CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207589Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	207589
Submission Date:	December 18, 2014
Brand Name:	Enstilar Foam
Generic Name:	Calcipotriene and betamethasone dipropionate Foam, 0.005%/0.064%
Dosage Form:	Foam
Dosage Strength:	Calcipotriene 0.005% + betamethasone dipropionate 0.064%
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
Division Director:	CAPT. Edward D. Bashaw, Pharm.D.
OCP Division:	Division of Clinical Pharmacology - 3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Leo Pharma A/S
Relevant IND(s):	114063
Submission Type:	New-submission
Indication:	Topical treatment of plaque psoriasis in adults

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1. Executive Summary

This NDA application is for LEO 90100 aerosol foam formulation of calcipotriene and betamethasone dipropionate (BDP), 0.005%/0.064% for once daily topical treatment of plaque psoriasis in adults. The applicant of this NDA currently markets the fixed dose combination product of calcipotriene (also known as calcipotriol) and BDP 0.005%/0.064% in ointment and suspension dosage forms in the US and in number of other countries worldwide, under the trade names of Taclonex® (in USA) and Daivobet®, Dovobet®, and Xamiol® (in Europe). Information on US approved products is shown below:

- Taclonex® Ointment (NDA 21-852, Approval date: 01/09/2006)

    - Indication: Treatment of psoriasis in patients 12 years of age and older
- Taclonex® Topical Suspension (NDA 22-185, Approval date: 05/09/2008)
    - Indication: Treatment of scalp and body psoriasis in patients 18 years of age and older and treatment of scalp psoriasis in patients 12 to 17 years of age

With this new foam formulation, the applicant is seeking indication for the treatment of plaque psoriasis in subjects 18 years of age and older. The proposed dosing regimen will be to apply to the affected area once daily for up to 4 weeks and if control is achieved, the subjects will be asked to discontinue the therapy. Patients using this product will also be instructed not to exceed a maximum weekly dose of (b) (4) g.

The applicant is relying on clinical safety and pharmacology-toxicology information from the above two NDAs. Since the applicant of this NDA also owns the other two NDAs for Taclonex® ointment and Taclonex® scalp topical suspension, this application will follow a 505(b)(1) regulatory pathway.

The clinical program consists of seven new clinical trials and these include the following:

- A maximal use pharmacokinetic (PK) trial that assessed PK of LEO 90100, calcium metabolism and hypothalamic pituitary adrenal (HPA) axis suppression (LEO90100-30)
- A vasoconstriction trial (LP0053-69)
- A dermal safety trial (LP0053-66)
- An exploratory plaque psoriasis trial (LEO90100-01)
- One Phase 2 comparative trial vs. Daivobet® Ointment (LEO90100-35) (Daivobet® is the European brand of Taclonex® Ointment)
- One Phase 2 proof of concept trial efficacy and safety trials (LEO90100-7)
- One Phase 3 trial (LP0053-1001)

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the Applicant.

1.2 Post-Marketing Requirements/Commitments

Post-Marketing Requirements:

Conduct a clinical trial to assess pharmacokinetics, HPA axis suppression potential and effect on calcium metabolism of Enstilar foam in subjects 12 years to 16 years 11 months of age with moderate (b) (4) psoriasis.

Post-Marketing Commitments:

Conduct a single point vasoconstriction assay with adequate bracketing using visual assessment to determine the topical corticosteroid potency classification for Enstilar foam.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics: The applicant assessed PK of calcipotriene and betamethasone dipropionate and their metabolites under maximal use conditions in a PK trial conduced in 35 adult male and female subjects with at least moderate psoriasis. The subjects had a mean body surface area involvement of 17.5% and mean scalp involvement of 50.2%. The plasma concentrations of betamethasone dipropionate, calcipotriol and MC1080 were below lower limit of quantification (LLOQ) in most of the subjects. For metabolite betamethasone 17-propionate PK parameters could be estimated in 27 out of 35 subjects; The mean ± SD Cmax and AUClast for betamethasone 17-propionate were 147.9 ± 224.0 pg/mL and 683.6 ± 910.6 pg*h/mL.

HPA axis suppression and effect on calcium metabolism: In the maximal use PK trial, the applicant also assessed hypothalamic pituitary axis (HPA) suppression and effect on calcium metabolism following once daily drug application for 28 days. The results indicated that none of the 35 subjects that completed the trial had any HPA axis suppression or showed any effects on calcium metabolism.

Vasoconstriction (VCA) trial: The VCA trial conducted by the applicant is not acceptable and the potency classification of LEO90100 could not be determined (for additional information see Section 2.3.6).

Dose finding: The applicant already markets the fixed dose combination of calcipotriene and betamethasone dipropionate, 0.005%/0.064% as ointment, gel, scalp suspension etc. under different trade names in USA and Europe. The applicant's reason of developing this new Foam formulation is to provide patients with a more cosmetically acceptable alternative compared to currently available ointment and gel formulations (Taclonex®/ Daivobet®/Dovobet®). The new Foam formulation (LEO 90100) consists of (b) (4) (b) (4) dimethyl ether and butane propellants. Apart from the propellants, the applicant claims to have added no new excipients in LEO 90100 Foam. The applicant has not conducted any new dose finding trial with the new Foam formulation however, they have conducted a Phase 2 proof of concept trial demonstrating superior efficacy of this new fixed dose combination product compared to individual monad in the same vehicle.

