0.16)	-1.59 (0.15)	
95% CI	(-2.61, -1.99)	(-1.89, -1.28)	
Gabapentin ER minus Placebo			
LS Mean Difference (SEM)	-0.71 (0.18)		
95% CI for Difference	(-1.07, -0.35)		
p-value (vs. Placebo)[2]			0.0001

Source: Applicant's submission (PN 81 0062 Clinical Study Report, page 69)

The sponsor originally did not offer an explanation why the key secondary endpoints failed to support the primary endpoint. At the request of Agency, the Sponsor provided the following reply regarding why the key endpoints failed to support the primary endpoint in the pivotal Phase 3 study (81-00620:

Study 81-0062 employed a very rigorous statistical hierarchy for secondary endpoints with the alpha being divided between the PGIC and CGIC (0.025 per endpoint) and only if one of these endpoints was met was the sleep interference data considered. In isolation, the change in the PGIC achieved a p-value of < 0.05 (p=0.0434) as did the change in CGIC (p=0.0268) and the change in sleep interference (p=0.0001). Each of these parameters demonstrates a strong trend in favor of the active therapy and this trend is also consistent across all three parameters.

For both the PGIC and CGIC approximately 10% more patients report being 'much' or 'very much improved' compared to placebo. This represents a proportionate increase of between one quarter and one third in the number of patients reporting such an improvement (from about 33% to about 43%) illustrating the clinical relevance of these results. In the case of the sleep interference scale, subjects at baseline have their sleep disturbed by PHN to an extent of 5 on a scale from 0 (pain does not interfere with sleep)

to 10 (pain completely interferes with sleep). Active drug is associated with an improvement of 42% (5.3 to 3.1) compared to placebo which is only associated with an improvement of 31% (5.2 to 3.6). This improvement in sleep is also likely to be clinically relevant to patients in a disease state characterized by nocturnal symptoms and disturbed sleep.

Additional Efficacy Parameters of Interest
There was no statistical adjustment for testing outside the primary and the three key secondary end points; thus, all remaining analyses should be considered descriptive.

Mean Change in LOCF Average Daily Pain Score
The applicant's analysis of LOCF average daily pain scores for the ITT population shows that the mean (SD) average daily pain score at baseline was 6.6 (1.4) for the G-ER group and 6.5 (1.4) for placebo group. Gabapentin ER (-2.40 ± 0.17) was superior to placebo (-1.85 ± 0.17) in reducing the LS mean ± SEM average daily pain score from baseline to LOCF endpoint (p = 0.007).

Proportion of Responders at Endpoint
According to Decile Groups (BOCF)
A decrease in average daily pain score was observed for 73.2% of patients in the G-ER treatment group and 67.0% of patients in the placebo group. Conversely, an increase from baseline in average daily pain score was observed for 8.2% of patients in the G-ER treatment group and 10.4% of patients in the placebo group.

Table 12 Responder Analysis

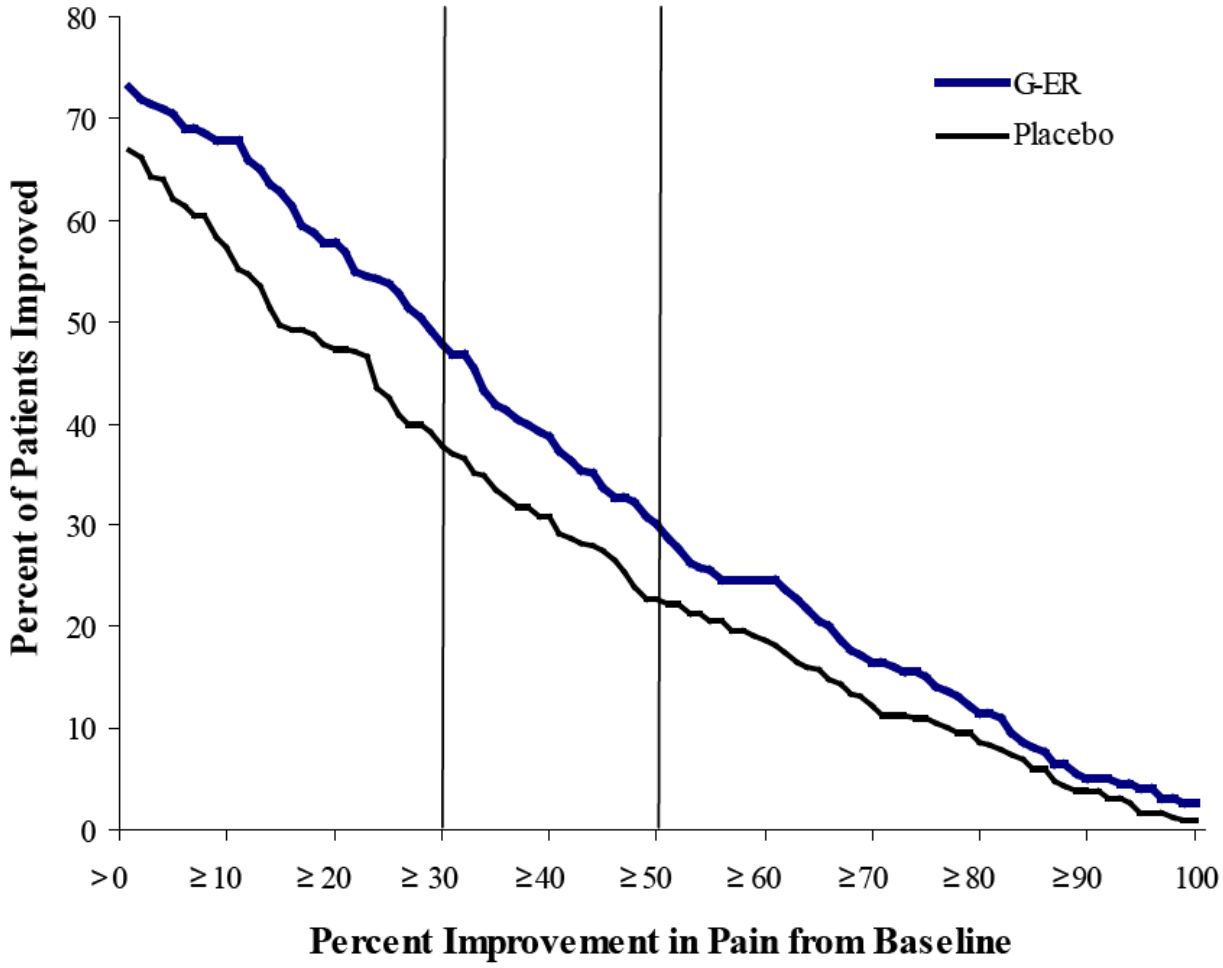
Average Daily Pain Score Percent Change from Baseline to BOCF Endpoint: n (%)	**Treatment Group**	
	Gabapentin ER 1800 mg (n = 220)	**Placebo (n = 230)**
Any Increase	18 (8.2%)	24 (10.4%)
No Change	41 (18.6%)	52 (22.6%)
> 0% to < 10% Decrease	12 (5.5%)	24 (10.4%)
≥ 10% to < 20% Decrease	24 (10.9%)	21 (9.1%)
≥ 20% to < 30% Decrease	20 (9.1%)	23 (10.0%)
≥ 30% to < 40% Decrease	21 (9.5%)	17 (7.4%)
≥ 40% to < 50% Decrease	19 (8.6%)	17 (7.4%)
≥ 50% to < 60% Decrease	11 (5.0%)	9 (3.9%)
≥ 60% to < 70% Decrease	18 (8.2%)	16 (7.0%)
≥ 70% to < 80% Decrease	11 (5.0%)	7 (3.0%)
≥ 80% to <90% Decrease	14 (6.4%)	11 (4.8%)
≥ 90% to < 100% Decrease	5 (2.3%)	7 (3.0%)
= 100% Decrease	6 (2.7%)	2 (0.9%)

Source: Post-text Table 14.2.3.
BOCF=baseline observation carried forward; ER=extended release.
Patients who had both baseline and endpoint are included in this data analysis.

Source: Applicant's submission (PN 81 0062 Clinical Study Report, page 71)

The proportion of patients within each decile reduction of ADP score is shown in Figure 5.

Figure 5 Responder Analysis



Source: Applicant's submission (Clinical Overview, page 25)

Proportion of Responders with ≥ 50% Reduction (BOCF Analysis)

The proportion of responders (patients with at least a 50% reduction in average daily pain score from baseline to BOCF endpoint) was 29.5% for the G-ER group and 22.6% for the placebo group. The difference between the 2 groups (7.0%) was not significant.

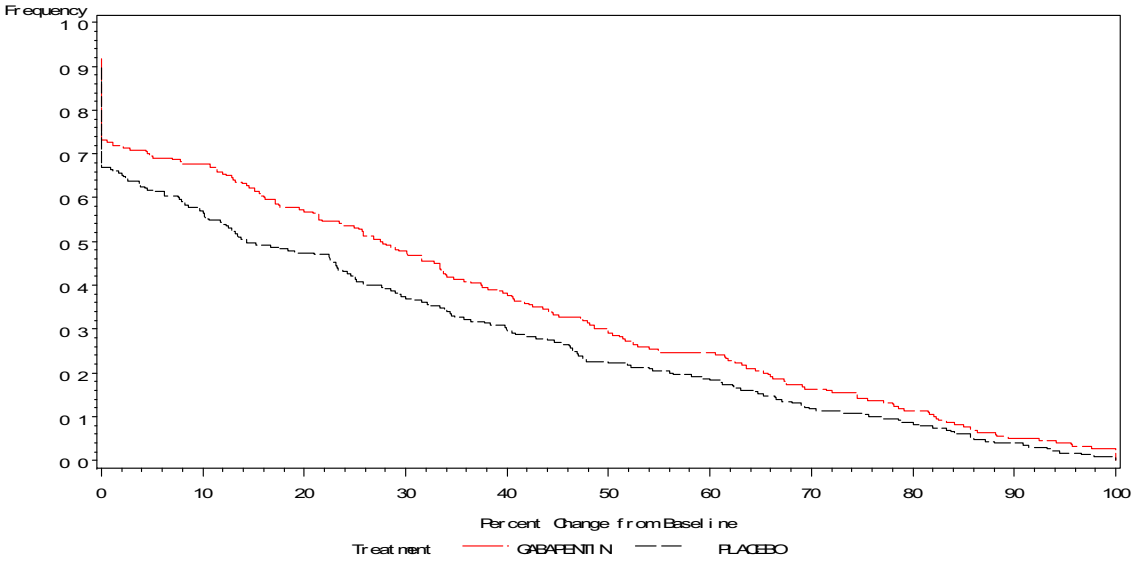
Table 13 Population of Responders at Endpoint

Average Daily Pain Score	Gabapentin ER 1800 mg (n = 220)	Placebo (n = 230)
Responders (≥ 50% Reduction in Average Daily Pain Score) at Endpoint: n (%)		
Yes	65 (29.5%)	52 (22.6%)
No	155 (70.5%)	178 (77.4%)
Gabapentin ER minus Placebo		
Difference in P(Yes)	0.07	
95% CI of DP	(-0.01, 0.15)	
p-value (vs. Placebo)[1]	0.094	

Source: Post-text Table 14.2.4.
Intent-to-treat patients who had baseline data are included in this data analysis
BOCF=baseline observation carried forward; P(Yes)= Proportion of patients who had at least 50% reduction in average daily pain score from baseline to endpoint; DP=difference in proportions; CI=confidence interval; NA=not applicable.
[1] The p-value (vs. placebo) for the pairwise test of treatment effect between gabapentin ER treatment group and placebo group is based on the Z test for the difference in proportions between two groups.
Source: Applicant's submission (PN 81 0062 Clinical Study Report, page 73)

A continuous responder analysis was conducted by Dr. Kim as figure below. The separation between treatment groups is statistically significant at p<.04.

Figure 6 Continuous Responder Analysis by the Agency

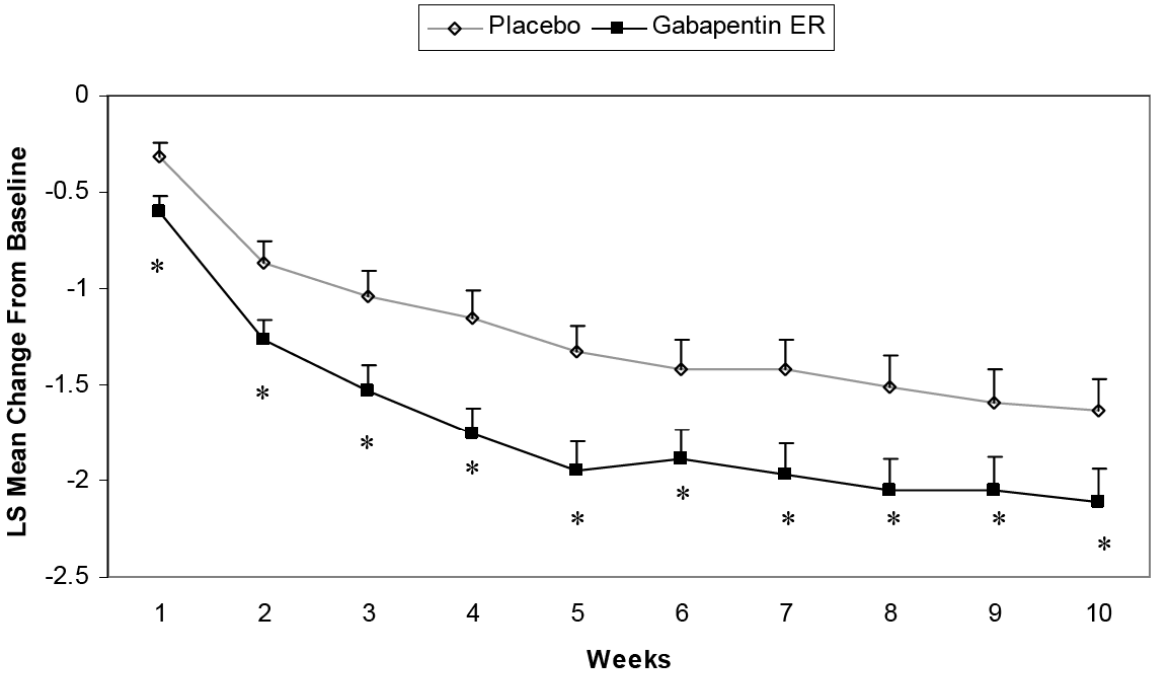


Mean Change in Average Daily Pain Score from Baseline to Follow-up Weeks by BOCF Analysis

The applicant's analysis of average daily pain score by week for the ITT population is presented in Figure 7.

G-ER 1800 mg was superior to placebo in reducing the mean changes in BOCF average daily pain score from baseline to treatment weeks 1 through 10. There were significant differences between the G-ER and placebo treatment groups for mean changes in BOCF average daily pain score for each week, from week 1 through week 10 (p=0.0027, p=0.0020, p=0.0016, p=0.0002, p=0.0003, p=0.0104, p=0.0030, p=0.0039, p=0.0199, and p=0.0146, respectively).

Figure 7 Mean Change in Average Daily Pain Score by Week



Source: Post-text Table 14.2.76.
LS=least squares; BOCF=baseline observation carried forward; gabapentin ER=gabapentin extended release 1800 mg once-daily.
Asterisk indicates P< 0.05

Source: Applicant's submission (PN 81 0062 Clinical Study Report, page 75)

Percent Change in Average Daily Pain Score from Baseline to Endpoint by BOCF Analysis

The applicant's analysis of percent change from baseline to endpoint in BOCF average daily pain score for the ITT population reveals that the LS mean (± SEM) difference (-7.14 ± 3.11) in percent change from baseline to endpoint in BOCF average daily pain score between G-ER (-32.44 ± 2.63) and placebo (-25.30 ± 2.60) was significant (p = 0.022).

Mean Change in LOCF Average Daily Sleep Interference Score from Baseline to Follow-up Weeks

The applicant's summary of the percent change in LOCF average daily sleep interference score from baseline to follow-up reveals that G-ER 1800 mg was superior

to placebo in reducing the LS mean changes in LOCF average daily sleep interference score from baseline to treatment weeks 1 through 10.

There were significant differences between the G-ER and placebo treatment groups for mean changes in LOCF average daily sleep interference score for each week, from week 1 through week 10 (p=0.0002, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.0001, p=0.0001, and p=0.0001, respectively).

Short Form McGill Pain Questionnaire
Applicant's analysis of SF-MPQ results reveals that the mean (SD) LOCF PRIS (sensory pain) score at baseline was similar for both the GER 1800 mg [14.4 (6.5)] and the placebo [14.4 (6.9)] groups. G-ER 1800 mg (-5.29 ± 0.50) had a numerically greater decrease compared to placebo (-4.37 ± 0.50) in the LS mean ± SEM change from baseline to endpoint in LOCF PRIS scores, but it did not reach significance.

The mean (SD) LOCF PRIA (affective pain) score at baseline was similar for both the GER 1800 mg [3.9 (3.0)] and the placebo [3.6 (3.0)] groups. G-ER 1800 mg (-1.46 ± 0.20) had a numerically greater decrease compared to placebo (-1.13 ± 0.20) in the LS mean ± SEM change from baseline to endpoint in LOCF PRIS scores, but it did not reach significance.

The mean (SD) LOCF PRIT (total pain) score at baseline was similar for both the G-ER 1800 mg [18.3 (8.7)] and the placebo [18.1 (9.2)] groups. G-ER 1800 mg (-6.77 ± 0.66) had a numerically greater decrease compared to placebo (-5.58 ± 0.65) in the LS mean ± SEM change from baseline to endpoint in LOCF PRIS scores, but it did not reach significance.

The mean (SD) LOCF pain intensity score on the visual analogue scale (VAS) at baseline was comparable for both the G-ER 1800 mg [74.6 (86.0)] and the placebo [78.3 (102.3)] groups. G-ER 1800 mg (-36.62 ± 2.32) had a significantly greater decrease compared to placebo (-30.42 ± 2.29) in the LS mean ± SEM change from baseline to endpoint in LOCF VAS scores, and it reached significance (p = 0.023).

The mean (SD) LOCF present pain intensity score at baseline was similar for both the GER 1800 mg [2.4 (1.0)] and the placebo [2.3 (0.9)] groups. G-ER 1800 mg (-0.84 ± 0.08) had a numerically greater decrease compared to placebo (-0.72 ± 0.08) in the LS mean ± SEM change from baseline to endpoint in LOCF present pain intensity scores, but it did not reach significance.

Neuropathic Pain Scale
Applicant's analyses of NPS reveal that the mean (SD) LOCF score for NPS10 at baseline was similar for both the G-ER 1800 mg [5.6 (1.6)] and the placebo [5.6 (1.5)] groups. G-ER 1800 mg (-2.15 ± 0.15) had a significantly greater decrease compared to

placebo (-1.72 ± 0.15) in the LS mean ± SEM change from baseline to endpoint in LOCF NPS10 scores (p = 0.019).

The mean (SD) LOCF score for NPS8 at baseline was comparable for both the G-ER 1800 mg [5.3 (1.7)] and the placebo [5.3 (1.6)] groups. G-ER 1800 mg (-2.05 ± 0.15) had a significantly greater decrease compared to placebo (-1.63 ± 0.15) in the LS mean ± SEM change from baseline to endpoint in LOCF VAS scores (p = 0.021).

The mean (SD) LOCF score for NPSNA at baseline was comparable for both the G-ER 1800 mg [5.4 (1.5)] and the placebo [5.4 (1.6)] groups. G-ER 1800 mg (-2.11 ± 0.15) had a significantly greater decrease compared to placebo (-1.70 ± 0.15) in the LS mean ± SEM change from baseline to endpoint in LOCF VAS scores (p = 0.022).