QTc interval prolongation: The applicant has submitted a waiver request for conducting a TQT trial, and the rationale provided is that there is no current data that indicate the effect of corticosteroids and calcipotriene on cardiac repolarization or an association with cardiac arrhythmias. The applicant also provided post-marketing reports from marketed calcipotriene and calcipotriene + betamethasone products and out of the 5800 post-marketing case reports, there were 5 reports identified with cardiac arrhythmias. The applicant has further mentioned that in the 5 cases, potential contributing factors

including comorbidities and concomitant medications would not constitute a safety signal. This reviewer finds the applicant's rationale reasonable. For additional information see Clinical review.

Pediatric assessment: The applicant has requested for a waiver of pediatric assessment for subjects aged 0 to 11 years as this product would be unsafe in this age group (b) (4) For Taclonex ointment and suspension, pediatric assessment was waived for subjects 0 to 11 years.

For subjects aged 12 years to 16 years and 11 months, the applicant has requested for a deferral because adult studies are completed and ready for approval at this stage.

Reviewer comments: *An initial pediatric study plan (iPSP) was submitted on June 27, 2013 following the End of Phase 2 meeting. Agreement on the PSP was reached on December 03, 2013 (see communication in DARRTS under IND 114063).*

Clinical Pharmacology Briefing: An optional intra-division level briefing was conducted on August 13, 2015 with the following in attendance: CAPT. E. Dennis Bashaw, Hae-Young Ahn, Doanh Tran and Chinmay Shukla.

2. Question Based Review

2.1 Regulatory pathway

2.1.1 What regulatory pathway has the Applicant followed?

The applicant is relying on clinical safety and pharmacology-toxicology information from NDA 21-852 (Taclonex® ointment) and NDA 22-185 (Taclonex® scalp topical suspension). Since the applicant of this NDA also owns the Taclonex® brand of products shown above, this application will follow a 505(b)(1) regulatory pathway.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of chemistry and formulation?

Drug substance: Calcipotriene hydrate (Figure 1) is a synthetic vitamin D_3 analog with empirical formula $C_{27}H_{40}O_3H_2O$ and molecular weight of 430.6. Betamethasone dipropionate (Figure 2) is a synthetic corticosteroid with empirical formula $C_{28}H_{37}FO_7$ and molecular weight of 504.6.

Figure 1: Structure of calcipotriene hydrate

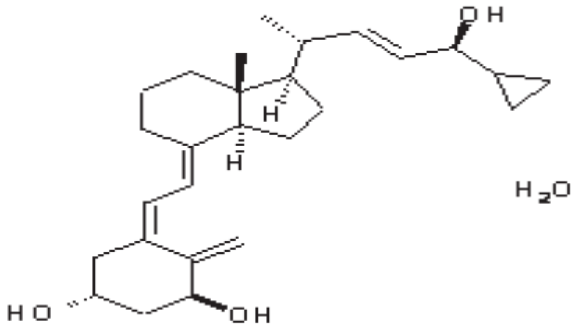
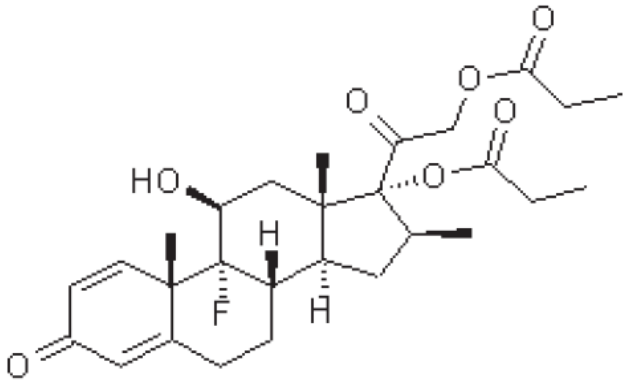


Figure 2: Structure of betamethasone dipropionate



Formulation: LEO 90100 consists of [redacted] (b) (4) propellants dimethyl ether and butane (Daivobet®

is the European brand of Taclonex® Ointment). The pressurized drug product is a white to off-white opalescent liquid in an aluminium spray can with a continuous valve and actuator. At administration the product is a white to off-white foam [redacted]. The composition of the formulation is shown in Table 1.

Reviewer comments: *As per the CMC reviewer, after the foam collapses, the structure of the formulation that remains on the skin is different from the ointment.*

Table 1: Qualitative and quantitative composition of to-be-marketed formulation

Name of components	Quantity per g as liquid in the container	Quantity per g [redacted] foam after evaporation of propellants	Function	Reference to quality standard(s)
Drug substance(s):	[redacted]			
Calcipotriol		50.0 mcg	Drug substance	Ph. Eur./LEO
[redacted] Betamethasone (as dipropionate)		0.5 mg*	Drug substance	Ph. Eur./USP
Excipients, from [redacted]				
PPG-11 Stearyl ether		[redacted]		LEO
[redacted] all-*rac*-α-Tocopherol				Ph. Eur./USP
[redacted]				Ph. Eur./USP
				Ph.Eur./USP
Excipients, propellants:				
Dimethyl ether		-	[redacted] propellant	LEO
Butane		-	propellant	NF/LEO

*corresponds to betamethasone dipropionate 0.643 mg/g

2.2.2 What are the proposed mechanism of action and the therapeutic indications?

Mechanism of action: The mechanism(s) by which both calcipotriene and betamethasone dipropionate act in the treatment of plaque psoriasis are unknown.

Therapeutic indication: Topical treatment of plaque psoriasis in adult subjects.

2.2.3 What is the proposed route of administration, dosage and dosing frequency?

Proposed route of administration: Topical.