The mean (SD) LOCF score for NPS4 at baseline was comparable for both the G-ER 1800 mg [5.7 (1.8)] and the placebo [5.6 (1.8)] groups. G-ER 1800 mg (-2.28 ± 0.18) had a significantly greater decrease compared to placebo (-1.83 ± 0.18) in the LS mean ± SEM change from baseline to endpoint in LOCF VAS scores (p = 0.033).

Brief Pain Inventory

Pain Severity Scores

According to applicant's analysis, there was not a significant difference between the G-ER 1800 mg group and the placebo group in LS mean (SEM) changes from baseline to LOCF endpoint in BPI in either the worst pain score during the previous 24 hours, the least pain score during the previous 24 hours, the current pain score, or the percent pain relief obtained. There was a significant difference between the G-ER 1800 mg group [-2.14 (0.17)] and the placebo group [-1.72 (0.17)] in LS mean (SEM) changes from baseline to LOCF endpoint in BPI for the average pain score, and this difference was significant (p=0.036).

Interference Scores

There was not a significant difference between the G-ER 1800 mg group and the placebo group in LS mean (SEM) changes from baseline to LOCF endpoint in BPI in either the general activity interference score, the mood interference score, the normal work interference score, the relationship interference score, the sleep interference score, or enjoyment of life interference score obtained from the BPI.

For the ITT population, there was not a significant difference between the GER 1800 mg group and the placebo group for changes from baseline to LOCF endpoint for BPI7. The difference for the mean change from baseline to LOCF endpoint for BPI7 was not significant (p=0.257) for the G-ER 1800 mg treatment group versus placebo.

Use of Rescue Medication

According to applicant's summary, overall, 24 (5.3%) patients used rescue medications during the efficacy treatment period; 13 (5.9%), and 11 (4.8%) in the G-ER 1800 mg

and placebo groups, respectively. Only 5 (1.1%) patients [2 (0.9%) in the G-ER 1800 mg group and 3 (1.3%) in the placebo group] received prohibited rescue medications, as defined by the protocol.

The most commonly used rescue medications were: sertraline, used by 6 (1.3%) patients (three patients in the G-ER 1800 mg group and three patients in the placebo group); paracetamol, (acetaminophen) used by 3 (0.7%) patients (two patients in the G-ER 1800 mg group and one patient in the placebo group); diclofenac, used by 3 (0.7%) patients (all three patients in the G-ER 1800 mg group); ibuprofen, used by two (0.4%) patients (both in the placebo group); and meloxicam , used by 2 (0.4%) patients (both in the G-ER 1800 mg group). All other rescue medications were used by only one patient each.

Examination of Subgroups

Country of Study
The LS mean change in BOCF average daily pain score from baseline to the final week of the efficacy treatment period comparison, for the US sites as table below, was significant for G-ER 1800 mg (-2.46; p = 0.006) vs. placebo (-1.67), with a LS (SEM) mean difference of -0.78 between the two groups.

The LS mean change in BOCF average daily pain score from baseline to the final week of the efficacy treatment period comparison, for the Russian sites, was not significant for G-ER 1800 mg (-1.59; p = 0.109) vs. placebo (-1.16).

The LS mean change in BOCF average daily pain score from baseline to the final week of the efficacy treatment period comparison, for the Argentinean sites, was not significant for G-ER 1800 mg (-1.69; p = 0.454) vs. placebo (-2.33).

Table 14 Exploratory Analysis of Average Daily Pain Score in Three Countries

Country	US	Russia	Argentina
ITT (%)	57%	36%	7%
Baseline ADP	6.5	6.7	7
LS Means in G-ER	-2.5	-1.6	-1.7
LS Means in Placebo	-1.7	-1.2	-2.3
G-ER-placebo (SEM)	-0.78 (0.28)	-0.43 (0.027)	0.64 (0.88)
P-value*	0.006	0.109	0.0454

*P-value calculated from ANCOVA
Source: Applicant's response to Agency's inquiry

Different Efficacy in Three Countries

It is interesting to note that the efficacy appears to be driven by the US sites which contributed the majority of subjects (57.2% of ITT, i.e. 126 of 220 in G-ER, and 131/230 in placebo). This study failed in Russia and Argentina. The sponsor did not initially explain why there is a marked difference in the primary efficacy endpoint across the three countries. At the request of the Agency, the Sponsor provided the following reply.:

The patients enrolled in study 81-0062 were recruited from three different continents and three different healthcare systems (United States, Russia and Argentina). Patients from the US (257 subjects, 57% of total) and Russia (161 subjects, 36% of total) contribute the overwhelming majority of the patients to the study with a small minority (32 subjects, 7% of total) coming from Argentina. The mean baseline Average Daily Pain (ADP) score was similar in the three countries (6.5, 6.7, 7.0 respectively for U.S., Russia and Argentina), but the reduction in ADP score during the study on active therapy was more pronounced in the US subjects compared to the others (-2.5 versus -1.6 and -1.7, respectively). There were even greater differences in the placebo response (-1.7, -1.2, -2.3, respectively) in the three countries with subjects in Argentina exhibiting by far the largest placebo response, greater in fact than the response to active therapy.

According to the Sponsor, the most likely causes for large difference in placebo responses are either cultural differences and/or healthcare system differences in interactions with health professionals. Similar variations in placebo response have been seen in migraine pain studies with a larger placebo response in Europe than North America. Differential placebo responses in Russia compared to the US have also been reported in schizophrenia[2] although in this case the difference over placebo was greatest in the Russian subjects.

Reviewer's comments: I do agree that there is a greater placebo effect in Argentina and sample size (7% ITT) is very small there.

Key Secondary Endpoints in US and Non-US

The Agency also requested that the applicant perform an exploratory subgroup efficacy analysis of the three key secondary endpoints for the US population and the non-US population. The Applicant submitted the following response:

A sample size of 382 patients (191 patients in the G-ER treatment group and 191 patients in the placebo group) provided 90% power to detect at least a 0.4 point difference between two treatment groups in the mean change of average daily pain score from baseline week to the final week of the efficacy treatment period. The study was not powered for sub groups, and the posthoc analyses of the three key secondary endpoints for the US population (257 patients) and the non-US population (193 patients) contained herein should be viewed in that context.

Clinical Global Impression of Change (CGIC)
In the US population, the proportion of patients who were rated as very much improved or much improved at endpoint was 13.3% higher for the G-ER group (49.2%) than for the placebo group (35.9%) (p-value=0.0307). In the non-US population, the proportion of patients who were rated as very much improved or much improved at endpoint was 6.1% higher for the G-ER group (37.2%) than for the placebo group (31.3%) (p-value=0.3887).

Patient Global Impression of Change (PGIC)
In the US population, the proportion of patients who rated themselves as very much improved or much improved at endpoint was 14.9% higher for the G-ER group (50.8%) than for the placebo group (35.9%) (p-value=0.0157). In the non-US population, the proportion of patients who rated themselves as very much improved or much improved at endpoint was 1.6% higher for the G-ER group (31.9%) than for the placebo group (30.3%) (p-value=0.8101).

Average Daily Sleep Interference Score
In the US population, the mean (SD) BOCF average daily sleep interference scores at baseline were 5.2 (2.3), and 5.2 (2.4) for the G-ER and placebo groups, respectively. Gabapentin ER (-2.61 ± 0.22) was superior to placebo (-1.70 ± 0.22) in reducing the LS mean ± SEM average daily sleep interference score from baseline to BOCF endpoint (p-value = 0.0006). In the non-US population, the mean (SD) BOCF average daily sleep interference scores at baseline were 5.5 (2.0), and 5.1 (2.0) for the G-ER and placebo groups, respectively. Gabapentin ER (-1.81 ± 0.21) was greater than placebo (-1.32 ± 0.20) in reducing the LS mean ± SEM average daily sleep interference score from baseline to BOCF endpoint (p-value = 0.0522).

Reviewer's Comments: Unexpectedly, PGIC, but not CGIC in US reached the nominal statistical significance according to statistical plan as alpha is set at 0.025. In the overall population, CGIC with P value of 0.027 is close to reaching statistical significance..

The Applicant's exploratory analyses of secondary endpoints in US and non-US were confirmed by Dr. Kim. The Analyses of PGI and CGI in US are summarized below by Dr. Kim.

Table 15 Exploratory Analysis of Patient Global Impression of Change in US

PGI	G-ER 1800mg QD (N=126)	Placebo (N=131)

Very Much or Much Improved at Endpoint	64 (51%)	47 (36%)
Difference from placebo	15%	
P-value*	0.016	

P-value calculated from Chi-square test.
Source: Dr. Youngman Kim

Table 16 Exploratory Analysis of Clinical Global Impression of Change in US

CGI	G-ER 1800mg QD (N=126)	Placebo (N=131)
Very Much or Much Improved at Endpoint	62 (49%)	47 (36%)
Difference from placebo	13%	
P-value*	0.031	

P-value calculated from Chi-square test.
Source: Dr. Youngman Kim

Age (across all three sites)
G-ER 1800 mg was superior to placebo in reducing the BOCF average daily pain score at endpoint, in patients who were less than 65 years old (n=170) and in those who were ≥65 years old (n=280) [(-0.26 ± 0.39; p =0.5107), (-0.65 ± 0.25; p = 0.0088), respectively], but only the ≥ 65 year age group reached significance. The study was not powered for analysis of these sub groups.

Gender (across all three sites)
G-ER 1800 mg was superior to placebo in reducing the BOCF average daily pain score at endpoint, in male (n=169) and in female (n=281) patients [(-0.14 ± 0.38; p =0.704), (-

0.67 ± 0.25; p = 0.0084), respectively], but only the female patient group reached significance. The study was not powered for analysis of these sub groups.

Race (across all three sites)
G-ER 1800 mg was superior to placebo in reducing the BOCF average daily pain score at endpoint, in Caucasian (n=400) patients [(-0.62 ± 0.21; p =0.0026)], but not in non-Caucasian (n=50) patients [(0.88 ± 1.03; p = 0.373)]. The study was not powered for analysis of racial subgroups.

Applicant's Efficacy Conclusions

1. Statistically and clinically significant differences in efficacy between G-ER 1800 mg daily and placebo were shown for the primary efficacy measure (change in BOCF average daily pain score from the baseline week to the final week of the efficacy treatment period).

2. The proportions of patients who were much or very much improved in the PGIC and the CGIC were greater in the G-ER1800 mg daily group than in the placebo group, supporting the clinical significance of the primary endpoint result, but these differences were not statistically significant at the required alpha level of 0.025.

3. The mean change in BOCF average daily sleep interference score was higher in the G-ER group than in the placebo group, also in support of the primary result. Since neither the PGIC nor CGIC analyses reached statistical significance, the analysis of change in BOCF average daily sleep interference score was performed on an exploratory basis only.

Statistical Reviewer's Efficacy Conclusions

1. Primary efficacy analysis was reproduced.

2. Continuous responder analysis was conducted. Separation is statistically significant.

3. A sensitivity analysis regarding rescue medication use was conducted. Primary endpoint is significant after treating those who took recue medication as treatment failures.

4. Key secondary endpoints analyses were reproduced.

5. Exploratory subgroup (US/non-US) analyses were reproduced.

Reviewer's Efficacy Conclusions and Discussion
Overall efficacy

The primary efficacy analysis supports a finding of efficacy for G-ER in the treatment of PHN in the studied population. However, the primary efficacy margin was small, 0.49 on the 11 point VAS scale. Key secondary endpoints trended in favor of G-ER although they failed statistically.

Key secondary endpoints
The reviewer agrees that the secondary endpoints were analyzed by a rigorous statistical hierarchy. There is a trend in secondary endpoints supporting the primary endpoint. Furthermore, CGIC (p=0.0268) was close to meeting the statistical significance of 0.025. Although the sleep interference endpoint was included as a key secondary endpoint, the Division does not accept this as a clinically relevant measure of a drug's effect on sleep, In order to adequately assess the effect of an analgesic on sleep, it is necessary to perform polysomnographic evaluations in order to establish a true effect on sleep, rather than simply the relief of pain leading to improved sleep.

Additional secondary endpoints
The additional secondary endpoints have mixed results in term of supporting the primary endpoint. Supportive secondary endpoints include:

- Mean change in LOCF average of daily pain score
- Proportion of responders at endpoint according to decile group BOCF, with >50% reduction (LOCF)
- Mean change in average daily pain score from baseline to follow-up weeks (BOCF)
- Percent change in average daily pain score from baseline to endpoint (BOCF)
- Mean change in LOCF average daily sleep interference score from baseline to follow-up weeks
- SF-MPQ LOCF pain intensity on VAS
- NPS 10, NPS 8, NPSNA, NPS
- BPI Average Pain Score

Non-supportive includes:

- Proportion of responders with >50% reduction (BOCF)
- SF-MPQ LOCF PRIS (sensory pain), LOCF PRIA (affective pain), LOCF PRIT (total pain), LOCF present pain
- BPI Worst Pain Score on Last 24 Hours, Least Pain Score in Last 24 hours, Current Pain Score, Percent Pain Relief
- Interference Scores
- Use of Rescue Medications

Efficacy in three countries
The reviewer acknowledges that the greater placebo effect and the small sample size are contributing factors to the different response in Argentina.

Efficacy in comparison with IR
There were two clinical studies (Study 945-211, and 945-295) to establish the efficacy of Neurontin to treat PHN. Patients in Study 945-211 were titrated to a dose of 3600 mg daily, while patients in Study 945-295 were titrated to either 1800 mg or 2400 mg daily. Discussion here will focus on Study 945-295.

In Study 945-295, patients were titrated over a 3-week period and maintained on the final stable dose for four weeks. A total of 334 subjects were enrolled and 272 (81.4%) completed the study, One hundred and fifteen patients received Neurontin 1800 mg daily, 108 patients received 2400 mg daily, and 111 patients received placebo. The primary outcome measure in both studies was the change in mean weekly Pain Rating Scale score from the patient diary from baseline to end of the treatment.

It is interesting to note that Neurontin 1800 mg daily as given 600 mg TID in Study 945-295 has a mean pain score reduction of 1 on the 11 point VAS scale using LOCF in Study 945-295 (NDA 21-397 Medical Review, page 46). According to the statistical review, "worst case" sensitivity analysis gave the efficacy margin of 0.7 as table below**.** The worst change at endpoint observed in Study 295 was in a patient whose pain increased by 3.5 points. The Study 945-295 was conducted in the UK and Ireland. Of note**,** "worst-case" sensitivity analysis is all dropouts, regardless of reason for discontinuation, were given a final pain change score equal to the worst change observed in the entire patient population for the particular trial.

Figure 8 Gapapentin IR Efficacy Margin ("worst case" sensitivity analysis)

"Worst-case" change from baseline

	Study 945-211		Study 945-295		
	Placebo	Gabapentin 3600 mg/day	Placebo	Gabapentin 1800 mg/day	Gabapentin 2400 mg/day
Mean (SD)	0.2 (2.2)	-1.1 (3.1)	-0.4 (2.6)	-1.1 (3.0)	-1.1 (3.1)

Source: Statistical Review, NDA 21-397

Neurontin 3600 mg daily as given 1200 mg TID (Study 945-211), the "worst case" sensitivity analysis gave the efficacy margin of 0.9.

Neurontin 1800 mg daily as given divided dose (TID) in Study 945-295 had a treatment effect of 07 compared to 0.5 for G-ER using "worst case" sensitivity analysis. The key difference in study design was that G-ER clinical trial had a shorter titration (two weeks) and longer stable dose (eight weeks) than Neurontin (three weeks titration followed by four weeks stable dose). The different durations of titration and stable dose in Neurontin and G-ER probably may affect the efficacy margin. The limitations of between study

comparisons must be kept in mind when comparing the treatment effects for the two products.

Final comments
The efficacy of G –ER has been established in one adequate and well-controlled Phase 3 study, based on the positive finding for the primary endpoint.

The smaller efficacy margin compared to the IR, the statistical failure of key secondary endpoints and different efficacy in three countries should not affect the approvability of G-ER from efficacy perspective. Efficacy margin of 0.5 by G-ER is comparable to the 0.7 of Neurontin using similar conservative methods of imputation. The key secondary endpoints trend in favor of G-ER. The efficacy in this study is mostly driven by the US population (57% of ITT). The greater placebo effect in Argentina makes this population not representative to US population in this study for the proposed indication.

PROTOCOL 81-0045; Phase 3

Title: A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Gabapentin Extended Release (G-ER) Tablets in the Treatment of Patients with Post-herpetic Neuralgia

Methodology:
The study was to have been a prospective, randomized, double-blind multicenter trial in patients with PHN who had experienced neuropathic pain for ≥ three months after the healing of acute herpes zoster skin rash (typically about four months after the rash first appeared). Eligible patients meeting study entry criteria at screening was to have an appropriate period of washout of any medications that needed to be discontinued. All patients were to have a 1-week pretreatment period to establish baseline measurements. At the end of the baseline period, patients who continued to meet the pain score eligibility requirements of ≥ 4 on the Likert scale of 0 to 10 were to be randomized to treatment with G-ER 1800 mg dosed once-daily, G-ER 1800 mg dosed as an asymmetric divided dose (600 mg AM/1200 mg PM), or G-ER placebo. The study treatment (including titration) for all patients was to be comprised a 10-week treatment period followed by 1-week of gabapentin dose tapering.

Number of Subjects:
A total of 407 patients were to be randomized into this study (G-ER daily, 136; G-ER asymmetric dose, 137; placebo, 134). A total of 405 patients had to receive study medication: 138 patients receive G-ER daily, 134 patients receive G-ER asymmetric dose, and 133 patients received placebo; eleven patients receive nonrandomized treatment. Four hundred patients were to be included in the ITT population, and a total of 405 patients were to be included in the analysis and summaries of safety data.

Primary Efficacy Results:

Primary efficacy variable was the mean change from baseline to BOCF endpoint in average daily pain score. The LS mean average daily pain scores at baseline were 6.50, 6.39 and 6.78 for the G-ER daily, G-ER asymmetric dose, and placebo groups, respectively. The LS mean (standard error of the mean, SEM) changes were -1.85 (0.21), -1.72 (0.21), and -1.42 (0.21) for the G-ER Daily, G-ER asymmetric dose, and placebo groups, respectively. There was no statistically significant difference across treatment groups for either the LS mean average daily pain score at BOCF endpoint or LS mean change from baseline to BOCF endpoint; however, greater decreases for average daily pain score were observed in the G-ER treatment groups than the placebo group. The differences between the G-ER treatment groups versus placebo for mean change from baseline were not statistically significant. The analysis of BOCF average daily pain score for the ITT population is presented in Table 17.

Table 17 Analysis of Average Daily Score (Study 81-0045)

ADP	G-ER 1800 mg Daily (n=134)	G-ER 1800 BID N=135)	Placebo (n=131)
LS Means (SE)	-1.85 (0.21)	-1.72 (0.21)	-1.42(0.21)
Difference from placebo (SE) 95% CI	-0.43 (0.27) (-0.95, 0.10)	-0.3 (0.26) (-0.82, 0.22)	
P-value*	0.11	0.255	

*P-value calculated from ANCOVA
Source: Modified from Applicant's submission (PN-81-0045 Clinical Study Report)

Reviewer's comment: Using conservative method of imputation (BOCF), there are no statistical differences between placebo and G-ER treatments. This Phase 3 study (81-0045) failed on the primary endpoints.