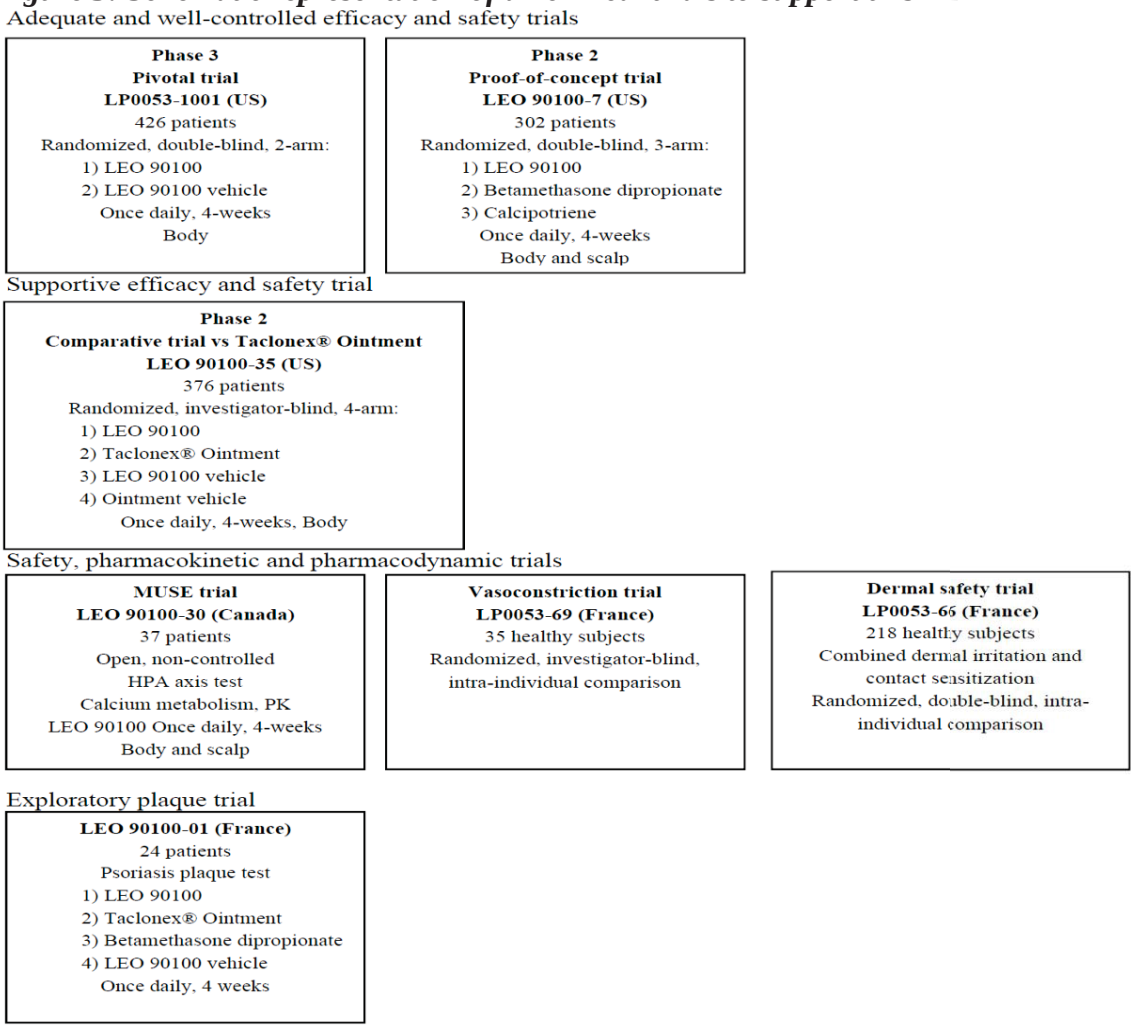
Proposed dosage and dosing frequency: Apply the foam to affected areas once daily for up to 4 weeks. Discontinue therapy when control is achieved. Patients should not exceed a maximum weekly dose of [redacted] g.

2.3 General Clinical Pharmacology

2.3.1 What were the clinical trials conducted to support this NDA?

A schematic representation of all the clinical trials to support this NDA is shown in Figure 3 below.

Figure 3: Schematic representation of all clinical trials to support this NDA



2.3.2 How was the dose selected?

The applicant already markets the fixed dose combination of calcipotriene and betamethasone dipropionate, 0.005%/0.064% as ointment, gel, scalp suspension etc. under different trade names in USA and Europe. The applicant's reason of developing this new Foam formulation is to provide patients with a more cosmetically acceptable alternative compared to currently available ointment and gel formulations (Taclonex®/ Daivobet®/Dovobet®). The new foam formulation (LEO 90100) consists of (b) (4) (b) (4) dimethyl ether and butane propellants. Apart from the propellants, the applicant claims to have added no new excipients in LEO 90100 Foam. The applicant

has not conducted any new dose finding trial with the new Foam formulation however, they have conducted a Phase 2 proof of concept trial demonstrating superior efficacy of this new fixed dose combination product compared to individual monad in the same vehicle.

2.3.3 What is the PK of LEO 90100 foam?

Maximal use PK trial design : This trial was a multi-center, open, non-controlled, single-group, 4-week trial in which subjects with at least moderate disease severity (according to Investigators Global Assessment [IGA]) on the trunk, limbs and scalp were enrolled. Drug was applied to all affected areas once daily (excluding skin folds, face and genitals) and the treatment lasted for 28 days with a maximum weekly application of 120g.

PK of parent calcipotriol (LLOQ 50 pg/mL) and betamethasone dipropionate (LLOQ 30 pg/mL) and their main metabolites [MC1080 (LLOQ 20 pg/mL) and betamethasone 17-propionate (LLOQ 30 pg/mL), respectively] was assessed. Plasma samples were obtained at baseline (before treatment), pre-dose at Day 14 and Day 28, and post-dose serial samples were obtained on Day 28 at 1, 2, 3, 5 and 7 hours.

A total of 37 adult male or female subjects with at least moderate to severe psoriasis with 15-30% of the body surface area (BSA) and 30% scalp involvement were enrolled and 35 subjects completed the trial (additional details on the trial design can be found in Section 4).

Reviewer comments: *For adult subjects with psoriasis, the maximal use PK trial has usually included subjects with at least 20% BSA and at least 25% scalp involvement. In this study the mean % BSA on the body was 17.5% and median was 16% (range 12-28%) and the mean scalp involvement was 50.2% and the median was 40% (range 30-100%). The mean total BSA treated was 20.9% and range was 16 - 30%.*

It is noted that the % BSA was lower than what is usually requested for a maximal use PK trial in psoriasis, however, it is worth noting that the % scalp involvement was higher than the minimum involvement requested in a maximal use PK trial in subjects with psoriasis. Hence in the opinion of this reviewer, the design of the maximal use PK trial in terms of body surface used for drug application, though not ideal, is reasonable.

PK results: Plasma samples for PK assessment were collected from all 37 subjects. However, PK samples from 2 subjects that were discontinued (Subject 1023 and Subject 1028) were only collected at baseline and at Day 14. Therefore these 2 subjects were excluded from PK analysis and 35 subjects were eligible for PK evaluation.

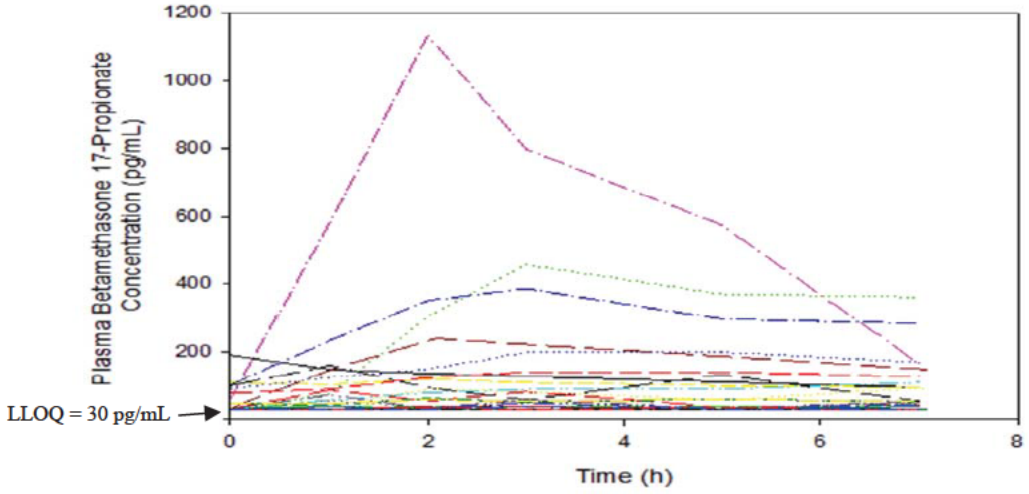
The results indicated that plasma concentrations were below LLOQ for betamethasone dipropionate, calcipotriol and MC1080 in most subjects and PK parameters C_{max} and AUC_{last} could be reliably determined only in few subjects as shown in Table 2 below. For calcipotriol only 1 subject had quantifiable plasma levels and no PK parameters could be

reliably determined. For metabolite betamethasone 17-propionate PK parameters were quantifiable in 27 out of 35 subjects and the mean ± SD C_{trough} concentrations on Day 14 (n = 16) and Day 28 (n = 14) were 36.95 ± 50.29 pg/mL (Range BLQ - 204 pg/mL) and 28.01 ± 44.65 pg/mL (Range BLQ - 190 pg/mL), respectively indicating steady state was achieved. The individual plasma concentration–time profiles for betamethasone 17-propionate on Day 28 are shown in Figure 4.

Table 2: Summary of PK parameters (mean ± SD) based on those subjects that had quantifiable plasma concentrations

Analyte	*No. of subjects*	*C_{max} (pg/mL) [Range]*	*AUC_{last} (h*pg/mL) [Range]*
Betamethasone dipropionate	5	52.2 ± 19.7 [33.7 - 81.1]	36.5 ± 27.4 [16.9 - 82.5]
Betamethasone 17-propionate	27	147.9 ± 224.0 [30.2 -1133]	683.6 ± 910.6 [18.5 - 4254]
Calcipotriol	1	55.9	82.5
MC1080	3	24.4 ± 1.9 [23.3 - 26.6]	59.3 ± 5.4 [55.3 - 65.5]

Figure 4: Plot of Plasma Betamethasone 17-Propionate Concentration-Time Profiles by Subject at Day 28 (LLOQ 30 pg/mL)