PROTOCOL 81-0038; Phase 2

Title: A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Gabapentin Extended Release (G-ER) Tablets in the Treatment of Patients with Postherpetic Neuralgia

Methodology:
The study was to be a randomized, double-blind multicenter trial in patients with PHN who had experienced neuropathic pain for at least three months after the healing of acute herpes zoster skin rash. Patients were to be randomly assigned to treatment with G-ER 1800 mg once daily, G-ER 1800 mg asymmetric divided dose, or placebo. Patients were to be randomized to active treatment had a gradual titration of gabapentin over two weeks up to the 1800 mg daily dose and remained at that dose for two weeks after titration. A 1-week blinded tapering of gabapentin was followed the 4-week efficacy

treatment period. All patients, regardless of treatment, were to have taken the same number of identically appearing tablets..

Number of Subjects:

A total of 192 patients entered the baseline period and were enrolled; 34 patients withdrew during the baseline period and were not randomized. A total of 158 patients were randomized into this study (G-ER once daily, 55 patients; G-ER twice daily, 52 patients; placebo, 51 patients). All 158 patients were to receive study medication and were to be included in the intent-to-treat (ITT) population for efficacy data analysis. Ten patients were to receive non-randomized treatment; the actual treatments received were to be: G-ER once-daily, 54 patients; G-ER twice-daily, 53 patients; placebo, 51 patients. All 158 patients were to receive at least one dose of study medication and were to be included in the analysis and summaries of safety data.

Efficacy Results:

Primary Efficacy Variable: LOCF Analysis of Average Daily Pain Score

The mean average daily pain scores at baseline were 6.52, 6.41, and 6.47 in the G-ER once-daily, G-ER twice-daily, and placebo groups, respectively. There was a significant difference (p=0.042) among treatment groups for the mean change from baseline to LOCF endpoint for average daily pain score. The LS mean (SEM) changes from baseline were -1.93 (0.28), -2.24 (0.29), and -1.29 (0.29) in the G-ER once-daily, G-ER twice-daily, and placebo groups, respectively. The difference (95% CI) between groups for mean change from baseline was statistically significant for G-ER twice-daily versus placebo: -0.95 (-1.71, -0.20; p=0.014), but not for G-ER once-daily versus placebo: -0.64 (-1.38, 0.10; p=0.089) as in Table 18 .

Table 18 Analysis of LOCF Average Pain Score (Study 81-0038)

ADP	G-ER 1800 mg Daily (n=55)	G-ER 1800 BID N=52)	Placebo (n=51)
LS Means (SE)	-1.93 (0.28)	-2.24 (0.29)	-1.29 (0.29)
Difference from placebo (SE) 95% CI	-0.64 (0.37) (-1.38, 0.10)	-0.95 (0.38) (-1.71, 0.20)	
P-value*	0.089	**0.014**	

*P-value calculated from ANCOVA

Source: Modified from Applicant's submission (PN-81-0038 Clinical Study Report)

Secondary Efficacy Variables: BOCF Analysis of Average Daily Pain Score

The LS mean (SEM) changes were -1.78 (0.26), -1.86 (0.27), and -1.17 (0.27) in the G-ER once-daily, G-ER twice-daily, and placebo groups, respectively. The difference (95% CI) between groups for mean change from baseline were: G-ER once-daily versus

placebo: -0.62 (-1.31, 0.07; p=0.080); G-ER twice-daily versus placebo: -0.70 (-1.40, 0.01; p=0.052).

Table 19 Analysis of BOCF Average Daily Pain Score (Study 81-0038)

ADP	G-ER 1800 mg Daily (n=55)	G-ER 1800 BID N=52)	Placebo (n=51)
LS Means (SE)	-1.78 (0.26)	-1.86 (0.27)	-1.17 (0.27)
Difference from placebo (SE) 95% CI	-0.62 (0.35) (-1.31, 0.07)	-0.7 (0.36) (-1.4, 0.01)	
P-value*	0.080	0.052	

*P-value calculated from ANCOVA
Source: Modified from Applicant's submission (PN-81-0038 Clinical Study Report)

Reviewer's comment: While asymmetric BID dosing reached statistical significance, there are no statistical differences overall between placebo and G-ER treatments using BOCF method of imputation. This Phase 2 study (81-0038) failed on the primary endpoints using conservative method of imputation.

6 Review of Efficacy

Efficacy Summary

Summary of Efficacy Results and Conclusions

In the pivotal Phase 3 study (81-0062), 452 patients were randomized in Study 81-0062, 221 to G-ER 1800 mg daily and 231 to placebo. These patients then began a two week titration to treatment with G-ER 1800 mg or G-ER placebo dosed daily with the evening meal for eight weeks (10 weeks total). A 1-week blinded tapering of gabapentin followed the 10-week treatment period.

The planned primary outcome measure was the average daily pain scores from the baseline week to the final week of the efficacy treatment period for patients treated with G-ER 1800 mg compared to placebo. There was statistically significantly greater reduction in pain when the G-ER group was compared to placebo. The least squares mean difference of G-ER vs. placebo was -0.49 with p-value of 0.0125, using the conservative method of imputation for missing data (BOCF). The three key secondary outcome measures (CGIC, PGIC, and DSI) did not reach statistical significance when the G-GT group was compared to placebo.

The study design, dose and dosing interval, and the endpoint selected for primary analyses, are appropriate for the proposed indication. However, the clinical relevance of the magnitude of the treatment effect (-0.49 in the 11 point scale) is questionable. In the comments made to the applicant in 2007 when the Agency rejected the applicant's (b) (4), the Agency stated "Of note, the division's assessment of efficacy will consider the overall risk and benefit and not just statistical outcomes." The Agency's medical review at the same time noticed that the "proposed difference o (b) (4) points appears to be of questionable clinical significance".

In conclusion, Study 81-0062 showed that G-ER 1800 mg given as a single daily dose with the evening meal was associated with a statistically significant reduction from baseline in the primary endpoint, ADP score compared to placebo. The analysis of the key secondary endpoints did offer a trend to support findings of efficacy for G-ER, but did not meet the pre-specified statistical significance.

Of note, the efficacy appears to be driven by the US sites which contributed to the majority of subjects (57.2% of ITT). This study failed in Russia and Argentina as discussed before. The sponsor was asked to provide an explanation for the discrepancy between countries. They stated that the reduction in ADP score during the study on active therapy was more pronounced in the US subjects compared to the others (-2.5 versus -1.6 and -1.7, respectively). There were even greater differences in the placebo response (-1.7, -1.2, -2.3, respectively) in the three countries with subjects in Argentina exhibiting by far the largest placebo response, greater in fact than the response to active therapy. The Sponsor concludes that the most likely causes for large difference in placebo responses are either cultural differences and/or healthcare system differences in interactions with health professionals.

At the request of the Agency, the sponsor performed an exploratory subgroup efficacy analysis of the three key secondary endpoints for the US population and the non-US population (Study 81-0062), G-ER reached nominal statistical significance at PGIC, but not CGIC with alpha of 0.025 in US population.

The other two studies, 81-0038 and 81-0045 did not demonstrate efficacy for G-ER for the treatment of PHN.

In Phase 3 Study 81-0045, a total of 407 subjects were randomized to G-ER 1800 mg daily, as either a single evening dose or a divided (600 mg AM/1200 mg PM) dose or placebo for a total treatment period of ten weeks. The primary outcome measure was mean change in ADP diary score (baseline week to final week). BOCF imputation was used to account for missing data for the primary efficacy endpoint.. There was no statistically significantly reduction in pain when the G-GT groups were compared to placebo.

In the Phase 2 Study 81-0038, a total of 158 subjects were randomized to titration over two weeks to doses of G-ER up to 1800 mg daily, as either a single evening dose or a divided (600 mg AM/1200 mg PM) dose, or placebo for an additional two weeks. The primary outcome measure was the mean change in ADP diary score (baseline week to final week). When LOCF was used as method of imputation, there was statistical difference of greater pain reduction between G-GT as asymmetric BID dosing compared to placebo. Using BOCF method of imputation, however, there are no statistical differences between the G-GT treatments and placebo

In conclusion, G-ER Tablets at 1800 mg daily for the treatment of patients with PHN met the pre-specified primary endpoint in one adequate and well-controlled clinical study (Study 81-0062). As stated in the End-of-Phase-2 meeting minutes, the sponsor was required to have only a single successful adequate and well-controlled study for the proposed indication of PHN.

Although the key secondary endpoints failed to support the primary efficacy endpoint statistically, they demonstrated a trend in favor of G-ER in Study 81-0062.

Although efficacy is markedly different in three countries in Study 81-0062, the overall results demonstrated efficacy for the primary endpoint.

6.1 Proposed Indication

The proposed indication is for the management of Post Herpetic Neuralgia (PHN) in adults.

6.2 Methods/Study Design

The pivotal study, 81-0062, and the supporting studies, 81-0038 and 81-0045, were all double-blind, placebo-controlled, parallel group design. To be eligible for randomization, subjects must have had an average daily pain score of 4 or more on the 0-10 point Likert numerical rating scale at entry and average score of 4 or more for the baseline week at randomization and have recorded a score in their electronic diary on four or more of the seven days. All three studies used a two week titration period to reach the target dose of 1800 mg per day. Inclusion and exclusion criteria were essentially the same for all three studies as detailed in Section 5.3.

Study 81-0038 had a total double-blind treatment period of four weeks. Both 1800 mg daily and asymmetric BID dosing were studied. LOCF as method of imputation was applied in analysis of the primary endpoint.

Both studies 81-0045 and 81-0062 had a total duration of treatment of 10 weeks, two weeks of titration and eight weeks at the target dose of 1800 mg per day. Study 81-

0045 included both daily and asymmetric BID dosing. Study 81-0062 included only daily dosing. BOCF as method of imputation was applied for both studies.

6.3 Demographics

Demographics for study 81-0062 are described in detail in Section 5.3.

The two treatment arms did not appear different from each other in any baseline demographic characteristic. Baseline ADP scores were also not significantly different for the two treatment arms.

6.4 Patient Disposition

Patient disposition for study 81-0062 are described in detail in Section 5.3.

6.5 Analysis of the Primary Endpoint(s)

The primary endpoint of all three efficacy trials was the change from baseline to the end of the efficacy treatment period of the ADP score compared to placebo. These were agreed upon with the Applicant at an End–of-Phase 2 meeting held in 2005.

Study Populations
The populations studied were representative of those with PHN with mean age of 65.6 and baseline pain scores of 6.6 for G-ER group and 6.5 for placebo group. The intent to treat population (ITT) included all randomized patients who had a valid baseline and who received at least one dose of study medication.

Imputation
Studies 81-0062 and 81-0045 both used the BOCF imputation method for the primary efficacy endpoint, as required by the Agency for approval for this indication. The Phase 2 study, 81-0038, used the LOCF method as primary analysis before the End-of-Phase 2 meeting, although BOCF was also used as a sensitivity analysis. In each of the efficacy trials a parallel lines analysis of covariance (ANCOVA) model was used for the analysis of the primary efficacy measurement of change from baseline in average daily pain score to the final week of efficacy treatment. The Applicant's approach of BOCF is acceptable and allows for adequate interpretation of the efficacy data.

Compliance
Overall the compliance rate was 80% or more in nearly all patients for both G-ER and placebo. For the pivotal study 81-0062, approximately 85% of both G-ER and placebo patients completed the study medication for the efficacy period.

Dose Selection

The Applicant presented the following rationale for dose selection for the Phase 3 studies.

A total daily dose of 1800 mg was studied in all three efficacy studies, consistent with the approved dose of Neurontin. As demonstrated in the pharmacokinetic studies, the formulation of G-ER being studied, given either as 1800 mg in a single dose with a meal or as 600 mg with the morning meal and 1200 mg with the evening meal, delivered an AUC comparable to that of Neurontin given as 600 mg taken three times per day. Based on the results of the first Phase 3 trial (Study 81-0045), 1800 mg taken as a single dose with the evening meal was chosen as this dose showed the largest absolute change from baseline and difference with placebo in the ADP score. In addition, once-daily dosing had the strongest support from secondary endpoints based on study 81-0045.

The rationale for dose selection as presented by the Applicant is acceptable.

6.6 Secondary endpoints

The key secondary endpoints that were evaluated in the two Phase 3 efficacy studies include PGIC, CGIC, and DSI. The endpoints selected for secondary analyses are appropriate for the proposed indication of PHN. However, it must be indicated that endpoints resulting in sleep claims must be measured in objectively using polysomnogram data, and may be supported by additional sleep evaluations. Assessment of sleep using only the DSI cannot yield adequate data that would result in sleep related claims.

Statistical testing for the analysis of secondary efficacy parameters was performed in a mixed simultaneous/hierarchical fashion. The analyses on PGIC and CGIC were conducted simultaneously at $\alpha = 0.05/2=0.025$, 2-sided significance level. If either test was statistically significant, the analysis on average daily sleep interference scores was performed at $\alpha = 0.05$, 2-sided significance level.

The Applicant also carried out Additional Efficacy Parameters of Interest as follows:

- Mean Change in LOCF Average Daily Pain Score
- Proportion of Responders at Endpoint
- Mean Change in Average Daily Pain Score from Baseline to Follow-up Weeks by BOCF Analysis
- Percent Change in Average Daily Pain Score from Baseline to Endpoint by BOCF Analysis
- Mean Change in LOCF Average Daily Sleep Interference Score from Baseline to Follow-up Weeks
- Short Form McGill Pain Questionnaire
- Neuropathic Pain Scale

- Brief Pain Inventory

There was no statistical adjustment for testing outside the primary and the three key secondary end points; all additional analyses should be considered descriptive or exploratory.

6.7 Subpopulations

The pivotal study 81-0062 was not powered for analysis of subgroups, so all analyses should be considered descriptive.

The primary endpoint is supported by the result in the US population, which accounted for 57.2% of the ITT. The absolute change from baseline to efficacy treatment endpoint in the ADP score was -2.46 compared to -1.67 for the placebo group. The difference of -0.78 resulted in a p-value of 0.006. Russia accounted for 35.8% of the ITT population and showed a difference from placebo similar to the overall ITT of -0.43 with a p-value of 0.109. Argentina accounted for only 7% of the ITT population, did not show greater reductions for G-ER 1800 mg vs. placebo. Surprisingly, change in ADP score with placebo for the Argentina sites was greater than that with active drug, which can not be explained.
.
Patients in the pivotal study 81-0062 who were 65 years or older (N=280) accounted for 62.2% of the ITT and showed a change from baseline in the LS mean ADP score of -1.94 in the G-ER group compared to -1.29 in the placebo group for a difference of -0.65 with a p-value of 0.0088 vs. placebo. The smaller group less than 65 years old showed a positive difference vs. placebo but this did not reach significance.

Patients in the pivotal study 81-0062 who were female (N=281) accounted for 62.4% of the ITT and showed a change from baseline in the LS mean ADP score of -2.4 in the G-ER group compared to -1.8 for placebo for a difference of -0.67 and a p-value of 0.0084. Although a positive difference from placebo was seen for males (N = 169; 37.6%), -0.14, the result was not significant. It is noted that there is a difference in margin of pain reduction in gender with female of -0.65 vs. male of -0.14.

Caucasian patients accounted for 88.9% of the patients in study 81-0062 (N = 400). In this group there was a change from baseline in the LS mean ADP score of -2.2 for the G-ER group compared to -1.57 for placebo for a difference of -0.63) and a p-value of 0.0026. The non-Caucasian population results were confounded by the fact that Argentina the change with placebo was greater than that with active drug, and the proportion of non Caucasian subjects was too small to form conclusions.

In conclusion subgroups of age, gender, and race are supportive of the primary result. However, the primary endpoint in the subgroup of country is not consistent as discussed before.

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose and dosing interval selection for the Phase 3 studies are described above in Section 6.5.

The dosing recommendation proposed for G-GR is 1800 mg once daily. This dosing recommendation is based on the efficacy shown in the pivotal Phase 3 study in patients 18 years or older with PHN, who have experienced neuropathic pain for ≥ six months after the healing of the herpes zoster skin rash.

6.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

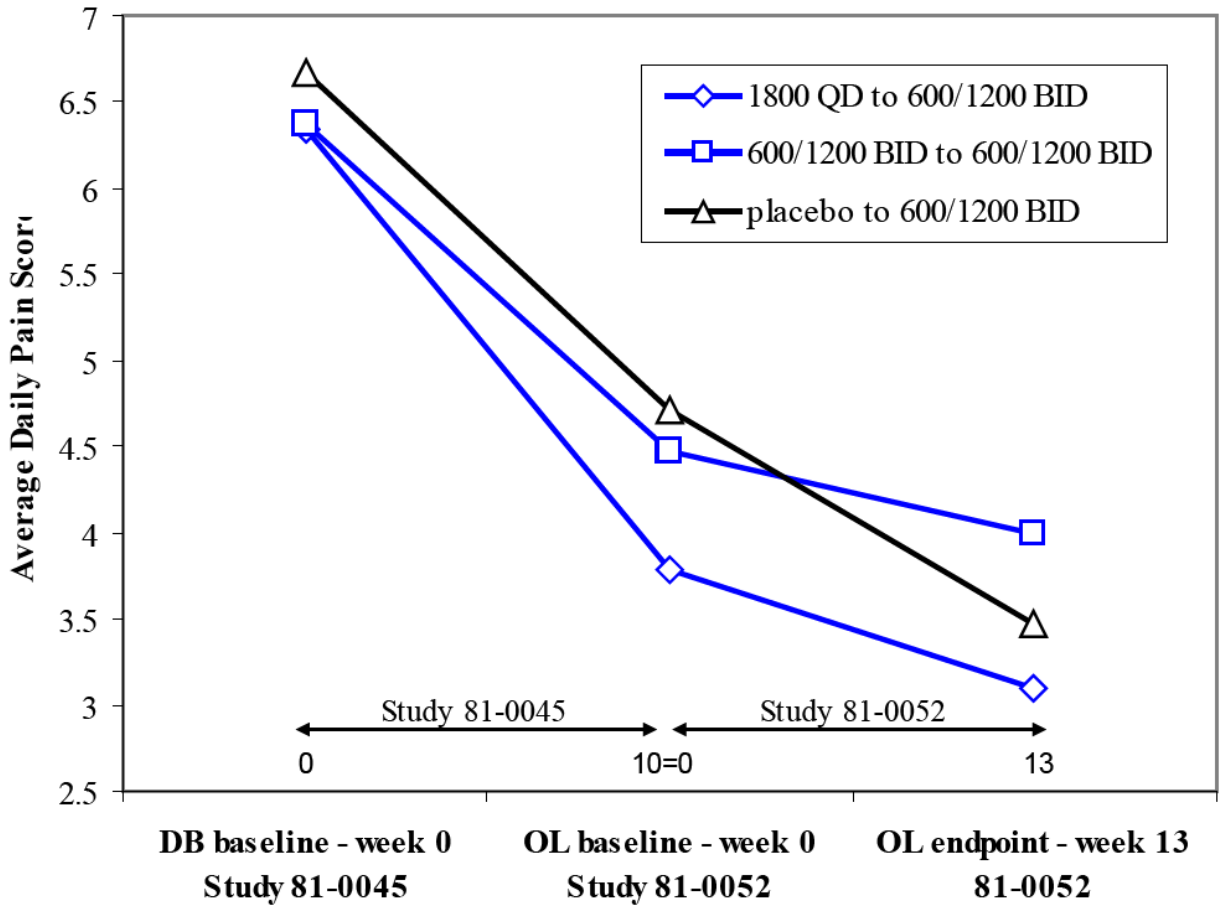
In the pivotal Phase 3 efficacy study (81-0062) there was a difference in the change from baseline in the BOCF ADP score compared to placebo as early as after one week of titration and this difference persisted for each individual week as shown in the Table 20. However, the analysis of data regarding onset of action and durability was adjusted for multiplicity and is therefore merely descriptive in nature.

Study 81-0052 was a longer-term safety study. In this 13-week open label extension of the 10-week double blind efficacy study, 81- 0045, efficacy assessments included daily pain diary scores and sleep interferences scores. Interpretation of the efficacy assessments is limited by the natures of an open-label design

For the ITT population for study 81-0052, the LS mean BOCF average daily pain scores at baseline were 3.79, 4.47, and 4.71 for patients who were on G-ER daily, G-ER asymmetric dose, and placebo groups in study 81-0045, respectively. There was a further decrease in mean BOCF average daily pain (ADP) diary score change from the baseline week of the open label study to final week (week 13) of study 81-0052 for both the G-ER 1800 mg daily group (mean: -0.69) and the G-ER 1800 mg AM/PM group (-0.47) group and with the largest decrease occurring in those who had been on placebo (-1.24) during the double blind phase.

The table below would suggest that there was no loss of efficacy during this additional 13-week period. However, the demonstration of efficacy in an open-label study is merely descriptive.

Table 20 Average Daily Pain Score (Study 81-0052)



Source: Applicant's submission (Clinical Overview, page 31)

6.10 Additional Efficacy Issues/Analyses

Refer to Section 3 for issues related to study conduct, good clinical practices and submission integrity.

7 Review of Safety

Summary of Safety Results and Conclusions

PHN data were pooled into two separate datasets. Analysis Set A comprises the Phase 3 studies, limited to the placebo and 1800 mg daily dose groups for duration of 10 weeks. Analysis Set B comprises the Phase 2 and Phase 3 PHN placebo-controlled studies regardless of duration of exposure.

A total of 359 patients in Analysis Set A received G-ER. In Analysis Set B, a total of 413 patients from received G-ER 1800 mg daily, and 187 patients received G-ER 1800 mg asymmetric BID (600 mg AM, and 1200 mg PM).

In the supportive Study 81-0046, a total of 147 DPN patients received G-ER doses of 3000 mg daily or 3000 mg as an asymmetric BID dose. There were 120 subjects who were treated with study drug in the Phase 1 studies. There was also one open-label study with a total of 119 patients treated up to 11 weeks.

Reviewer's comments: With regard to the sought indication, an adequate number of subjects have been exposed to G-ER to meet the Agency guidelines for exposure of 300 to 500.

There were three deaths during the double-blind PHN clinical studies. There was only one death reported in a patient who received treatment with G-ER. The patient (# 011009) is a 73 years old woman with cardiac risk factors who died of cardiac arrest so there was no reason to suspect any contributory role of the study medication. Details are located in Section 7.3.1.

A total of 21 (3.5%) G-ER treated patients experienced one or more SAEs during the double-blind period of the PHN studies (Analysis Set B) compared with 11 (2.7%) SAEs in placebo-treated patients. However, there were only two of those 21 SAEs for which a contributory role could be assigned to G-ER. G-ER likely played a role in one case of severe headache, may also have played a role in one case chronic pancreatitis. In addition, G-ER likely played a role in one case of allergic reaction in open-label phase. Details regarding all SAEs are located in Section 7.3.2.

Adverse events occurred in more in G-ER 1800 mg daily treated patients (55%) than placebo treated patients (43%) in the Analysis Set B. The most commonly reported treatment emergent AEs in patients who were treated with G-ER 1800 mg daily were dizziness (12.3%), somnolence (5.1%), headache (4.8%), peripheral edema (4.4%), and nausea (3.9%). A full discussion of TEAEs may be found in Section 7.4.1.

The Division requested that SMQs be performed on the pooled TEAEs data for severe cutaneous reactions and possible drug-related hepatic disorders. One patient who received G-ER 1800 mg BID as open-label treatment and one patient who received placebo reported blisters. Increased GGT (gamma-glutamyltransferase) was the most common possible drug-related hepatic disorder AE, occurring in five patients in Analysis Set B: three placebo patients, one patient in the G-ER 1800 mg daily treatment group, and one in the G-ER 1800 mg asymmetric BID treatment group. Details of the SMQ analyses are located in Section 7.5.5

For Analysis Set B, 12 patients (2.9%) in the G-ER 1800 mg daily treatment group, seven patients (3.7%) in the G-ER 1800 mg asymmetric BID treatment group, and 12 patients (2.9%) in the placebo treatment experienced an AE that was a laboratory-based abnormality. There does not appear to be a relationship between markedly abnormal laboratory abnormalities and the G-ER treatment.

Adverse events related to vital sign abnormalities occurred in a higher proportion of patients in the G-ER 1800 mg daily treatment groups than in the placebo treatment group of Analysis Set B. The applicant included “dizziness” as an AE related to vital sign abnormalities. Since the dizziness is unlikely related to the vital sign abnormalities, if “dizziness” is excluded, the overall AEs related to vital sign abnormality is similar in G-ER daily (4%), G-ER BID (2.1%) and placebo groups (3.9%).

There were no reports of suicidal thoughts or behavior, or seizures during the development of G-ER for PHN. These are relevant because of the known risk of suicidal thoughts or behavior, and seizures associated with antiepileptic drugs.

There was no evidence of treatment-emergent gastrointestinal AEs to gastrointestinal obstruction related to the G-ER formulation. The safety profile of G-ER was compared to the premarketing safety profile for Neurontin,

Overall conclusions
G-ER appears reasonably well tolerated in patients with PHN at the proposed dose regimen of 1800 mg daily. It appears that G-ER has a comparable overall and GI profile as Neurontin IR. The data provided by the Applicant appears adequate, as does the exposure to study drug.

7.1 Methods

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

Eleven clinical trials have been completed during the development of G-ER (six Phase 1, and three Phase 2/3 double-blind studies for PHN, one open-label extension, and one Phase 2 for DPN). There were two additional Phase 3 studies (81-0058, 81-0059) conducted for the treatment of vasomotor symptoms (VMS) in postmenopausal women.

PHN data were pooled into two separate datasets as described below.

Analysis Set A comprises the Phase 3 studies, limited to the placebo and 1800 mg daily dose groups for a 10 week duration of treatment. According to the Applicant, this analysis set serves to identify the safety profile after 10 weeks of treatment at the proposed dose regimen of 1800 mg daily.

Analysis Set B comprises the Phase 2 (two weeks titration and two weeks stable dose) and Phase 3 PHN placebo-controlled studies, all treatment groups, to characterize the safety profile for all patients who received 1800 mg G-ER compared with placebo, irrespective of duration of exposure up to 10 weeks.

Table 21 Data Pooling of Studies

Study	Phase	Dose Levels Included	Dosing Duration
Analysis Set A			
81-0045	3	1800 mg QD placebo	2 weeks titration, 8 weeks stable, 1-week taper
81-0062	3	1800 mg QD placebo	2 weeks titration, 8 weeks stable, 1-week taper
Analysis Set B			
81-0038	2	1800 mg QD 1800 mg asymmetric BID placebo	2 weeks titration, 2 weeks stable, 1-week taper
81-0045	3	1800 mg QD 1800 mg asymmetric BID placebo	2 weeks titration, 8 weeks stable, 1-week taper
81-0062	3	1800 mg QD placebo	2 weeks titration, 8 weeks stable, 1-week taper
BID = Twice daily, QD = Once daily.			

Source: Applicant's submission (Integrated Summary of Safety, page 18)

7.1.2 Adequacy of Data

In the individual study reports, AEs were coded to preferred terms using various versions of Medical Dictionary of Regulatory Activities (MedDRA) version 9.0.

A review was performed comparing the verbatim terms to the preferred terms. The Applicant's approach to safety coding appeared adequate.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence.

This review of safety emphasized the Phase 2/3 studies for PHN, the Phase 3 Open-Label Extension for PHN, summarized the findings from the Phase 2 DPN study, and the two additional Phase 3 studies for VMS.

The double-blind safety analysis set allows for the comparison of adverse event rates between those receiving study drug and placebo. The Phase 3 Open-Label extension safety analysis set shows adverse events occurring after longer term use of G-ER.

7.2 Adequacy of Safety Assessments

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

The exposure to G-ER in terms of numbers of subjects, dose and duration, and demographics was acceptable. The details are delineated below by safety analysis sets.

Exposure
A total of 1587 subjects were exposed to at least one dose of G-ER during the development program. The breakdown by study phase is shown below.

Table 22 Overall Exposure of G-ER

Study Phase	Number of subjects exposed to G-ER
Phase 1	120
Phase 2/3 Controlled PHN	600
Phase 3 DPN	147
Phase 3 VMS	720*
Total	1587

* From Sponsor's response (Tables 1 and 2) to Agency's inquiry on August 12, 2010.

Phase 1
The Applicant conducted six Phase 1 studies (81-0008, 0040, 0044, 0048, 0049, and 0050). All of the 120 subjects who were treated with study drug in the Phase 1 studies; all 120 were exposed to a G-ER dose of 300 mg to 600 mg for up to three days. Of these, 48 also received doses from 600 to 1200 mg, and doses from 1200 to 1800 mg and 24 patients were exposed to 1800 to 2400 mg for that period of time.

Phase 2/3 Controlled PHN
Of the 359 patients in Analysis Set A who received G-ER, a total of 332 (92.5%) were exposed to active G-ER 1800 mg daily treatment for at least four weeks and a total of 298 (83.0%) were exposed to active treatment for at least ten weeks (as shown in table below). Of the 413 patients from Analysis Set B who received G-ER 1800 mg daily, a total of 382 (92.5%) were exposed to active G-ER treatment for at least four weeks and a total of 298 (72.2%) were exposed to active treatment for at least ten weeks (as shown in table below). Of the 187 patients from Analysis Set B who received G-ER 1800 mg asymmetric BID, a total of 161 (86.1%) were exposed to active G-ER treatment for at least four weeks and a total of 97 (51.9%) were exposed to active treatment for at least ten weeks. A lower proportion of patients were exposed to the G-ER asymmetric dose compared to the G-ER daily and placebo treatments beginning at Week 6 for Analysis Set B (57.8% compared with 77.7% and 74.0%, respectively) since a larger proportion of BID patients were included in the 5-week Study 81-0038. Exposure data for the placebo treatment group was generally comparable to that for G-ER daily treatment for both Analysis Sets.

Table 23 Study Medication Exposure: Analysis Set A

	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set A	**N=359**	**NA**	**N=364**	**N=723**
Exposure through:				
1 week	351 (97.8)	--	357 (98.1)	708 (97.9)
2 weeks	347 (96.7)	--	348 (95.6)	695 (96.1)
3 weeks	338 (94.2)	--	337 (92.6)	675 (93.4)
4 weeks	332 (92.5)	--	327 (89.8)	659 (91.1)
5 weeks	329 (91.6)	--	317 (87.1)	646 (89.3)
6 weeks	321 (89.4)	--	313 (86.0)	634 (87.7)
7 weeks	318 (88.6)	--	307 (84.3)	625 (86.4)
8 weeks	311 (86.6)	--	303 (83.2)	614 (84.9)
9 weeks	308 (85.8)	--	298 (81.9)	606 (83.8)
10 weeks	298 (83.0)	--	284 (78.0)	582 (80.5)
11 weeks (taper period)	191 (53.2)	--	189 (51.9)	380 (52.6)

Source: Applicant's submission (Integrated Summary of Safety, page 23)

Table 24 Study Medication Exposure: Analysis Set B

	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set B	**N=413**	**N=187**	**N=415**	**N=1015**
Exposure through:				
1 week	403 (97.6)	179 (95.7)	407 (98.1)	989 (97.4)
2 weeks	399 (96.6)	174 (93.0)	398 (95.9)	971 (95.7)
3 weeks	390 (94.4)	164 (87.7)	386 (93.0)	940 (92.6)
4 weeks	382 (92.5)	161 (86.1)	376 (90.6)	919 (90.5)
5 weeks	362 (87.7)	145 (77.5)	348 (83.9)	855 (84.2)
6 weeks	321 (77.7)	108 (57.8)	314 (75.7)	743 (73.2)
7 weeks	318 (77.0)	104 (55.6)	307 (74.0)	729 (71.8)
8 weeks	311 (75.3)	104 (55.6)	303 (73.0)	718 (70.7)
9 weeks	308 (74.6)	104 (55.6)	298 (71.8)	710 (70.0)
10 weeks	298 (72.2)	97 (51.9)	284 (68.4)	679 (66.9)
11 weeks (taper period)	191 (46.2)	46 (24.6)	189 (45.5)	426 (42.0)

BID = Twice daily; G-ER = Gabapentin-extended release; QD = Once daily; asymmetric BID = 600 mg AM/1200 mg PM.
Reference: Table 14.1.6

Source: Applicant's submission (Integrated Summary of Safety, page 24)

Phase 3 Open-label Extension
A total of 119 patients were treated with at least one dose of study medication during the Phase 3 open-label extension study (81-0046). A total of 99 patients were exposed to G-GT for at least 11 weeks. The mean length of exposure to study drug in study 81-0052 was 74.8 days.

Demographics

The demographic and baseline characteristics of age, gender, and race were similar across the placebo, and G-ER treatment group (s) but more than 88% of patients were Caucasian in Sets A and B.

The Analysis Set A comprised 415 (57.4%) female and 308 (42.6%) male patients. The majority of patients (88.5%) were Caucasian and the mean age of the patient population was 66.1 years. Demographic characteristics were well-balanced between the G-ER 1800 mg and placebo treatment groups.

The Analysis Set B patient population comprised 1,015 patients of whom 565 (55.7%) were female and 450 (44.3%) were male. The mean age of the population was 66.7 years and the majority of patients (88.4%) were Caucasian. Demographic characteristics of the individual treatment groups were similar with the only notable difference being a slightly higher proportion of males and of black patients in the G-ER 1800 mg asymmetric BID treatment group compared to the other two treatment groups.

The Applicant's table below illustrates the demographic characteristics of subjects the two Analysis Sets.

Table 25 Demographics: Analysis Set A

	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set A	**359**	**NA**	**364**	**723**
Age (years)				
n	**359**	**NA**	**364**	**723**
Mean (SD)	66.3 (12.9)	--	65.9 (11.8)	66.1 (12.4)
Median	69.0	--	68.0	69.0
Min, max	25.0, 89.0	--	21.0, 87.0	21.0, 89.0
Age, n (%)				
<65 years	132 (36.8)	--	146 (40.1)	278 (38.5)
≥65 years	227 (63.2)	--	218 (59.9)	445 (61.5)
Gender, n (%)				
Female	213 (59.3)	--	202 (55.5)	415 (57.4)
Male	146 (40.7)	--	162 (44.5)	308 (42.6)
Race, n (%)				
Caucasian	313 (87.2)	--	327 (89.8)	640 (88.5)
Non-Caucasian	46 (12.8)	--	37 (10.2)	83 (11.5)
Black	17 (4.7)	--	10 (2.7)	27 (3.7)
Asian	4 (1.1)	--	3 (0.8)	7 (1.0)
Hispanic	22 (6.1)	--	22 (6.0)	44 (6.1)
Other	3 (0.8)	--	2 (0.5)	5 (0.7)

Source: Applicant's submission (Integrated Summary of Safety, page 32)

Table 26 Demographics: Analysis Set B

Analysis Set B	413	187	415	1015
Age (years)				
n	413	187	415	1015
Mean (SD)	66.9 (12.7)	67.0 (12.5)	66.4 (11.8)	66.7 (12.3)
Median	70.0	69.0	68.0	69.0
Min, max	25.0, 90.0	20.0, 88.0	21.0, 87.0	20.0, 90.0
Age, n (%)				
<65 years	146 (35.4)	65 (34.8)	164 (39.5)	375 (36.9)
≥65 years	267 (64.6)	122 (65.2)	251 (60.5)	640 (63.1)
Gender, n (%)				
Female	241 (58.4)	95 (50.8)	229 (55.2)	565 (55.7)
Male	172 (41.6)	92 (49.2)	186 (44.8)	450 (44.3)
Race, n (%)				
Caucasian	361 (87.4)	163 (87.2)	373 (89.9)	897 (88.4)
Non-Caucasian	52 (12.6)	24 (12.8)	42 (10.1)	118 (11.6)
Black	20 (4.8)	13 (7.0)	11 (2.7)	44 (4.3)
Asian	4 (1.0)	2 (1.1)	4 (1.0)	10 (1.0)
Hispanic	25 (6.1)	9 (4.8)	25 (6.0)	59 (5.8)
Other	3 (0.7)	0 (0.0)	2 (0.5)	5 (0.5)

BID = Twice daily; G-ER = Gabapentin-extended release; ITT = Intent-to-treat; NA = Not applicable; QD = Once daily; asymmetric BID = 600 mg AM/1200 mg PM; SD = Standard deviation.
Reference: Table 14.1.3

Source: Applicant's submission (Integrated Summary of Safety, page 33)

Phase 3 Open-label Extension
A total of 119 patients were treated with at least one dose of study medication: 66 (55.5%) were male and 53 (44.5%) were female, with a mean age of 67 years (28-85 years). The majority (86.6%) was Caucasian.

7.2.2 Explorations for Dose Response

See Section 7.4.1

7.2.3 Special Animal and/or In Vitro Testing

One study of G-ER was conducted in beagle dogs to evaluate the systemic exposure of gabapentin from G-ER and Neurontin® tablets given twice daily for at least 28 days. In this bridging study (Study 81-0014), beagle dogs were randomly assigned to one of the following five treatment groups: placebo, G-ER 600 mg/day, G-ER 1200 mg/day, G-ER 2400 mg/day, or Neurontin® 2400 mg/day.

No animals died or were sacrificed due to moribund condition and no treatment-related clinical observations were recorded. No biologically meaningful differences were observed in the assessments of body weight, food consumption, ECG parameters, hematology, coagulation, clinical chemistry or urinalysis parameters in this study. Postmortem examinations showed no distinct or definitive gross pathology changes related to dosing with G-ER or Neurontin®. Slightly increased absolute testicular weight values were recorded for males that received 2400 mg G-ER; however, relative to body weight, there was no difference in this parameter during the study.

For details regarding preclinical studies and their results, the reader is referred to Dr. Emami's pharmacological and toxicological review.

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of G-ER appears adequate. Clinical laboratory tests, namely hematology and serum chemistry, were performed at the screening and the end-of-study visits for three phase 2 and phase 3 PHN studies. Patients who continued onto study 81-0052 had labs taken at the Week 10 visit of Study 81-0045 and at the end of the study visit.

The changes in the normal and abnormal status of the laboratory test data from baseline to the end-of-study and maximum absolute change were summarized, as were the abnormal high/low laboratory values, identified by means of the reference ranges and markedly abnormal values, identified with the pre-defined criteria as seen in table below.

Table 27 Critical Values for Laboratory Parameters

Parameter	Unit	Lower limit	Upper limit
Blood Biochemistry			
Alanine aminotransferase (ALT)	U/L	NA	≥3.0 × URL
Alkaline phosphatase (ALP)	U/L	NA	≥2.0 × URL
Aspartate aminotransferase (AST)	U/L	NA	≥3.0 × URL
Bilirubin (Total)	µmol/L	NA	≥2.0 × URL
Creatinine	µmol/L	NA	≥177
Uric acid	µmol/L	NA	≥505
Calcium (Total)	µmol/L	≤2.1	≥3.0
Gamma glutamyltransferase (GGT)	U/L	NA	≥90
Potassium	mmol/L	≤2.5	≥6.5
Hematology			
Eosinophils	%	NA	≥10
Hematocrit	%	≤32	NA
Hemoglobin	g/dL	≤9.5	NA
Leukocytes	10^9/L	≤2.8	≥16.0
Neutrophils	%	≤15	NA
Thrombocytes	10^9/L	≤75	≥700
Basophils	%	NA	≥15
Erythrocytes	10^{12}/L	≤2.0	NA
Lymphocytes	%	NA	≥80
Monocytes	%	NA	≥40

Source: Applicant's submission (Integrated Summary of Safety, page 21)

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 and the Clinical Pharmacology Review (Dr. Naraharisetti) for information regarding the metabolic, clearance and interaction workup.