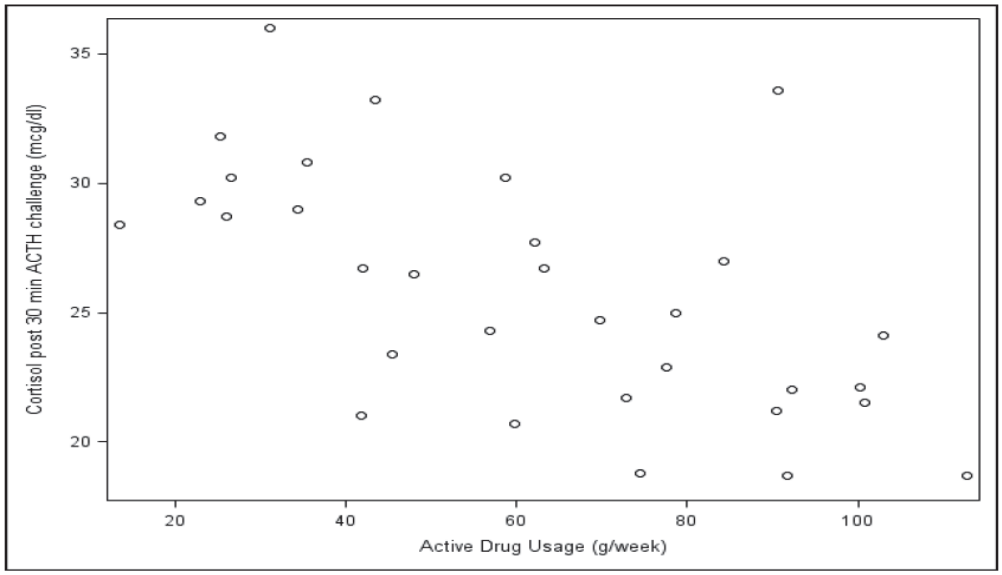
2.3.4 What are the results of HPA axis suppression test?

In the maximal use PK trial, approximately 3 to 7 days before Visit 1 (Day 0), baseline Adreno-corticotrophic Hormone (ACTH)-challenge test and the albumin-corrected serum calcium tests were conducted. The subjects were advised to maintain the intake of calcium-rich nutrients (number of servings). Post treatment ACTH-challenge test was performed at Day 28.

On Day 28 (last day of treatment), the CORTROSYN injection was administered after the pre-dose trough PK sample. The last dose of LEO 90100 foam was applied at the

clinic following the 30 and 60 minute blood samples for ACTH challenge test. The primary response criterion for evaluation of HPA axis function was percentage of subjects with serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test. None of the 35 subjects who completed 28 days of treatment as per protocol had a serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test at Day 28. The applicant also evaluated the effect on serum cortisol concentrations at 30 minutes after ACTH-challenge at Day 28 versus average weekly use of study medication (Figure 5). There appears to be a trend of decreasing cortisol levels 30 minutes post ACTH stimulation with increasing amount of the drug applied.

Figure 5: Serum Cortisol 30 minutes after ACTH-challenge at Day 28 versus Average Weekly Drug Use



2.3.5 What are the results of calcium metabolism assessments?

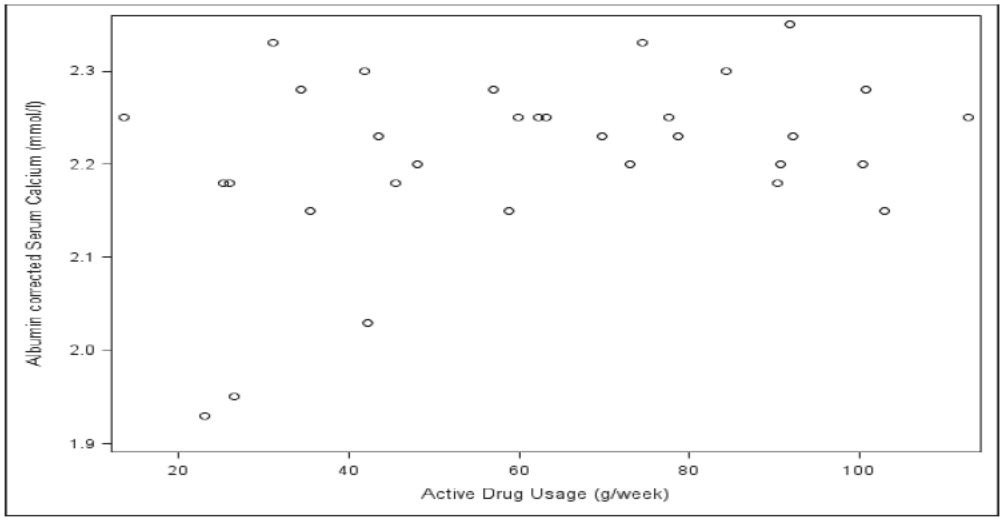
The effect of LEO 90100 on calcium metabolism was evaluated based on change from baseline to Day 28 in the following parameters:

- Albumin-corrected serum calcium, 24-hour urinary calcium excretion and urinary calcium:creatinine ratio (primary response criteria)
- Serum phosphate, serum ALP, plasma PTH, 24-hour urinary phosphate excretion and urinary phosphate:creatinine ratio (secondary response criteria -see Clinical review for the secondary response criteria assessment)

Albumin-corrected Serum Calcium: The mean and median values for albumin-corrected serum calcium were within the normal range (2.15 to 2.55 mmol/L) and the mean change in albumin corrected serum calcium from baseline to Day 28 was 0.014 mmol/L, which is not considered to be a clinically relevant increase. None of the subjects had elevated albumin-corrected serum calcium values above the normal range at any visit.

The effect on albumin corrected serum calcium by average weekly use of study medication is illustrated in Figure 6. There appears to be no clear trend towards increasing serum calcium levels with increasing amount of the drug applied within the range of doses in the trial.

Figure 6: Albumin Corrected Serum Calcium at Day 28 versus Average Weekly Drug Use



24-hour Urinary Calcium Excretion: The mean and median values for 24-hour urinary calcium were within the normal range (2.5 to 7.5 mmol/24 h).The mean decrease from baseline to Day 28 was 0.5 mmol/24 h; this decrease was not considered to be of clinical significance.

Urinary Calcium:Creatinine Ratio: The mean and median values for urinary calcium:creatinine ratio were within the reference range (0.225 to 8.2 mmol/g for women and 0.3 to 6.1 mmol/g for men) both before and after treatment. The mean decrease from baseline to Day 28 of 0.03 mmol/g was not considered to be of clinical significance.