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

G-ER is an antiepileptic drug, and an extended release formulation of immediate release of gabapentin. Expected adverse events include those related to the central nervous system, (i.e., dizziness, headache, and somnolence), the gastrointestinal system (i.e., nausea, and diarrhea), and others including peripheral edema and nasopharyngitis.

In addition, laboratory data, vital signs, and ECGs were collected throughout the trials. SMQs were performed on the pooled TEAE data for 1) severe cutaneous reactions and 2) possible drug-related hepatic disorders. Results of these analyses may be found in Section 7.3.5.

7.3 Major Safety Results and Discussion

7.3.1 Deaths

No deaths were reported in any subject who received study drug in the Phase 1 studies or Phase 3 open-label extension study (Study 81-0052). Two patients (Patients 007001 and 055008) who received placebo treatment and one patient (Patient 011009) who received G-ER treatment during the Phase 3 Double-Blind clinical studies died. The narrative for the reported death in the patient who received G-ER (Patient 011009) is summarized by the Applicant as follows:

Patient 011009, a 73-year-old Caucasian female patient enrolled in Study 81-0038 died following a cardiac arrest which occurred 13 days after randomization. The patient had a history of postherpetic neuralgia, subclavian aneurysm, and hypertension. Concomitant medications included Hyzaar® (for hypertension) and zolpidem tartrate (for insomnia). The patient was randomized to the G-ER 1800 mg asymmetrical BID treatment group. Thirteen days after her initial dose of study medication the patient experienced a cardiac arrest. At the time of the event, the patient was still in the titration phase of the study, and on a twice-daily dose of 600 mg G-ER. Cardiopulmonary resuscitation was instituted at the time of the event and the patient was transported to the hospital where she was admitted to the critical care unit in stable but serious condition. Treatment included heparin, acetylsalicylic acid, clopidogrel bisulfate, and beta-blockers. Per the clinical site, the patient died three days later. The discharge summary and death certificate were not available.

The Applicant judged death was the result of cardiac arrest related to severe coronary artery disease (CAD). The event was considered by the Investigator to be unrelated to study drug.

Reviewer's comment: I am in agreement with the Applicant that this death was probably unrelated to study drug (G-ER). It must be noted that patient's only modifiable cardiac risk factor was hypertension, her full degree of preexisting cardiovascular disease was not known. Of note, the fatal event happened when the patient was still in the titration phase so she was not at the full dosing regimen.

7.3.2 Nonfatal Serious Adverse Events

No SAEs were reported in any subject who received study drug in the Phase 1 studies.

As shown in the table below, there were a total of 32 nonfatal SAEs reported from the double-blind treatment periods in controlled PHN studies, 21 of 32 occurred in G-ER treatment arms as 1800 mg daily or asymmetric BID (12 in daily, and 9 in BID). Of note, the Applicant counted only 31 nonfatal SAEs, of which 20 occurred in G-ER treatment arm. The one SAE the Applicant did not count is the patient who was diagnosed with Pancoast's tumor in Study 81-0062 three days after the last dose of study medication.

Pneumonia was the most commonly reported SAE, occurring in four patients in the G-ER 1800 mg daily treatment group. Other SAEs that were reported in more than one patient during the treatment phases of the controlled PHN studies included chest pain, myocardial infarction, and upper limb fracture.

All four cases of pneumonia occurred in the G-ER treatment group. The clinical features of these four pneumonia SAEs are summarized below. It must be noted that all are community acquired pneumonia. One case (Patient 089003) with co-morbidity of chronic obstructive pulmonary diseases (COPD) and congestive heart failure (CHF) required intubation and extensive hospitalization. The reviewer does not believe these four cases of community acquired pneumonia are related to the G-ER.

Table 28 Clinical Features of Pneumonia as SAEs

Study #	Identification	Age	Major Co-morbidity	Community Acquired	ICU Admission	Days of Hospitalization
81-0038	23001	86	Hypertension Hyperlipidemia	Yes	No	3
81-0045	034003	73	Diabetes Mellitus	Yes	No	2

			Hypertension			
81-0045	089003	82	COPD CHF Hypertension Arrhythmia	Yes	Yes (Intubation)	13
81-0045	101005	81	Osteoarthritis Cardiomegly Pace-maker	Yes	No	3

It is also noted that a higher proportion of patients (4.8%) in the G-ER 1800 mg asymmetric BID treatment group had an SAE than in the G-ER 1800 mg daily or placebo treatment groups (2.7% each).

Table 29 SAE in Phase 2 and Phase 3 PHN studies

	G-ER Daily N=413	G-ER BID N=187	Placebo N=415	Total N=1015
# (%) of Patients with any SAEs	11 (2.7)	9 (4.8)	11 (2.7)	31 (3.1)
Pneumonia	4 (1)	0	0	4 (0.4)
Chest pain	1 (0.2)	0	1 (0.2)	2 (0.2)
Myocardial infarction	0	0	2 (0.5)	2 (0.2)
Upper limb fracture	1 (0.2)	0	1 (0.2)	2 (0.2)
Anemia	0	1 (0.5)	0	1 (0.1)
Atrial fibrillation	0	1 (0.5)	1 (0.2)	1 (0.1)
Cardiac arrest	0	1 (0.5)	0	1 (0.1)
Congestive heart failure	0	0	1 (0.2)	1 (0.1)
Cellulitis	0	0	1 (0.2)	1 (0.1)
Colon cancer	0	0	1 (0.2)	1 (0.1)
Chronic obstructive pulmonary disease	0	1 (0.5)	0	1 (0.1)
Dehydration	0	1 (0.5)	0	1 (0.1)
Hematuria	0	0	1 (0.2)	1 (0.1)
Headache	0	1 (0.5)	0	1 (0.1)
Inguinal hernia	0	0	1 (0.2)	1 (0.1)
Osteochondrosis	1 (0.2)	0	0	1 (0.1)
Pancreatitis	1 (0.2)	0	0	1 (0.1)

Pancoast's tumor	1 (0.2)	0	0	1 (0.1)
Prostate cancer	0	1 (0.5)	0	1 (0.1)
Respiratory failure	1 (0.2)	0	0	1 (0.1)
Rheumatoid arthritis	0	1 (0.5)	0	1 (0.1)
Syncope	0	1 (0.5)	0	1 (0.1)
Syncope vasovagal	1 (0.2)	0	0	1 (0.1)
Thrombophebitis	0	0	1 (0.2)	1 (0.1)
Tropical spastic paresis	0	1 (0.5)	0	1 (0.1)
Ventricular hypertrophy	1 (0.2)	0	0	1 (0.1)

Source: Modified from Applicant's submission (Integrated Summary of Safety, page 64)

The events of respiratory failure, chest pain, pneumonia, cardiac arrest, chronic obstructive pulmonary disease (COPD) exacerbated and headache were severe in intensity. At the end of study, five events (colon cancer, prostate cancer, Pancoast's tumor, upper limb fracture, and pancreatitis chronic) were continuing, one event (tropical spastic paresis) was reported as a chronic stable condition and the remainder of these events was reported as resolved. As described previously, three patients (007001, 110009, and 055008) experienced SAEs with fatal outcomes.

The case of severe headache was considered by the Investigator to be related to treatment. Another case of chronic pancreatitis was deemed to be probably related to treatment. The narratives of these two cases are provided by the Applicant:

Severe headache (Patient 078005, Study 81-0045), an 80-year-old male subject was started on January 15, 2007 with study medication. He complained severe headache in (b) (6), also experienced unsteadiness, drowsiness and "hurting all over". He relayed that he had these symptoms since two weeks prior but they had progressively worsened. He was admitted to the hospital. "The cause of the symptoms was unknown". On (b) (6), the patient's symptoms were improved, and he was discharge. The last dose of study medication was taken on (b) (6)

Reviewer comment: I am in agreement with the Applicant that this severe headache was probably associated with the study drug.

Chronic Pancreatitis Exacerbation (Patient 082005, Study 81-0062), a 70-year old female subject with history of cholecystectomy, hepatomegaly, and "chronic pancreatitis" in 2005 received the first dose of the study medication on 24 March 2009. Patient reported weakness, fatigue, hyperhydrosis, pain in the anterior torso, deep pain in the liver region, and headache on (b) (6). Ultrasound of liver on (b) (6) revealed hapatomegaly (slightly larger than in 2008), and she had normal AST, ALT, amylase and lipase. The study medication was discontinued on (b) (6) On May 25, 2009, the patient reported "improve of the condition", though still complained about the periodic pain at the anterior torso (the Herpes Zoster site). Patients denied taking alcohol.

Reviewer comment: I am in agreement with the Applicant that this pancreatitis case was not able to be excludedas possibly related to study drug. Of note, the CRF did not indicate whether or not there was stone in common bile duct on Ultrasound.

Overall comment on SAEs: I am in agreement with the Applicant that all other 21 SAEs were probably unrelated to study drug after reviewing the patient narratives, CRFs and datasets provided by the Applicant.

Of note, after reviewing the narrative and CRF, the case of tropical spastic paresis (case 81-0045-51011) happened in a patient with history of Human T-cell lymphotrophic virus type 1 (HTLV-1) who presented with worsening of myelopathy. I agree with the Sponsor that this SAE is unlikely associated with the study drug.

While SAEs were more common among the G-ER patients (21 patients, 3.5%) than placebo-treated patients (11 patients, 2.7%), there were two out of 21 SAEs for which a contributory role could be assigned to G-ER. In addition, G-ER likely played a role in one case of severe allergic reaction in open-label phase as descried below.

Phase 3 Open-Label Extension
A total of five patients (4.3%) experienced a total of seven SAEs. The case of hypersensitivity was considered by the Investigator to have relationship to study drug as narratives described below.

All but one of the SAEs was considered to be severe in intensity. Three of the SAEs (hypersensitivity, myocardial infarction, and GI hemorrhage) resulted in permanent discontinuation of study drug. All SAEs subsequently resolved. A listing of the five patients experiencing an SAE during this long-term study is provided in table below by the applicant.

Table 30 SAEs for Open-Label Extension (Study 81-0052)

Patient Number	Study 81-0045 Treatment	Preferred term	Onset day	Duration (days)	Relationship to study drug	Action taken	Outcome
16004	1800 mg/day asymmetric BID	Hypersensitivity	81	16	Probable	Dose discontinued	Resolved
27002	1800 mg/day QD dose	Carotid artery stenosis	138	2	Not related	Dose interrupted	Resolved
52001	Placebo	Pneumonia	98	3	Not related	None	Resolved
53002	1800 mg/day QD	Myocardial infarction	148	25	Not related	Dose discontinued	Resolved
		Pulmonary embolism	174	8	Not related	None	Resolved
77001	1800 mg/day asymmetric BID	Gastrointestinal hemorrhage	151	4	Not related	Dose discontinued	Resolved
		Pneumonia	151	4	Not related	Dose interrupted	Resolved
Reference: Study 81-0052 CSR, Table 40.							

Source: Applicant's submission (Integrated Summary of Safety, page 99)

The following narrative reflects the SAE that was determined to be either possibly or probably related to study drug following review of the patient narratives, CRFs and datasets provided by the Applicant.

Subject 016004, a 78-year-old male subject who had previously received G-ER in study 45 was enrolled in the Study 52 on November 8, 2006. On (b) (6), after taking two tablets of study medication in the morning, he became visually impaired to the point that he could not see anything. He presented to the ER for evaluation of swelling eyes on (b) (6). He had a pain of 10/10 for both eyes, and examination revealed puffy eyes. He received IV Benadryl, Solu-Medrol, Pepcid, and cool compression. He was discharged from ER after improvement of symptoms. His last dose of study drug was on (b) (6)

Reviewer comment: I am in agreement that the study drug was probably related to the adverse events of hypersensitivity, which is consistent with anaphylaxis or angioedema. It is interesting to note that the patient's vision was severely impaired, but he did not seek medical attention till three days later.

Overall comment on SAEs: I am in agreement with the Applicant that the all other six SAEs were probably unrelated to study drug after reviewing the patient narratives, CRFs and datasets provided by the Applicant.

DPN study (Study 81-0046)

There were no deaths reported during the study. A single treatment emergent SAE of myocardial infarction was reported in a placebo-treated patient.

SAEs in NDA 21-397 (Neurontin IR)
Based on the primary clinical review of NDA 21-397, there were 32 patients treated with Neurontin IR who reported SAEs, representing approximately 4% of the group (total 820 subjects) in controlled trials. These 32 patients experienced 44 SAEs.

The SAEs that occurred more than once in gabapentin treated patients were accidental injury (4, 0.5%), chest pain (3, 0.4%), cellulitis (2, 0.4%), myocardial infraction (2, 0.2%), nausea (2, 0.2%), vomiting (2, 0.2%), and pneumonia (3, 0.4%).

7.3.3 Dropouts and/or Discontinuations

Subject Disposition
The Applicant's tables below illustrate the disposition of all randomized subjects in the in Analysis Set A and Analysis Set B.

In Analysis Set A, a higher proportion of patients in the placebo treatment group (19.5%) discontinued study treatment early than in the G-ER treatment group (16.4%). Of those treated with G-ER 1800 mg daily who discontinued treatment, 59.3% discontinued due to an AE compared to 31.0% of the placebo group. Conversely, 31.0% of the placebo group who discontinued did so due to lack of efficacy compared to 15.3% of the G-ER 1800 mg daily treatment group who discontinued for that reason. Patient disposition for the G-ER 1800 mg daily and the placebo treatment groups in Analysis Set B was similar to that of Analysis Set A. For the G-ER 1800 mg asymmetric BID treatment group, the overall incidence of patients who discontinued early was slightly higher than the other two groups.

Table 31 Patient Disposition: Analysis Set A

	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set A				
Randomized	**N=357**	**NA**	**N=365**	**N=722**
Treated as Randomized	**354 (99.2)**	--	**361 (98.9)**	**715 (99.0)**
Treated but Randomized to a Different Treatment	**5**		**3**	**8**
Safety Population	**N=359**		**N=364**	**N=723[1]**
Discontinuation from study	**59 (16.4)**	--	**71 (19.5)**	**130 (18.0)**
Adverse Event	35 (59.3)	--	22 (31.0)	57 (43.8)
Lack of Efficacy	9 (15.3)	--	22 (31.0)	31 (23.8)
Protocol violation	2 (3.4)	--	5 (7.0)	7 (5.4)
Lost to Follow-up	1 (1.7)	--	2 (2.8)	3 (2.3)
Patient died	0 (0.0)	--	2 (2.8)	2 (1.5)
Patient withdrew consent	6 (10.2)	--	10 (14.1)	16 (12.3)
Other	6 (10.2)	--	8 (11.3)	14 (10.8)

Source: Applicant's submission (Integrated Summary of Safety, page 28)

Table 32 Patients Disposition: Analysis Set B

	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set B				
Randomized	**N=412**	**N=189**	**N=416**	**N=1017**
Treated as Randomized	**405 (98.3)**	**180 (95.2)**	**409 (98.3)**	**994 (97.7)**
Treated but Randomized to a Different Treatment	**8**	**7**	**6**	**21**
Safety Population	**N=413**	**N=187**	**N=415**	**N=1015**
Discontinuation from study	**64 (15.5)**	**42 (22.5)**	**75 (18.1)**	**181 (17.8)**
Adverse Event	39 (60.9)	21 (50.0)	23 (30.7)	83 (45.9)
Lack of Efficacy	9 (14.1)	4 (9.5)	23 (30.7)	36 (19.9)
Protocol violation	2 (5.6)	2 (4.8)	5 (6.7)	9 (5.0)
Lost to Follow-up	1 (1.6)	4 (9.5)	2 (2.7)	7 (3.9)
Patient died	0 (0.0)	0 (0.0)	2 (2.7)	2 (1.1)
Patient withdrew consent	6 (9.4)	6 (14.3)	11 (14.7)	23 (12.7)
Other	7 (10.9)	5 (11.9)	9 (12.0)	21 (11.6)

BID = Twice daily; G-ER = Gabapentin-extended release; NA = Not applicable; QD = Once daily; asymmetric BID = 600 mg AM/1200 mg PM.
[1]Safety population is based on actual treatment received; this can be different from the number of patients randomized, because some patients received a treatment different to their randomized treatment.
Reference: Tables 14.1.1.1 and 14.1.2

Source: Applicant's submission (Integrated Summary of Safety, page 28)

Open-Label Extension (Study 81-0052)

Of the 119 patients who comprised the safety population in this study, 25 patients (21.0%) discontinued early. The most common reasons for discontinuation were AEs (12 patients), lack of efficacy (five patients), and consent withdrawn (five patients).

Supportive DPN Study (Study 81-0046)

A total of 147 patients were enrolled and received at least one dose of study medication. Of these, 16 patients (10.9%) discontinued treatment early. The most common reasons for discontinuation were AEs (six patients), 'other' reasons (four patients), and consent withdrawn (three patients). There were no notable differences across the treatment groups (G-ER 3000 mg daily, 3000 mg as asymmetric BID or placebo) as to the reasons for treatment withdrawals.

Discontinuations due to AEs

Six subjects discontinued from the Phase 1 studies due to an AEs. The AEs leading to discontinuation included diarrhea, pyrexia and pharygolaryngeal pain (in one subject), facial pain, hypertension, emesis, and first degree AV block. All of the AEs leading to discontinuation were mild in intensity and only the AE of emesis was judged by the Investigator to be related to study treatment.

A summary of discontinuations due to AEs in two or more patients by individual treatment group, and overall, for Analysis Set A and Analysis Set B is provided in the table below.

For Analysis Set A, the proportion of patients who discontinued due to AEs was higher in the G-ER treatment group (9.7%) than in the placebo treatment group (6.9%). Most AEs causing discontinuation were within the Nervous System Disorders SOC. Dizziness was the most commonly occurring AE that led to discontinuation in the G-ER treatment group, occurring at a rate of 2.2%. No other AE led to discontinuation in more than 1% of G-ER treated patients in Analysis Set A. Diarrhea and nausea were the most commonly occurring AEs that led to discontinuation in the placebo treatment group, occurring at a rate of 0.8% each.

For Analysis Set B, the highest rate of discontinuation due to AEs (11.2%) was observed in patients receiving G-ER asymmetric BID dosing; compared with rates of 9.4% in the G-ER daily treatment group and 6.3% in the placebo treatment group. Dizziness was the AE that was most commonly reported as leading to discontinuation in both G-ER treatment groups, occurring at a rate of 2.2% in the G-ER daily treatment group and 4.3% in the G-ER asymmetric BID treatment group. The AEs of nausea, disorientation, and headache were the only other AEs leading to discontinuation in >1% of G-ER treated patients. Nausea was the most commonly occurring AE that led to discontinuation in the placebo treatment group, occurring at a rate of 1.0%.