Reviewer comments: *See additional assessment by the Clinical reviewer for calcium metabolism endpoints.*

2.3.6 What was the potency classification of this product based on vasoconstrictor assay?

The applicant provided results of a vasoconstriction (VCA) assay study but it is not considered acceptable for review. (b) (4)

[redacted]

In addition, while the multipoint VCA is currently an acceptable method for establishing bioequivalence (BE) for topical corticosteroids; however, this method is not acceptable

(b) (4)

[redacted]

Reviewer comments: *Though the Agency advises that similar blanching scores do not imply therapeutic equivalence, the information on potency classification of topical corticosteroids is useful in helping the prescriber narrow down their treatment choice from the realm of topical corticosteroids. In view of this, the applicant should conduct a single point VCA trial with adequate bracketing and visual assessment in healthy subjects to identify the potency classification of Enstilar Foam.*

2.3.7 What information is submitted to assess or waive TQT trial?

The applicant has submitted a waiver request for conducting a TQT trial, and the rationale provided is that there is no current data that indicate the effect of corticosteroids and calcipotriene on cardiac repolarization or an association with cardiac arrhythmias. The applicant also provided post-marketing reports from marketed calcipotriene and calcipotriene + betamethasone products and out of the 5800 post-marketing case reports, there were 5 reports identified with cardiac arrhythmias. The applicant has further mentioned that in the 5 cases, potential contributing factors including comorbidities and concomitant medications would not constitute a safety signal. This reviewer finds the applicant's rationale reasonable. For additional information see Clinical review.

2.3.8 What is the summary of safety?

The most common adverse events were local reactions and included application site irritation, application site pruritus, folliculitis, skin hypopigmentation, hypercalcemia, hypersensitivity, and rebound effect. According to the applicant there were no adverse reactions that occurred in ≥ 1% of the subjects treated with Enstilar® Foam and at a rate

higher than in subjects treated with vehicle. There were no deaths reported in any of the trials. For additional information, see Clinical review.

2.3.9 What is the summary of efficacy?

Two multicenter, randomized, double-blind trials were conducted in subjects with plaque psoriasis. In Trial One, 302 subjects were randomized to 1 of 3 treatment groups: Enstilar® Foam, betamethasone dipropionate in the same vehicle, or calcipotriene hydrate in the same vehicle. In Trial Two, 426 subjects were randomized to 1 of 2 treatment groups: Enstilar® Foam or the vehicle alone. In both trials, subjects were treated once daily for up to 4 weeks. Baseline disease severity was graded using a 5-point Investigator's Global Assessment (IGA). At baseline subjects scored "Mild", "Moderate" or "Severe". Efficacy was assessed with treatment success defined as the proportion of subjects with clear or almost clear disease (IGA) at Week 4. Subjects with mild disease at baseline were required to be clear to be considered a treatment success. Results for the primary response criterion treatment success (IGA) at Week 4 showed Enstilar® Foam to be statistically significantly more effective than all the comparators included (Table 3). For additional information, see Clinical and Biostatistics reviews.

Table 3: Efficacy results

Percentage of Patients with Treatment Success According to the Investigator's Global Assessment of Disease Severity				
	Enstilar® Foam	**Betamethasone dipropionate in vehicle**	**Calcipotriene in vehicle**	**Vehicle**
Trial One	(N=100)	(N=101)	(N=101)	-
Week 4	45.0%	30.7%	14.9%	-
Trial Two	(N=323)	-	-	(N=103)
Week 4	53.3%	-	-	4.8%

2.4 Intrinsic Factors

What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.1 Effect of age and gender

The applicant has not evaluated the effect of age and gender on the PK of the foam formulation.

2.4.2 Pediatric subjects

The applicant has requested for a waiver of pediatric assessment for subjects aged 0 to 11 years as this product would be unsafe in this age group because of safety concerns (b) (4)

(b) (4). For Taclonex ointment and suspension, pediatric assessment was waived for subjects 0 to 11 years.

For subjects aged 12 years to 16 years and 11 months, the applicant has requested for a deferral because adult studies are completed and ready for approval at this stage.

Reviewer comments: *An initial pediatric study plan (iPSP) was submitted on June 27, 2013 following the End of Phase 2 meeting. Agreement on the iPSP was reached on December 03, 2013 (see communication in DARRTS under IND 114063), and the applicant proposed to conduct an open-label trial to assess PK, HPA axis suppression and calcium metabolism in subjects aged 12 to* (b) (4) *years with psoriasis. The applicant has proposed to enroll 100 subjects to evaluate the effect on calcium metabolism.* (b) (4) (b) (4) *, the applicant will assess PK and HPA* (b) (4) *suppression,* (b) (4) *30 subjects will be under maximal use conditions* (b) (4) *at least* (b) (4) (b) (4) *at least moderate psoriasis.*

2.4.3 Renal and hepatic impairment

The effect of renal and hepatic impairment on PK of calcipotriene and betamethasone dipropionate and its metabolites was not evaluated by the applicant.

2.4.4 What pregnancy and lactation use information is there in the application?

The applicant has not conducted any trials in pregnant and lactating women.

2.5 Extrinsic Factors

2.5.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The influence of extrinsic factors on dose-exposure and/or response was not evaluated.

2.5.2 Drug interactions

The applicant has not conducted any new drug interaction studies with this NDA.

2.6 General Biopharmaceutics

2.6.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The concept of BCS classification does not apply to topically applied products.

2.6.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation was used in the maximal use PK trial and the Phase 3 trial and there was no manufacturing site change. Hence relative bioavailability assessment to bridge between clinical and to-be-marketed formulation is not needed.