Table 33 Discontinuations Due to AEs

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set A	**N=359**	**NA**	**N=364**	**N=723**
Any AE	**35 (9.7)**	--	**25 (6.9)**	**60 (8.3)**
Cardiac disorders	**1 (0.3)**	--	**4 (1.1)**	**5 (0.7)**
Myocardial infarction	0 (0.0)	--	2 (0.5)	2 (0.3)
Ear and labyrinth disorders	**2 (0.6)**	--	**0 (0.0)**	**2 (0.3)**
Vertigo	2 (0.6)	--	0 (0.0)	2 (0.3)
Gastrointestinal disorders	**7 (1.9)**	--	**9 (2.5)**	**16 (2.2)**
Abdominal distension	0 (0.0)	--	2 (0.5)	2 (0.3)
Diarrhoea	1 (0.3)	--	3 (0.8)	4 (0.6)
Nausea	3 (0.8)	--	3 (0.8)	6 (0.8)
General disorders and administration site conditions	**3 (0.8)**	--	**3 (0.8)**	**6 (0.8)**
Fatigue	0 (0.0)	--	2 (0.5)	2 (0.3)
Infections and Infestations	**6 (1.7)**	--	**2 (0.5)**	**8 (1.1)**
Pneumonia	2 (0.6)	--	0 (0.0)	2 (0.3)
Nervous system disorders	**12 (3.3)**	--	**6 (1.6)**	**18 (2.5)**
Dizziness	8 (2.2)	--	2 (0.5)	10 (1.4)
Headache	1 (0.3)	--	2 (0.5)	3 (0.4)
Somnolence	1 (0.3)	--	2 (0.5)	3 (0.4)
Psychiatric disorders	**2 (0.6)**	--	**0 (0.0)**	**2 (0.3)**
Confusional state	2 (0.6)	--	0 (0.0)	2 (0.3)

Respiratory, thoracic and mediastinal disorders	**2 (0.6)**	--	**1 (0.3)**	**3 (0.4)**
Dyspnoea	2 (0.6)	--	1 (0.3)	3 (0.4)
Analysis Set B	**N=413**	**N=187**	**N=415**	**N=1015**
Any AE	**39 (9.4)**	**21 (11.2)**	**26 (6.3)**	**86 (8.5)**
Cardiac disorders	**1 (0.2)**	**1 (0.5)**	**4 (1.0)**	**6 (0.6)**
Myocardial infarction	0 (0.0)	0 (0.0)	2 (0.5)	**2 (0.2)**
Ear and labyrinth disorders	**2 (0.5)**	**1 (0.5)**	**0 (0.0)**	**3 (0.3)**
Vertigo	2 (0.5)	1 (0.5)	0 (0.0)	3 (0.3)
Gastrointestinal disorders	**7 (1.7)**	**4 (2.1)**	**10 (2.4)**	**21 (2.1)**
Abdominal distension	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.2)
Diarrhoea	1 (0.2)	0 (0.0)	3 (0.7)	4 (0.4)
Nausea	3 (0.7)	3 (1.6)	4 (1.0)	10 (1.0)
General disorders and administration site	**5 (1.2)**	**3 (1.6)**	**3 (0.7)**	**11 (1.1)**
conditions				
Chest pain	2 (0.5)	0 (0.0)	1 (0.2)	3 (0.3)
Fatigue	0 (0.0)	1 (0.5)	2 (0.5)	3 (0.3)
Infections and Infestations	**7 (1.7)**	**0 (0.0)**	**2 (0.5)**	**9 (0.9)**
Pneumonia	3 (0.7)	0 (0.0)	0 (0.0)	3 (0.3)

Source: Applicant's submission (Integrated Summary of Safety, page 59)

7.3.4 Significant Adverse Events

All adverse events are discussed in Sections 7.3 and 7.4.

7.4 Supportive Safety Results and Discussion

7.4.1 Common Adverse Events

Among all patients in Analysis Set A, 54% of patients treated with G-ER experienced at least one AE, compared to 42% of placebo treated patients. In Set B, 55% patients treated with G-ER 1800 mg daily and 56% treated with G-ER 1800 mg asymmetric BID experienced at least one AE, compared to 43% of placebo-treated patients. The Applicant's table below illustrates the overall TEAEs.

Table 34 Overall TEAEs: Analysis Sets A and B

	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set A	**N=359**	**NA**	**N=364**	**N=723**
Patients with any AE	194 (54.0)	--	154 (42.3)	348 (48.1)
Patients with AEs leading to discontinuation	35 (9.7)	--	25 (6.9)	60 (8.3)
Patients with serious AEs	7 (1.9)	--	10 (2.7)	17 (2.4)
Patients with non-serious AEs	194 (54.0)	--	154 (42.3)	348 (48.1)
Analysis Set B	**N=413**	**N=187**	**N=415**	**N=1015**
Patients with any AE	229 (55.4)	105 (56.1)	180 (43.4)	514 (50.6)
Patients with AEs leading to discontinuation	39 (9.4)	21 (11.2)	26 (6.3)	86 (8.5)
Patients with serious AEs	11 (2.7)	9 (4.8)	11 (2.7)	31 (3.1)
Patients with non-serious AEs	229 (55.4)	105 (56.1)	180 (43.4)	514 (50.6)

Source: Modified from Applicant's submission (Integrated Summary of Safety, page 44)

The most commonly reported treatment emergent AEs reported by patients in Analysis Set A who were treated with G-ER 1800 mg daily were dizziness (10.9%), somnolence (4.5%), headache (4.2%), peripheral edema (3.9%), diarrhea (3.3%), and nausea (3.3%). For all of these commonly reported AEs except nausea, the incidence rate was higher in the G-ER treatment group than in the placebo, although not markedly so for the AEs of headache and diarrhea.

The most commonly reported treatment emergent AEs in Analysis Set B patients who were treated with G-ER 1800 mg daily were dizziness (12.3%), somnolence (5.1%), headache (4.8%), peripheral edema (4.4%), and nausea (3.9%). The most commonly reported AEs reported by patients treated with G-ER 1800 mg asymmetric BID were dizziness (13.9%), somnolence (7.0%), headache (4.8%), nausea (4.8%), dry mouth (4.3%), constipation, peripheral edema and diarrhea (3.7% each). For all of these commonly reported AEs, the incidence rate was higher in one or both of the G-ER treatment groups than in the placebo group, although not markedly so for the AEs of headache, nausea and diarrhea.

The Applicant's table below illustrates all AEs occurring in at least 1% of patients in any G-ER treatment group, and at rate greater than that observed in placebo treatment group, for each analysis set.

Table 35 TEAEs Reported >1%

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set A	**N=359**	**NA**	**N=364**	**N=723**
Ear and labyrinth disorders				
Vertigo	5 (1.4)	--	2 (0.5)	7 (1.0)
Gastrointestinal disorders				
Constipation	5 (1.4)	--	1 (0.3)	6 (0.8)
Diarrhoea	12 (3.3)	--	10 (2.7)	22 (3.0)
Dry Mouth	10 (2.8)	--	5 (1.4)	15 (2.1)
Dyspepsia	5 (1.4)	--	3 (0.8)	8 (1.1)
General disorders and administration site conditions				
Oedema peripheral	14 (3.9)	--	1 (0.3)	15 (2.1)
Pain	4 (1.1)	--	2 (0.5)	6 (0.8)
Infections and Infestations				
Nasopharyngitis	9 (2.5)	--	8 (2.2)	17 (2.4)
Urinary tract infection	6 (1.7)	--	2 (0.5)	8 (1.1)
Investigations				
Weight increased	7 (1.9)	--	2 (0.5)	9 (1.2)
Musculoskeletal and connective tissue disorders				
Back pain	6 (1.7)	--	4 (1.1)	10 (1.4)
Pain in extremity	7 (1.9)	--	2 (0.5)	9 (1.2)

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Nervous system disorders				
Dizziness	39 (10.9)	--	8 (2.2)	47 (6.5)
Headache	15 (4.2)	--	15 (4.1)	30 (4.1)
Lethargy	4 (1.1)	--	1 (0.3)	5 (0.7)
Somnolence	16 (4.5)	--	10 (2.7)	26 (3.6)
Analysis Set B	**N=413**	**N=187**	**N=415**	**N=1015**
Ear and labyrinth disorders				
Vertigo	6 (1.5)	1 (0.5)	2 (0.5)	9 (0.9)
Eye disorders				
Lacrimation increased	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.2)
Vision blurred	3 (0.7)	3 (1.6)	1 (0.2)	7 (0.7)
Gastrointestinal disorders				
Constipation	7 (1.7)	7 (3.7)	1 (0.2)	15 (1.5)
Diarrhoea	14 (3.4)	7 (3.7)	13 (3.1)	34 (3.3)
Dry Mouth	14 (3.4)	8 (4.3)	7 (1.7)	29 (2.9)
Dyspepsia	6 (1.5)	2 (1.1)	5 (1.2)	13 (1.3)
Nausea	16 (3.9)	9 (4.8)	18 (4.3)	43 (4.2)
Vomiting	5 (1.2)	3 (1.6)	5 (1.2)	13 (1.3)
General disorders and administration site conditions				
Chest discomfort	1 (0.2)	3 (1.6)	1 (0.2)	5 (0.5)
Fatigue	9 (2.2)	5 (2.7)	6 (1.4)	20 (2.0)
Gait disturbance	5 (1.2)	2 (1.1)	0 (0.0)	7 (0.7)
Oedema peripheral	18 (4.4)	7 (3.7)	1 (0.2)	26 (2.6)

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Infections and Infestations				
Gastroenteritis viral	2 (0.5)	3 (1.6)	1 (0.2)	6 (0.6)
Sinusitis	1 (0.2)	2 (1.1)	4 (1.0)	7 (0.7)
Upper respiratory tract infection	3 (0.7)	5 (2.7)	5 (1.2)	13 (1.3)
Urinary tract infection	7 (1.7)	2 (1.1)	2 (0.5)	11 (1.1)
Injury, poisoning and procedural complications				
Excoriation	0 (0.0)	2 (1.1)	1 (0.2)	3 (0.3)
Muscle strain	0 (0.0)	2 (1.1)	1 (0.2)	3 (0.3)
Investigations				
Weight increased	8 (1.9)	2 (1.1)	2 (0.5)	12 (1.2)
Metabolism and nutrition disorders				
Increased appetite	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.2)
Musculoskeletal and connective tissue disorders				
Arthralgia	2 (0.5)	5 (2.7)	3 (0.7)	10 (1.0)
Back pain	6 (1.5)	4 (2.1)	4 (1.0)	14 (1.4)
Pain in extremity	7 (1.7)	0 (0.0)	2 (0.5)	9 (0.9)

Source: Applicant's submission (Integrated Summary of Safety, page 46)

Based on the Medical Review of NDA 21-397 (Neurontin), the top five TEAEs (n=115) for Neurontin IR 1800 mg daily are: dizziness (28.7%), somnolence (17.4%), diarrhea (7%), dry mouth (6.1%) and peripheral edema (4.4%). While it must be acknowledged that intra-study comparison has limitations, the common AEs appear comparable between G-ER and Neurontin IR.

Gastrointestinal AERS in Post-marketing data have been requested to OSE.

GI profile in comparison to gabepentin IR

As a gastric retentive formulation potentially resulting in gastrointestinal adverse events, the occurrence of GI related events has been reviewed. The table below compares the common GI AEs between the G-ER and placebo in controlled Phase 2 and 3 studies.

Table 36 Gastrointestinal AEs in Phase 2 and 3 PHN studies

	G-ER Daily N=413 N (%)	G-ER BID N=187 N (%)	Placebo N=415 N (%)	Total N=1015 N (%)
Abdominal distension	0 (0)	1 (0.5)	3 (0.7)	4 (0.3)
Abdominal pain*	5 (1.2)	1 (0.5)	8 (1.9)	14 (1.3)
Constipation	7 (1.7)	7 (3.7)	1 (0.2)	15 (1.5)
Diarrhea	14 (3.4)	7 (3.7)	15 (3.1)	34 (3.3)
Dry mouth	14 (3.4)	8 (4.3)	7 (1.7)	29 (2.9)
Dyspepsia	6 (1.5)	2 (1.1)	5 (1.2)	13 (1.3)
Nausea	16 (3.9)	9 (4.8)	18 (4.3)	43 (4.2)
Vomiting	5 (1.2)	3 (1.6)	5 (1.2)	13 (1.3)

* combined abdominal pain and abdominal pain (upper)
Source: Applicant's submission (Integrated Summary of Safety)

As table above, constipation and dry mouth occurred more frequently in the G-ER treatment groups than placebo, other GI AEs appears to occur comparably between G-ER and placebo treatments.

The gastrointestinal (GI) profile of Neurontin IR is summarized below based on the medical review of NDA 21-397. While it must be acknowledged that intra-study comparison has its limitations, the GI profile between G-ER and Neurontin appears comparable.

Table 37 Gastrointestinal AEs by Neurontin IR

	Neurontin 1800 mg N=115 N (%)	Placebo N=537 N (5)
Diarrhea	8 (7)	26 (4.8)
Dry mouth	7 (6.1)	5 (0.9)
Abdominal pain	3 (2.6)	18 (3.4)
Constipation	4 (3.5)	9 (1.7)
Flatulence	1 (0.9)	6 (1.1)

Source: Medical Review, NDA 21397

Of note, similar gastric retentive formulations marketed as Glumetza® (metformin HCL extended release tablets) and Proquin® XR (ciprofloxacin hydrochloride) have been previously approved by the FDA.

Post-marketing data of Glumetza and Proquin XR related GI AEs were reviewed in AERS by the Agency's OSE staff using GI obstruction specific term (e.g. gastrointestinal obstruction) and non-specific terms (e.g. vomiting, abdominal distension). Up to September 28, 2010, there were no reports in specific terms for either Glumztza or Proquin XR. For the non-specific terms, there were no reports for Proquin XR but four for Glumetza. The four Glumetza reports (FDA 3500A, ISRNUM 5365188, 6083857, 6767416, and 6907629) containing one or more non-specific GI obstruction term were reviewed. Based on co-morbidity and/or the quality of the reports, it is difficulty to relate the non-specific terms to Glumtza. Of note, the report 6083857 suggests that the patient experienced nausea, diarrhea and vomiting after taking generic form of metformin (IR), but tolerated Glumetza.

Reviewer comment: There is no evidence of treatment-emergent gastrointestinal AEs to suggest gastric obstruction related to the gastric retentive formulation as evidenced by postmarketing adverse event reporting for Proquin XR and Glumetza..

Supportive DPN Study (Study 81-0046)
The AE profile in which patients received placebo or G-ER 3000 mg daily or as an asymmetric BID was consistent with that seen in the controlled PHN studies. In this study a total of 69 patients (46.9%) experienced at least one AE. The most commonly reported AEs were dizziness (9.5% overall: 17.0% G-ER daily, 12.2% G-ER asymmetric BID, and 0% placebo), somnolence (5.4% overall: 12.8% G-ER daily, 4.1% G-ER asymmetric BID, and 0% placebo), and headache (4.8% overall: 4.3% G-ER daily, 6.1% G-ER asymmetric BID, and 3.9% placebo).

Open-label extension study in patients with DPN (Study 81-0052)
The most commonly reported AEs were URTI (5.9%), nasopharyngitis and diarrhea (each at 4.2%), and dizziness and rash (each at 3.4%). The incidence of dizziness and somnolence were both low in this study (dizziness 3.4%, somnolence 0.8%) possibly because these patients became tolerant to the adverse events since they were on the drug for an extended period of time.

The Applicant's table below illustrates the most frequent AEs of the Open-label extension.

Table 38 AEs Occurring in >1% (Study 81-0052)

	G-ER 1800 mg BID asymmetric dose
Received Study Drug	**119 (100)**
Gastrointestinal disorders	
Diarrhoea	5 (4.2)
Dry Mouth	2 (1.7)
Nausea	3 (2.5)
Vomiting	3 (2.5)
General disorders and administration site conditions	
Fatigue	2 (1.7)
Oedema peripheral	3 (2.5)
Infections and Infestations	
Bronchitis	2 (1.7)
Gastroenteritis viral	2 (1.7)
Influenza	2 (1.7)
Nasopharyngitis	5 (4.2)
Pneumonia	3 (2.5)
Sinusitis	2 (1.7)

	G-ER 1800 mg BID asymmetric dose
Upper respiratory tract infection	7 (5.9)
Musculoskeletal and connective tissue disorders	
Arthralgia	2 (1.7)
Back Pain	2 (1.7)
Nervous system disorders	
Dizziness	4 (3.4)
Headache	3 (2.5)
Psychiatric disorders	
Insomnia	2 (1.7)
Skin and subcutaneous tissue disorders	
Rash	4 (3.4)
Vascular disorders	
Hypertension	2 (1.7)

BID = Twice daily; G-ER = Gabapentin-extended release; asymmetric BID = 600 mg AM/1200 mg PM.
A patient may be reported in more than 1 category.
Adverse events occurring while patients were on study medication during Study 81-0052 treatment period or within 3 days after the discontinuation of study medication are included.
References: Tables 14.2.1.4 and 14.2.2.4.

Source: Applicant's submission (Integrated Summary of Safety, page 97)

AEs by Subpopulations

The analysis of AEs by age, race, and gender and by CrCl (Study 81-0062 only) indicate no differences in the AE profile between the individual subgroups.

The AE profile was generally consistent regardless of age. Nausea and increased weight appeared to be somewhat more frequently reported in the younger G-ER group whereas peripheral edema is more frequently reported in G-ER treated subjects 65 years and over.

Gastrointestinal AEs were more frequently reported in females on G-ER compared to males although no single AE term accounted for the difference. Similarly, infections were more frequently reported in females but this was true in both the G-ER and placebo groups. Peripheral edema occurred more frequently in females on G-ER compared to males whereas there was a minimal incidence in the placebo group for both genders. Dizziness and somnolence showed no major gender difference.

Over 85% of the patient population in the controlled PHN studies was Caucasian. Although the frequencies and pattern of AEs appear generally similar between the race categories, it is difficult to evaluate differences given the relatively small non-Caucasian population. Non-Caucasian G-ER treated patients reported dizziness and somnolence somewhat more frequently than Caucasian patients.

The table below by applicant displays the most common AEs in patients receiving G-ER 1800 mg daily by age subgroup for Analysis Sets A and B. The next two tables display corresponding rates for AEs by gender and race subgroups, respectively.

Table 39 Five Most Common TEAEs by Age

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System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
ANALYSIS SET A				
AGE <65 YEARS	**N=132**	**NA**	**N=146**	**N=278**
Any AE	**76 (57.6)**	--	**61 (41.8)**	**137 (49.3)**
Dizziness	17 (12.9)	--	1 (0.7)	18 (6.5)
Headache	10 (7.6)	--	4 (2.7)	14 (5.0)
Nausea	9 (6.8)	--	2 (1.4)	11 (4.0)
Nasopharyngitis	7 (5.3)	--	5 (3.4)	12 (4.3)
Somnolence	7 (5.3)	--	7 (4.8)	14 (5.0)
AGE ≥65 YEARS	**N=227**	**NA**	**N=218**	**N=445**
Any AE	**118 (52.0)**	--	**93 (42.7)**	**211 (47.4)**
Dizziness	22 (9.7)	--	7 (3.2)	29 (6.5)
Oedema peripheral	12 (5.3)	--	1 (0.5)	13 (2.9)
Diarrhoea	9 (4.0)	--	5 (2.3)	14 (3.1)
Somnolence	9 (4.0)	--	3 (1.4)	12 (2.7)
Pain in extremity	7 (3.1)	--	2 (0.9)	9 (2.0)
ANALYSIS SET B				
AGE <65 YEARS	**N=146**	**N=65**	**N=164**	**N=375**
Any AE	**84 (57.5)**	**36 (55.4)**	**74 (45.1)**	**194 (51.7)**
Dizziness	17 (11.6)	6 (9.2)	3 (1.8)	26 (6.9)
Headache	11 (7.5)	3 (4.6)	6 (3.7)	20 (5.3)
Nausea	9 (6.2)	2 (3.1)	6 (3.7)	17 (4.5)
Somnolence	8 (5.5)	4 (6.2)	9 (5.5)	21 (5.6)
Nasopharyngitis	7 (4.8)	2 (3.1)	6 (3.7)	15 (4.0)

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
AGE ≥65 YEARS	**N=267**	**N=122**	**N=251**	**N=640**
Any AE	**145 (54.3)**	**69 (56.6)**	**106 (42.2)**	**320 (50.0)**
Dizziness	34 (12.7)	20 (16.4)	10 (4.0)	64 (10.0)
Oedema peripheral	15 (5.6)	7 (5.7)	1 (0.4)	23 (3.6)
Somnolence	13 (4.9)	9 (7.4)	5 (2.0)	27 (4.2)
Diarrhoea	11 (4.1)	4 (3.3)	7 (2.8)	22 (3.4)
Dry mouth	9 (3.4)	5 (4.1)	4 (1.6)	18 (2.8)
Headache	9 (3.4)	6 (4.9)	12 (4.8)	27 (4.2)

AE = Adverse event; BID = Twice daily; G-ER = Gabapentin-extended release; NA = Not applicable; QD = Once daily; asymmetric BID = 600 mg AM/1200 mg PM.
Reference: Tables 14.2.3.1.1.0, 14.2.3.1.2.0, 14.2.3.2.1.0, and 14.2.3.2.2.0.

Source: Applicant's submission (Integrated Summary of Safety, pages 52 and 53)

Table 40 Five Most Common TEAEs by Gender

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
ANALYSIS SET A				
FEMALE	**N=213**	**NA**	**N=202**	**N=415**
Any AE	**127 (59.6)**	--	**88 (43.6)**	**215 (51.8)**
Dizziness	25 (11.7)	--	4 (2.0)	29 (7.0)
Oedema peripheral	12 (5.6)	--	1 (0.5)	13 (3.1)
Somnolence	10 (4.7)	--	6 (3.0)	16 (3.9)
Diarrhoea	7 (3.3)	--	5 (2.5)	12 (2.9)
Nausea	7 (3.3)	--	9 (4.5)	16 (3.9)
MALE	**N=146**	**NA**	**N=162**	**N=308**
Any AE	**67 (45.9)**	--	**66 (40.7)**	**133 (43.2)**
Dizziness	14 (9.6)	--	4 (2.5)	18 (5.8)
Headache	6 (4.1)	--	5 (3.1)	11 (3.6)
Somnolence	6 (4.1)	--	4 (2.5)	10 (3.2)
Diarrhoea	5 (3.4)	--	5 (3.1)	10 (3.2)
Nausea	5 (3.4)	--	4 (2.5)	9 (2.9)

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
ANALYSIS SET B				
FEMALE	**N=241**	**N=95**	**N=229**	**N=565**
Any AE	**146 (60.6)**	**60 (63.2)**	**104 (45.4)**	**310 (54.9)**
Dizziness	33 (13.7)	14 (14.7)	6 (2.6)	53 (9.4)
Somnolence	14 (5.8)	5 (5.3)	8 (3.5)	27 (4.8)
Oedema peripheral	14 (5.8)	3 (3.2)	1 (0.4)	18 (3.2)
Headache	12 (5.0)	4 (4.2)	12 (5.2)	28 (5.0)
Nausea	10 (4.1)	6 (6.3)	13 (5.7)	29 (5.1)
MALE	**N=172**	**N=92**	**N=186**	**N=450**
Any AE	**83 (48.3)**	**45 (48.9)**	**76 (40.9)**	**204 (45.3)**
Dizziness	18 (10.5)	12 (13.0)	7 (3.8)	37 (8.2)
Headache	8 (4.7)	5 (5.4)	6 (3.2)	19 (4.2)
Diarrhoea	7 (4.1)	4 (4.3)	5 (2.7)	16 (3.6)
Somnolence	7 (4.1)	8 (8.7)	6 (3.2)	21 (4.7)
Dry mouth	6 (3.5)	3 (3.3)	4 (2.2)	13 (2.9)
Nausea	6 (3.5)	3 (3.3)	5 (2.7)	14 (3.1)

AE = Adverse event; BID = Twice daily; G-ER = Gabapentin-extended release; NA = Not applicable; QD = Once daily; asymmetric BID = 600 mg AM/1200 mg PM.
Reference: Tables 14.2.4.1.1.0, 14.2.4.1.2.0, 14.2.4.2.1.0, and 14.2.4.2.2.0.

Source: Applicant's submission (Integrated Summary of Safety, pages 54 and 55)

Table 41 Five Most Common TEAEs by Race

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
ANALYSIS SET A				
CAUCASIAN	**N=313**	**NA**	**N=327**	**N=640**
Any AE	**170 (54.3)**	--	**134 (41.0)**	**304 (47.5)**
Dizziness	31 (9.9)	--	8 (2.4)	39 (6.1)
Headache	12 (3.8)	--	12 (3.7)	24 (3.8)
Oedema peripheral	12 (3.8)	--	0 (0.0)	12 (1.9)
Somnolence	12 (3.8)	--	8 (2.4)	20 (3.1)
Diarrhoea	11 (3.5)		9 (2.8)	20 (3.1)
NON-CAUCASIAN	**N=46**	**NA**	**N=37**	**N=83**
Any AE	**24 (52.2)**	--	**20 (54.1)**	**44 (53.0)**
Dizziness	8 (17.4)	--	0 (0.0)	8 (9.6)
Nasopharyngitis	4 (8.7)	--	1 (2.7)	5 (6.0)
Nausea	4 (8.7)	--	1 (2.7)	5 (6.0)
Somnolence	4 (8.7)	--	2 (5.4)	6 (7.2)
Headache	3 (6.5)	--	3 (8.1)	6 (7.2)

System Organ Class	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
ANALYSIS SET B				
CAUCASIAN	**N=361**	**N=163**	**N=373**	**N=897**
Any AE	**201 (55.7)**	**91 (55.8)**	**157 (42.1)**	**449 (50.1)**
Dizziness	43 (11.9)	23 (14.1)	12 (3.2)	78 (8.7)
Somnolence	17 (4.7)	11 (6.7)	12 (3.2)	40 (4.5)
Headache	17 (4.7)	7 (4.3)	14 (3.8)	38 (4.2)
Oedema peripheral	16 (4.4)	6 (3.7)	0 (0.0)	22 (2.5)
Diarrhoea	13 (3.6)	6 (3.7)	11 (2.9)	30 (3.3)
Dry mouth	13 (3.6)	7 (4.3)	6 (1.6)	26 (2.9)
NON-CAUCASIAN	**N=52**	**N=24**	**N=42**	**N=118**
Any AE	**28 (53.8)**	**14 (58.3)**	**23 (54.8)**	**65 (55.1)**
Dizziness	8 (15.4)	3 (12.5)	1 (2.4)	12 (10.2)
Nausea	5 (9.6)	4 (16.7)	1 (2.4)	10 (8.5)
Somnolence	4 (7.7)	2 (8.3)	2 (4.8)	8 (6.8)
Nasopharyngitis	4 (7.7)	0 (0.0)	1 (2.4)	5 (4.2)
Fatigue	3 (5.8)	1 (4.2)	0 (0.0)	4 (3.4)
Headache	3 (5.8)	2 (8.3)	4 (9.5)	9 (7.6)

AE = Adverse event; BID = Twice daily; G-ER = Gabapentin-extended release; NA = Not applicable; QD = Once daily; asymmetric BID = 600 mg AM/1200 mg PM.
Reference: Tables 14.2.5.1.1.0, 14.2.5.1.2.0, 14.2.5.2.1.0, and 14.2.5.2.2.0.

Source: Applicant's submission (Integrated Summary of Safety, pages 56 and 57)

For Study 81-0062, AEs were summarized by baseline CrCl (<80 mL/min, 80 mL/min) to examine the impact of renal function on AE rates. Of the 452 patients comprising the safety population of the study, 45.3% (205 patients; 100 in the G-ER treatment group and 105 in the placebo group) had baseline CrCl <80 mL/min. The proportion of these patients who experienced at least one AE during the study was slightly higher (49.8%) than observed for patients whose baseline CrCl was 80 mL/min (45.0%). Other than the AE of dizziness, none of the other commonly occurring AEs associated with G-ER treatment occurred at a higher percentage in patients with CrCl <80 mL/min than in patients with CrCl 80 mL/min. The incidence of dizziness in G-ER treated patients was 13% in the former subpopulation and 9.2% in the latter.

For the supportive DPN study, summary tables for all AEs by subgroups of age, gender and race were provided by applicant. A review of these data indicates no important differences by subgroup.

Adverse Events in VMS Clinical Studies

VMS Studies 81-0058 and 81-0059 are completed but are not yet fully summarized by the Applicant. Brief summaries of the deaths and SAEs from these two studies and AEs most commonly leading to withdrawals are provided.

Study 81-0058

This study was a multicenter, randomized, double-blind placebo-controlled trial in 541 postmenopausal women 18 to 79 years old who reported seven or more moderate to severe hot flashes per day for at least 30 days prior to enrollment. Patients were randomly assigned to treatment with G-ER 1200 mg daily, G-ER 1800 mg asymmetric BID or placebo and treated for 25 weeks including a 1-week titration period for those randomized to G-ER treatment.

Two patients in the G-ER 1200 mg daily dose group, six patients in the G-ER 1800 mg asymmetric BID group, and four patients in the placebo treatment group experienced an SAE during the study.

The SAEs included: breast cancer and gastroesophageal reflux disease (GERD) in the G-ER1200 mg daily treatment group; urinary tract infection (UTI), nerve compression, lung neoplasm malignant, rib fracture, breast cancer, and pneumothorax in the G-ER 1800 mg asymmetric BID group; and abdominal hernia, cerebrovascular disorder, chest pain, and CAD in the placebo treatment group. The SAEs of breast cancer, UTI, nerve compression, and lung neoplasm malignant were severe in intensity. With the exception of breast cancer (both events), lung neoplasm malignant, and rib fracture, all SAEs were reported as resolved. None were considered by the Investigator to be related to study treatment.

Reviewer comment: At the request of the Agency, the Sponsor submitted the Narratives and CRFs of Clinical Study 81-0058. I am in agreement with the Applicant that all the SAEs were unrelated to the study medication.

The proportion of patients who discontinued due to an AE was 16.1% in the G-ER 1200 mg daily treatment group, 11.0% in the G-ER 1800 mg asymmetric BID treatment group, and 4.0% in the placebo group. Somnolence and dizziness were the AEs most commonly leading to discontinuation. Somnolence led to withdrawal in a total of nine patients (1.7%) overall: six patients (3.4%) in the G-ER 1200 mg treatment group, three patients (1.7%) in G-ER 1800 mg asymmetric BID treatment group and no placebo patients. Dizziness led to withdrawal in a total of seven patients (1.3%) overall: five patients (2.9%) in the G-ER 1200 mg treatment group, two patients (1.1%) in G-ER

1800 mg asymmetric BID treatment group and no placebo patients. Other AEs leading to discontinuation in two or more patients receiving G-ER included vertigo, fatigue, sedation and weight increase.

Study 81-0059
This study was a multicenter, randomized, double-blind, placebo-controlled trial in 565 postmenopausal women 18 to 79 years old, who reported seven or more moderate to severe hot flashes per day for at least 30 days. Patients were randomly assigned to treatment with G-ER 1200 mg daily, G-ER 1800 mg asymmetric BID or placebo and treated for 13 weeks including a 1-week titration period for those randomized to G-ER treatment.

One patient died during the double-blind treatment period of VMS Study 81-0059 due to an accidental overdose of fentanyl. The following narrative is provided by the Applicant.

Patient 29002/(b) (6), a 49-year old female subject received the first dose of study medication on 12 December 2008. The subject has a medical history of overactive bladder, C-spine spinal fusion, pins, rods and plates in right foot, and insomnia. Concomitant medications include Trazadone. On (b) (6), the subject experienced an event of "Patient Died." On (b) (6), the subject's family found her deceased at home and informed the site they suspected the cause of death was due to a “brain aneurism”. The site reports that autopsy will be performed to determine the cause of death. The subject's last study visit was on (b) (6). On (b) (6), the outcome of the event was considered fatal. Study medication was discontinued due to this event of death. The Investigator assessed the causal relationship to study medication as not related.

The autopsy report could not be obtained. The cause of death was listed as accidental fentanyl overdose with unprescribed medication and the event term was clarified as Death of Accidental Fentanyl Overdose.

Reviewer comment: Despite the lack of autopsy report, I am in agreement with the Applicant that this death appears unrelated to the study medication.

A total of six patients (two in the G-ER 1200 mg daily dose group, two in the G-ER 1800 mg asymmetric BID group, and two in the placebo treatment group) experienced at least one SAE during study treatment. The SAEs included: ovarian cancer and overdose/suicide attempt in the G-ER 1200 mg daily treatment group, chest pain and accidental overdose fentanyl; death in the G-ER 1800 mg asymmetric BID treatment group, and road traffic accident and meniscus lesion in the placebo treatment group. All events except chest pain were severe in intensity. None were considered by the Investigator to be related to study treatment.

Reviewer comment: At the request of the Agency, the Sponsor submitted the Narratives and CFRs of Clinical Study 81-0059. I am in agreement with the Applicant that all the SAEs appear unrelated to the study medication.

The proportion of patients who discontinued due to an AE was 8.6% in the G-ER 1200 mg daily treatment group, 11.6% in the G-ER 1800 mg asymmetric dose treatment group, and 5.5% in the placebo group. Dizziness and somnolence were the AEs most commonly leading to discontinuation. Dizziness led to withdrawal in a total of 11 patients (2.0%) overall: five patients (2.7%) in the G-ER 1200 mg treatment group, six patients (3.2%) in G-ER 1800 mg asymmetric BID treatment group and no placebo patients. Somnolence led to withdrawal in a total of six patients (1.1%) overall: one patient (0.5%) in the G-ER 1200 mg treatment group, four patients (2.1%) in G-ER 1800 mg asymmetric BID treatment group and one patient (0.5%) in the placebo treatment group. Other AEs leading to discontinuation in two or more patients receiving G-ER included nausea, fatigue, weight increase and rash.

7.4.2 Laboratory Findings

Overview of laboratory testing in the development program

Clinical laboratory tests were to be performed at the screening and at the end-of-study visits. Unscheduled blood draws for serum chemistry and hematology were occasionally obtained if deemed necessary by the Investigator.

Laboratory values were to have been reported as AEs only if the event led to medical intervention (eg, addition of a concomitant medication, discontinuation of study drug, blood transfusions, etc).

Laboratory test results were summarized by treatment at screening, end-of-study, and maximum absolute change. Patients who had baseline data and at least one follow-up result were included in this analysis. For maximum absolute change in patients with more than one follow-up result, the result with maximum absolute difference from baseline was utilized.

The changes in the normal and abnormal status of the laboratory test data from baseline to the end-of-study and maximum absolute change were summarized, as were the abnormal high/low laboratory values.

Clinical laboratory evaluations were conducted at a single central laboratory for the two controlled PHN studies conducted in the US (Studies 81-0038 and 81-0045) and at central laboratories in the US, Argentina, and Russia for the single controlled study (Study 81-0062) conducted in those countries.

Laboratory data in the Phase 1 studies were not provided. Phase 2 and 3 studies were pooled into two sets (A and B) as described before, only set B is discussed in details.

AEs related to Laboratory-based Abnormalities

For Analysis Set B, 12 patients (2.9%) in the G-ER 1800 mg daily treatment group, seven patients (3.7%) in the G-ER 1800 mg asymmetric BID treatment group, and 12 patients (2.9%) in the placebo treatment experienced an AE that was a laboratory-based abnormality. Adverse events of hematocrit decreased and hemoglobin decreased were the only AEs that occurred in more than one patient receiving G-ER 1800 mg daily; each AE occurred in two patients (0.5%). No AE occurred in more than one patient in the G-ER 1800 mg BID asymmetric dose group. For the placebo treatment group, AEs occurring in more than one patients included ALT increased, blood potassium decreased, and GGT increased; these AEs were experienced by two patients (0.5%), two patients (0.5%), and three patients (0.7%), respectively.

For the supportive DPN study, AEs related to laboratory-based abnormalities were reported by a similar proportion of patients (2.1%, 2.0%, and 2.0% of the patients in the G-ER 3000 mg daily treatment group, G-ER 3000 mg BID asymmetric dose treatment group, and placebo treatment group, respectively with no single AE occurring in more than one patient.

Hematology

Analysis focused on measures of central tendency

Mean changes from baseline in clinical laboratory parameters are summarized by the Sponsor (table is not included in this review). I agree with the Applicant, the changes were numerically small and were not considered clinically significant.

Markedly Abnormal Hematology Parameters

A summary of all hematology parameters that were markedly abnormal at the end of study in one patient or more in Analysis Sets A and B is provided in the table below. Markedly abnormal values were identified in accordance with the pre-defined criteria as in table blow.

Table 42 Markedly Abnormal Change in Hematology

End Of Study	G-ER 1800 mg QD		G-ER 1800 mg asymmetric BID		Placebo		Total	
ANALYSIS SET A	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Eosinophils (%)	321	3 (0.9)	--	--	325	5 (1.5)	646	8 (1.2)
Hematocrit (%)	327	2 (0.6)	--	--	334	2 (0.6)	661	4 (0.6)
Hemoglobin (g/dL)	327	1 (0.3)	--	--	334	0 (0.0)	661	1 (0.2)
RBCs (10^6/UL)	327	1 (0.3)	--	--	334	0 (0.0)	661	1 (0.2)
WBCs (10^3/UL)	327	2 (0.6)	--	--	334	1 (0.3)	661	3 (0.5)
ANALYSIS SET B	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Eosinophils (%)	374	4 (1.1)	176	1 (0.6)	373	5 (1.3)	923	10 (1.1)
Hematocrit (%)	380	3 (0.8)	177	1 (0.6)	382	4 (1.0)	939	8 (0.9)
Hemoglobin (g/dL)	380	2 (0.5)	177	0 (0.0)	382	0 (0.0)	939	2 (0.2)
RBCs (10^6/UL)	380	1 (0.3)	177	0 (0.0)	382	0 (0.0)	939	1 (0.1)
WBCs (10^3/UL)	380	3 (0.8)	177	1 (0.6)	382	1 (0.3)	939	5 (0.5)

BID = Twice daily; G-ER = Gabapentin-extended release; QD = Once daily; asymmetric BID 600 mg AM/1200 mg PM; RBC = Red blood cells; WBC = White blood cells.
Reference: Tables 14.3.3.1.0 and 14.3.3.2.0.

Source: Applicant's submission (Integrated Summary of Safety, page 75)

Eosinophils achieved a markedly abnormal level at the end of study in 1.2% of the overall population; 0.9% in the G-ER treatment group and 1.5% in the placebo treatment group. All other parameters were markedly abnormal in four (0.6%), or fewer, patients.

Chemistry

Analysis focused on measures of central tendency

Mean changes from baseline in clinical chemistry parameters are summarized by the sponsor (Table is not included in the review). I agree with the Applicant, any differences noted were numerically small and were not considered clinically relevant.

Markedly Abnormal Biochemical Parameters

A summary of all biochemistry parameters that were markedly abnormal in one patient or more in Analysis Sets A and B is provided in the table below.