2.6.3 What data support or do not support a waiver of in vivo BE data?

The to-be-marketed formulation was used in the all the clinical trials submitted with this application.

2.6.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Effect of food on the BA is not evaluated for topical formulations.

2.7 Analytical Section

2.7.1 How are the active moieties measured in the clinical trials?

Plasma concentrations of calcipotriene, betamethasone dipropionate, MC1080 and betamethasone 17-propionate were measured using high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) (CRO – (b) (4) (b) (4)).

2.7.2 Which metabolites have been selected for analysis and why?

MC1080 and betamethasone 17-propionate are the major metabolites of calcipotriene and betamethasone dipropionate, respectively, and were selected for analysis.

2.7.3 For all moieties measured, is free, bound, or total measured?

Total concentration was measured.

2.7.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of standard curve was:

- For calcipotriene: 50 pg/mL to 250 pg/mL
- For MC1080: 20 pg/mL to 400 pg/mL
- For betamethasone dipropionate: 30 pg/mL to 400 pg/mL
- For betamethasone 17-propionate: 30 pg/mL to 500 pg/mL

This range was adequate as none of the plasma concentrations for azelaic acid and pimelic acid clinical trials exceeded the upper limit of the concentration range.

2.7.5 What are the accuracy and precision at lower limit of quantification (LLOQ) and the quality control (QC) samples?

The accuracy and precision at LLOQ are shown in Table 4 below and for the QC samples are shown in Table 5. All values were within acceptable limits of ± 15%.

Table 4: Accuracy and precision at LLOQ

Analyte	**Accuracy (% Error)**		**Precision (CV%)**	
	Interday	**Intraday**	**Interday**	**Intraday**
Calcipotriene	0.0 (n=24)	-3.8 (n=3)	5.6 (n=24)	1.6 (n=3)
MC1080	0.5 (n=22)	1.0 (n=3)	4.3 (n=22)	3.9 (n=3)
Betamethasone dipropionate	-1.0 (n=19)	1.3 (n=3)	9.1 (n=19)	6.3 (n=3)
Betamethasone 17-propionate	0.0 (n=22)	0.3 (n=3)	8.6 (n=22)	11.3 (n=3)

Table 5: Accuracy and precision at QC

Analyte	**QC (pg/mL)**	**Accuracy (% Error)**		**Precision (CV%)**	
		Interday	**Intraday**	**Interday**	**Intraday**
Calcipotriene	100	1.0 (n=18)	10.0 (n=6)	8.6 (n=18)	6.7 (n=6)
	150	2.0 (n=17)	10.7 (n=6)	7.8 (n=17)	4.9 (n=6)
	200	5.0 (n=18)	10.5 (n=6)	5.2 (n=18)	4.3 (n=6)
MC1080	60	-0.5 (n=18)	-1.0 (n=6)	3.5 (n=18)	2.4 (n=6)
	220	-1.4 (n=17)	0.0 (n=6)	5.0 (n=17)	3.1 (n=6)
	400	2.3 (n=18)	2.8 (n=6)	2.8 (n=18)	1.5 (n=6)
Betamethasone dipropionate	90	-6.2 (n=18)	-9.2 (n=6)	6.5 (n=18)	6.0 (n=6)
	200	-4.5 (n=17)	-8.5 (n=6)	5.5 (n=17)	4.1 (n=6)
	320	-3.8 (n=18)	-10.3 (n=6)	7.3 (n=18)	4.0 (n=6)
Betamethasone 17-propionate	90	1.4 (n=18)	3.8 (n=6)	5.5(n=18)	5.4 (n=6)
	200	7.0 (n=17)	8.5 (n=6)	5.1 (n=17)	3.1 (n=6)
	400	1.5 (n=18)	0.3 (n=6)	5.0 (n=18)	4.4 (n=6)

2.7.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler, etc.)?

Parameter	***Calcipotriene***	***MC1080***	***Betamethasone dipropionate***	***Betamethasone 17-propionate***
Freeze/Thaw cycle stability	4 cycles at - 80ºC	4 cycles at - 80ºC	4 cycles at - 80ºC	4 cycles at - 80ºC
Room temperature stability	6 hours	6 hours	6 hours	6 hours

Stability at -20 ºC	77 days	77 days	77 days	77 days
Long term stability at -80 ºC	218 days	218 days	218 days	218 days

Reviewer comments: *The duration of long term PK sample stability was adequate to cover the duration of PK sample storage for the maximal use PK trial.*

2.7.7 What are the results of incurred sample reanalysis (ISR)?

At least 10% of the two hundred and eighty-two (282) total samples were reanalyzed for ISR purposes. The data obtained from reanalysis were compared to the original results. For acceptance, the agreement between the original and the repeat value had to be within ± 20% of the mean result for two-thirds of the repeated samples.

For purposes of calculating a percent difference between an original result and an ISR result, the LLOQ value was used for any result that was below the limit of quantitation (BLQ). For betamethasone dipropionate, calcipotriol and MC1080, most of the concentrations were below LLOQ and 100% of the ISR samples were in agreement with the original results with values with overall bias of less than 1%. For betamethasone 17-propionate 88.6% of the ISR samples had results within 20% of the mean values, with a mean overall bias of -6.81%.

3. Detailed Labeling Recommendations

The following changes are recommended in Sponsor's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

5.3 Hypothalamic-Pituitary-Adrenal Axis Suppression
Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for clinical glucocorticosteroid insufficiency. This may occur during treatment or upon withdrawal of the topical corticosteroid.