Table 43 Markedly Abnormal Change in Clinical Biochemistry

END OF STUDY	G-ER 1800 mg QD		G-ER 1800 mg asymmetric BID		Placebo		Total	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
ANALYSIS SET A								
ALT (SGPT) (IU/L)	331	0 (0.0)	--	--	334	1 (0.3)	665	1 (0.2)
AST (SGOT) (IU/L)	332	0 (0.0)	--	--	333	1 (0.3)	665	1 (0.2)
Calcium (mg/dL)	333	0 (0.0)	--	--	335	1 (0.3)	668	1 (0.1)
Creatinine (mg/dL)	333	1 (0.3)	--	--	334	1 (0.3)	667	2 (0.3)
GGT (IU/L)	333	8 (2.4)	--	--	335	14 (4.2)	668	22 (3.3)
Potassium (mEq/L)	332	0 (0.0)	--	--	335	1 (0.3)	667	1 (0.1)
Total bilirubin (mg/dL)	333	0 (0.0)	--	--	335	1 (0.3)	668	1 (0.1)
Uric acid (mg/dL)	333	11 (3.3)	--	--	334	9 (2.7)	667	20 (3.0)
ANALYSIS SET B								
Alkaline phosphatase	384	0 (0.0)	177	2 (1.1)	384	0 (0.0)	945	2 (0.2)
ALT (SGPT) (IU/L)	385	0 (0.0)	177	0 (0.0)	382	1 (0.3)	944	1 (0.1)
AST (SGOT) (IU/L)	385	0 (0.0)	177	0 (0.0)	382	1 (0.3)	944	1 (0.1)
Calcium (mg/dL)	386	1 (0.3)	177	0 (0.0)	384	1 (0.3)	947	2 (0.2)
Creatinine (mg/dL)	386	1 (0.3)	177	0 (0.0)	383	2 (0.5)	946	3 (0.3)
GGT (IU/L)	386	10 (2.6)	177	5 (2.8)	384	15 (3.9)	947	30 (3.2)
Potassium (mEq/L)	385	0 (0.0)	177	0 (0.0)	384	1 (0.3)	946	1 (0.1)
Total bilirubin (mg/dL)	386	0 (0.0)	177	1 (0.6)	384	1 (0.3)	947	2 (0.2)
Uric acid (mg/dL)	386	12 (3.1)	177	4 (2.3)	383	10 (2.6)	946	26 (2.7)

ALT (SGPT) = Alanine aminotransferase; AST (SGOT) = Aspartate aminotransferase; BID = Twice daily; G-ER = Gabapentin-extended release; GGT = Gamma glutamyltransferase; QD = Once daily; asymmetric BID 600 mg AM/1200 mg PM; SD = Standard deviation.
Reference: Tables 14.3.6.1.0 and 14.3.6.2.0.

Source: Applicant's submission (Integrated Summary of Safety, page 80)

In Analysis Set B, GGT reached a markedly abnormal level at the end of study in 3.2% of the overall population; 2.6% in the G-ER treatment group and 3.9% in the placebo treatment group. Uric acid reached a markedly abnormal level in 2.7% of patients overall; 3.1% in the G-ER treatment group and 2.6% in the placebo treatment group. All other parameters were markedly abnormal in no more than two patients (0.3%).

Dropouts due to laboratory abnormalities

There were no subjects who discontinued treatment due to laboratory abnormalities.

Hepatic Reactions
No subjects had elevations in liver function parameters that met the criteria for the composite hepatotoxicity analysis (i.e., an ALT or AST value >3 x ULN and alkaline phosphatase value below the normal reference range and a total bilirubin above the normal reference range), and no subject had an ALT or AST value >10 x ULN in any pooled analysis treatment group in the two analysis Sets.

Reviewer's conclusion: There do not appear to be any consistent laboratory abnormalities related to study drug administration.

7.4.3 Vital Signs

Overview of vital signs testing in the development program

Vital sign measurements of blood pressure, heart rate, respiration rate, body temperature, weight and body mass index (BMI) were summarized by treatment group at screening, end-of-study, and maximum absolute change. Patients who had baseline data and at least one follow-up result were included in this analysis. For maximum absolute change in patients with more than one follow-up result, the result with maximum absolute difference from baseline was utilized.

Additionally, markedly abnormally vital signs (blood pressure, pulse rate and temperature) were identified according to predefined criteria and summarized.

Vital data in the Phase 1 studies were not provided. Phase 2 and 3 studies were pooled into two sets as described before.

The results of the vital signs measurements for Analysis Sets A and B are summarized by the sponsor. No clinically important differences in vital sign changes from baseline were observed across treatment groups for either Analysis Set.

AEs Related to Vital Sign Abnormalities
AEs related to vital sign abnormalities occurred in a higher proportion of patients in the G-ER 1800 mg daily treatment group (15.0%) than in the placebo treatment group (6.6%) of Analysis Set A. The applicant included "dizziness" as an AE related to vital sign abnormalities. This is discussed in more detail below.

For Analysis Set B, overall rates of AEs related to vital sign abnormalities were 16.5% for the G-ER 1800 mg daily treatment group, 16.0% for the G-ER 1800 mg asymmetric BID treatment group, and 7.0% for the placebo treatment group. Dizziness was the

most commonly reported AE for each of the three treatment groups, occurring in 12.3% of patients in the G-ER 1800 mg daily treatment group, 13.9% of patients in the G-ER 1800 mg asymmetric BID treatment group, and in 3.1% of patients in the placebo treatment group. It is interesting to note that overall rates of AEs related to vita sign abnormality will become similar if dizziness is excluded. The AEs rates excluding dizziness are 4% (16.5%-12.5%), 2.1 (16%-13.9%) and 3.9 (7%-3.1%) for G-ER daily, G-ER BID, and placebo respectively.

The reviewer posted the following inquiry to the Sponsor: In section 4.5.6 of ISS (page 68 and 69), you reported 39 patients with dizziness (10.9%) in G-ER treatment group. Provide the vital signs including Systolic BP Diastolic BP, HR (all with mean, minimal, maximal values) at baseline and end of treatment matched with patient and study ID. Provide any available additional information regarding the temporal association of changes in blood pressure with the reported adverse event of dizziness.

The Sponsor provided the following reply:

These studies were not specifically designed to collect data on changes in blood pressure. For most patients the Final Study Visit took place after tapering of the study medication. Furthermore, vital signs were not collected at the time of the reporting of dizziness as an adverse event and as such contemporaneous data is not available.

The Sponsor provided the subset of vital signs data for patients with treatment emergent adverse event of dizziness reported in treatment group G-ER 1800mg daily (Set A). Only one subject (81-0062-094001) reported dizziness as an adverse event in combination with markedly abnormal vital signs (an increase in systolic blood pressure of 53 mmHg at Final Study Visit compared to Baseline). For this subject a worsening of arterial hypertension was reported in the same period. For none of the other subjects dizziness was reported as an adverse event in combination with markedly abnormal changes in blood pressure or heart rate.

Closer examination of blood pressure and heart rate changes at baseline and end of study of the individual patients with the reported dizziness do not show a consistent pattern. For blood pressure and heart rate, both increases and decreases were observed compared to baseline. The mean change from baseline was for systolic blood pressure +0.21 mmHg (-32 to +53), for diastolic blood pressure-1.26 mmHg (-20 to +26) and for heart rate -2.68 bpm (-22 to +10).

Reviewer comment: I am in agreement with the Applicant that there was no temporal association between G-ER related changes in blood pressure and dizziness. Therefore, adverse events related to vital sign abnormalities appear similar among all treatment groups.

For the supportive DPN study, AEs relating to vital sign abnormalities were reported by 17.0%, 12.2%, and 2.0% of the patients in the G-ER 3000 mg daily treatment group, G-ER 3000 mg asymmetric BID treatment group, and placebo treatment group, respectively. Eight patients (17.0%) in the G-ER 3000 mg daily treatment group and six patients (12.2%) of patients in the G-ER 3000 mg asymmetric BID treatment group reported dizziness and one patient (2.0%) in the placebo treatment group reported weight increased.

Analysis focused on measures of central tendency

In Study 81-0062, there was a statistically significant difference between the G-ER treatment and placebo treatment in mean diastolic blood pressure (p = 0.0183) at end of study. There was no significant change in mean diastolic blood pressure, respiration rate, heart rate, temperature, body weight or BMI at end of study.

In Study 81-0045, there were no statistically significant differences between either G-ER treatment group versus the placebo group for changes from baseline to end of study visit for systolic or diastolic blood pressure, body weight or BMI. There were, however, statistically significant differences between the G-ER treatment and placebo treatment in respiration rate (p = 0.0007), heart rate (p = 0.0037), and temperature (p = 0.0168) at end of study.

In Study 81-0038, there were no statistically significant changes from baseline to end of study in any of the vital sign measurements.

Markedly Abnormal Vital Parameters

Markedly abnormal vital signs were identified in accordance with the pre-defined criteria as table below:

Table 44 Pre-Defined Criteria for Markedly Abnormal Vitals Signs

Variable	Unit	Markedly Low	Markedly High
SBP[a]	mmHg	Value ≤ 90 and ≥ 20 decrease from Baseline	Value ≥ 180 and ≥ 20 increase from Baseline
DBP[a]	mmHg	Value ≤ 50 and ≥ 15 decrease from Baseline	Value ≥ 105 and ≥ 15 increase from Baseline
Pulse Rate[a]	bpm	Value ≤ 50 and ≥ 15 decrease from Baseline	Value ≥ 120 and ≥ 15 increase from Baseline
Temperature	˚F	NA	Value ≥ 101 and ≥ 2 increase from Baseline

Source: Applicant's submission (SAP)

Vital sign measurements that attained a markedly abnormal status for Analysis Set A and Set B are displayed in the table below. Systolic blood pressure was markedly abnormal for 1.1% of G-ER treatment patients in Analysis Set A and in no patients in the placebo treatment group.

Table 45 Markedly Abnormal Change in Vital Signs

END OF STUDY	G-ER 1800 mg QD		G-ER 1800 mg asymmetric BID		Placebo		Total	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
ANALYSIS A								
Diastolic BP	351	2 (0.6)	--	--	350	2 (0.6)	701	4 (0.6)
Heart Rate	351	2 (0.6)	--	--	349	0 (0.0)	701	2 (0.3)
Systolic BP	351	4 (1.1)	--	--	350	0 (0.0)	701	4 (0.6)
ANALYSIS B								
Diastolic BP	405	2 (0.5)	176	1 (0.6)	400	2 (0.5)	981	5 (0.5)
Heart Rate	405	2 (0.5)	176	0 (0.0)	399	0 (0.0)	980	2 (0.2)
Systolic BP	405	4 (1.0)	176	0 (0.0)	400	1 (0.3)	981	5 (0.5)

BID – Twice daily; BP = Blood pressure; QD = Once daily; asymmetric BID 600 mg AM/1200 mg PM.
Reference: Tables 14.4.2.1.0 and 14.4.2.2.0

Source: Applicant's submission (Integrated Summary of Safety, page 82)

7.4.4 Electrocardiograms (ECGs)

Based on the Study Schedule, ECGs were recorded at screening only.
In Study 81-0045, one patient (G-ER asymmetric dose treatment group) had a clinically significant ECG finding at screening (sinus bradycardia with first degree atrioventricular block and anterior infarct of undetermined age). This finding was not considered clinically significant by the Investigator. This patient reported no AEs during the study.

7.4.5 Special Safety Studies

A Thorough QT Study was not required for this study drug.

7.4.6 Immunogenicity

This category is not applicable to this study drug.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

No studies have been conducted specifically to evaluate the adverse-effect dose response of G-ER treatment. The clinical Phase 2 and Phase 3 PHN studies described within this application employed daily doses of 1800 mg G-ER solely.

7.5.2 Drug-Demographic Interactions (gender, race)

No studies have been conducted specifically to evaluate the pharmacokinetic and/or pharmacodynamic properties of G-ER by demographic characteristics. The results of the subgroup evaluations described previously in Section 4.4, which did not indicate a safety concern based on age, race or gender.

7.5.3 Drug Disease Interactions

No studies have been conducted specifically to evaluate the pharmacokinetic and/or pharmacodynamic properties of G-ER by disease state.

7.5.4 Drug-Drug Interactions

No drug-drug interaction studies specific to G-ER have been conducted.

7.5.5 SMQs

At the Division's request, the Applicant performed SMQs for Possible Drug Related Serious Cutaneous Reactions and Hepatic Reactions.

Cutaneous Reaction
The SMQ for severe cutaneous AEs identified a total of two patients who experienced such AEs. Patient 28008 who was in the placebo treatment group in Study 81-0038 experienced an AE of blisters and Patient 28001 who received G-ER 1800 mg BID as open-label treatment in Study 81-0052 reported an AE of blisters on scalp.

Hepatic Reactions
The SMQ for possible drug-related hepatic disorders identified a total of nine patients in the safety database. Drug-related hepatic disorder AEs for Analysis Sets A and B are summarized in table below. The incidence of these events was low, with no more than 0.5% of patients in any of the individual treatment groups reporting such PTs. Increased gamma-glutamyltransferase was the most common possible drug-related hepatic disorder AE, occurring in five patients altogether in Analysis Set B: three placebo

patients, one patient in the G-ER 1800 mg daily treatment group, and one in the G-ER 1800 mg asymmetric BID treatment group. Other possible drug-related hepatic disorder AEs reported in more than one patient included: liver function tests abnormal, blood bilirubin increased, and alanine aminotransferase increased.

Table 46 TEAEs: Hepatic Reactions

	G-ER 1800 mg QD n (%)	G-ER 1800 mg asymmetric BID n (%)	Placebo n (%)	Total n (%)
Analysis Set A	**N=359**	**NA**	**N=364**	**N=723**
Any AE with at least one AE of SMQ06	**2 (0.6)**	--	**3 (0.8)**	**5 (0.7)**
Investigations	**2 (0.6)**	--	**3 (0.8)**	**5 (0.7)**
Alanine aminotransferase increased	0 (0.0)	--	2 (0.5)	2 (0.3)
Aspartate aminotransferase increased	0 (0.0)	--	1 (0.3)	1 (0.1)
Blood alkaline phosphatase increased	0 (0.0)	--	1 (0.3)	1 (0.1)
Blood bilirubin increased	1 (0.3)	--	1 (0.3)	2 (0.3)
Gamma-glutamyltransferase increased	1 (0.3)	--	2 (0.5)	3 (0.4)
Liver function test abnormal	0 (0.0)	--	1 (0.3)	1 (0.1)
Analysis Set B	**N=413**	**N=187**	**N=415**	**N=1015**
Any AE with at least one AE of SMQ06	**3 (0.7)**	**2 (1.1)**	**4 (1.0)**	**9 (0.9)**
Investigations	**3 (0.7)**	**2 (1.1)**	**4 (1.0)**	**9 (0.9)**
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.2)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Blood alkaline phosphatase increased	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Blood bilirubin increased	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.2)
Gamma-glutamyltransferase increased	1 (0.2)	1 (0.5)	3 (0.7)	5 (0.5)
Liver function test abnormal	1 (0.2)	1 (0.5)	1 (0.2)	3 (0.3)

AE = Adverse Event; BID = Twice daily; G-ER = Gabapentin-extended release; MedDRA = Medical Dictionary of Regulatory Affairs; QD = Once daily; asymmetric BID 600 mg AM/1200 mg PM; SMQ06 = Standarized MedDRA Query for possible drug-related hepatic disorders.
Reference: Tables 14.2.12.1.0 and 14.2.12.2.0.

Source: Applicant's submission (Integrated Summary of Safety, page 67

Reviewer comment: It appears that G-ER is not associated with serious cutaneous reactions and hepatic disorders as evidenced by the results of the SMQs.

7.6 Additional Safety Evaluations

7.6.1 Human Reproduction and Pregnancy Data

There are no reports of pregnancy in patients who have been treated with G-ER. One pregnancy was reported in a patient who had received placebo treatment (Patient 28003) in the PHN clinical studies.

7.6.2 Pediatrics and Assessment and/or Effects on Growth

No studies have been carried out in pediatric patients. As part of this NDA submission, the Applicant has submitted a request for waiver of pediatric studies. The Applicant requests a waiver of all pediatric age groups including newborn to 18 years of age.

The Applicant offered the following reason(s) for requesting waiver of pediatric studies.

The Applicant requests a waiver from pediatric studies based on section 505B(a)(4)(B)(i) of the Pediatric Research Equity Act. The indication studied and applied for in this New Drug Application is for the management of postherpetic neuralgia (PHN). This is a disease that is not prevalent in the pediatric age groups of 18 years and younger, which would make recruitment of clinical studies impossible or highly impractical due to the small number of pediatric patients.

Reviewer comment: According to an article by Stankus and Dlugopolskin in the American Family Physician (April 15, 2000), the incidence of herpes zoster increases sharply with advancing age, roughly doubling in each decade past the age of 50 years. Herpes zoster is uncommon in persons less than 15 years old. In a recent study, patients more than 55 years of age accounted for more than 30 percent of herpes zoster cases despite representing only 8 percent of the study population. In this same study, children less than 14 years old represented only 5 percent of herpes zoster cases. The development of chronic post herpetic neuralgia is even rarer in children than in adults.

A recent article by well respected researchers in pediatric pain, Walco and Dworkin et al in the May Clinic Proceedings (March 2010) state that conditions such as postherpetic neuralgia, trigeminal neuralgia, radiculopathies, and complications of stroke are of extremely low incidence in young patients, and are very difficult to study systematically.

While there do not appear to be exact numbers for the rate of PHN in children, it is clear from the literature that it occurs very rarely, and would be difficult to study in a systematic manner.

The Division met with PeRC on November 3, 2010 and the waiver request was granted.
.

7.6.3 Overdose, Drug Abuse Potential/ Withdrawal and Rebound

No studies have been conducted to evaluate the abuse and dependence potential of G-ER.

Withdrawal effects were not specifically assessed within the G-ER PHN clinical studies.

7.7 Additional Submissions

There were no additional safety submissions. There is no additional data in 120-day safety update, since all data was supplied with the original submission.

8 Postmarket Experience

There is no postmarketing experience with G-ER.

A review of the postmarketing data for gabapentin is provided by the Sponsor.

Of the 12 studies identified in the literature, seven studies were of duration of two years or more and five studies (42%) involved 80 or more patients. In the largest study (post-marketing surveillance) involving 1587 females of mean age 35.6 years (range, 18-86 years), the most frequently reported AEs, over a mean duration of treatment of 8.1 months, were drowsiness/sedation (11.5%), malaise/lassitude (10%), and headache (8.5%). In the other 3 largest long-term studies, involving a total of 708 patients, the rate of SAEs ranged from 2% to 7.4% and the rate of AEs leading to withdrawal ranged from 4.0% to 17.0%. Adverse events most common to these three studies were somnolence (15% to 29.3%), dizziness (13%), and weight gain (2.0% to 8.8%). Five studies, involving 115 patients, reported no SAEs over periods ranging from six months to four years.

Overall, in these 12 studies the rate of SAEs ranged from 0% to 7.4%, AEs from 31% to 88%, and AEs leading to withdrawal from 4% to 22%. Adverse events listed in these 12 studies involved: drowsiness, increased saliva secretion, hand tremors, ataxia,

dizziness, nystagmus, diplopia, tremor, ataxia, unpleasant taste, forgetfulness, nausea, diarrhea, malaise, rash, vertigo, fatigue, headache, and weight gain. Weight gain was reported in 1.4% to 56% of the patients.

Reviewer's Comments: No new safety signals were identified as a result of my review of the literature provided by the Sponsor. As stated earlier, there is an OSE consult pending for an AERS search for Neurontin.

9 Appendices

9.1 Literature Review/References

The Applicant provided adequate references for review of this submission.

9.2 Labeling Recommendations

DDMAC has tentatively accepted the proposed trade name “Gralise”.

At this writing, a preliminary review of the proposed labeling has identified the following issues that will be addressed during scheduled labeling sessions for this product:

1. The safety data set B should be used in stead of set A.
2. Renal dosage adjustment table and related languages.
3. (b) (4). These will be removed.

Other issues are likely to arise during the labeling sessions and will be addressed as needed. The completed label will be attached to this review.

9.3 Advisory Committee Meeting

There was no Advisory Committee held related to this NDA submission.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIMOTHY T JIANG
12/07/2010

ELLEN W FIELDS
12/07/2010