(b) (4)

Evaluation of HPA Axis Suppression

(b) (4) systemic absorption, (b) (4) of topical corticosteroids may (b) (4). Factors that predispose a patient (b) (4) topical corticosteroid (b) (4) (b) (4), use (b) (4) large surface areas, use (b) (4) prolonged (b) (4), (b) (4), use (b) (4) altered skin barrier, (b) (4) patients (b) (4) liver failure.

(b) (4) ACTH stimulation test (b) (4) for HPA axis suppression.

If HPA axis suppression is documented, (b) (4) withdraw the drug, reduce the frequency of application, or substitute with a less potent steroid. (b) (4) (b) (4) systemic corticosteroids. (b) (4) (b) (4)

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. [*See Use in Specific Populations (8.3)*]

Reviewer comments: *See additional edits in this section from Clinical.*

(b) (4)

8.4 Pediatric Use

Safety and effectiveness of the use of Enstilar® Foam in pediatric patients have not been studied. Because of a higher ratio of skin surface area to body mass, children ~~under the age of 12 years~~ are at particular risk of systemic adverse effects when they are treated with topical corticosteroids. [*See Warnings and Precautions (5.3,* (b) (4)]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enstilar® Foam combines the pharmacological effects of calcipotriene hydrate as a synthetic vitamin D_3 analog and betamethasone dipropionate as a synthetic corticosteroid. **However, while their pharmacologic and clinical effects are known, the exact mechanisms of their actions in plaque psoriasis are unknown.**

(b) (4)

12.2 Pharmacodynamics

(b) (4)

Effects on Calcium Metabolism

(b) (4)

(b) (4), effects of once daily application of Enstilar® Foam for 4 weeks on calcium metabolism in adult subjects (N=564) with plaque psoriasis were examined in three randomized, multicenter, prospective vehicle- and/or active-controlled clinical trials (b) (4). Following once daily application of Enstilar® Foam, elevated serum calcium levels outside the normal range were observed in 3 subjects. Elevated urinary calcium levels outside the normal range were observed in 17 subjects.

12.3 Pharmacokinetics

Absorption

The **pharmacokinetics (PK)** (b) (4) of Enstilar® Foam (b) (4) was investigated in (b) (4). **Plasma concentrations** (b) (4) of calcipotriene and betamethasone dipropionate and their main

metabolites were measured after 4 weeks of once daily application of Enstilar® Foam [redacted] Calcipotriene was quantifiable in 1 of 35 (2.9%) subjects and its main metabolite, MC1080, in 3 of 35 (8.6%) subjects. **For subjects with measurable concentrations, t**~~T~~he maximal plasma concentrations (C_{max}) **and area under the concentration curve until the last measured time point (AUC_{last})** [redacted] **for** calcipotriene **were** [redacted] 55.9 pg/mL **and 82.5 pg*h/mL, respectively;** and **the mean ± SD C_{max} and AUC_{last} for MC1080 was** [redacted] **24.4 ± 1.9** pg/mL **and 59.3 ± 5.4 pg*h/mL**, respectively. Betamethasone dipropionate was quantifiable in 5 of 35 (14.3%) subjects and its main metabolite, betamethasone 17-propionate (B17P), was quantifiable in 27 of 35 (77.1%) subjects. The **mean ± SD C_{max} and AUC_{last} for** [redacted] betamethasone dipropionate **were 52.2 ± 19.7 pg/mL and 36.5 ± 27.4 pg*h/mL, respectively** and **for** B17P were **147.9 ± 224.0** [redacted] pg/mL and **683.6 ± 910.6 pg*h/mL** [redacted], respectively. The clinical significance of these findings is unknown.

Metabolism

Calcipotriene:
Calcipotriene metabolism following systemic uptake is rapid and occurs in the liver. The primary metabolites of calcipotriene are less potent than the parent compound.

Calcipotriene is metabolized to MC1046 (the α,ß-unsaturated ketone analog of calcipotriene),which is metabolized further to MC1080 (a saturated ketone analog). MC1080 is the main metabolite in plasma. MC1080 is slowly metabolized to calcitroic acid.

Betamethasone dipropionate:
Betamethasone dipropionate is metabolized to betamethasone 17-propionate (B17P) and betamethasone, including the 6ß-hydroxy derivatives of those compounds by hydrolysis. B17P is the [redacted] **primary** metabolite.

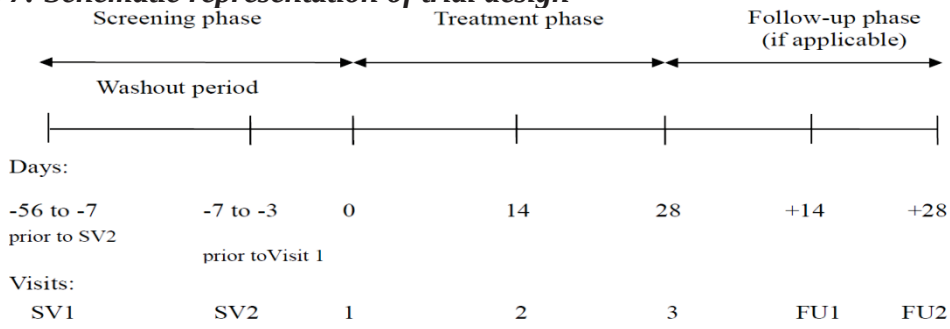
4. INDIVIDUAL STUDY REVIEW

Trial Number: LEO 90100-30 Maximal Use PK Trial

Objective: The primary objective of this trial was to evaluate the effect of once daily use of Leo 90100 on hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism in subjects with psoriasis vulgaris and the secondary objectives were to assess the PK of the active components and major metabolites as well as evaluate the safety and efficacy.

Trial design: This trial was conducted in Canada and it was a multi-center, open, non-controlled, single-group, 4-week trial in which subjects with at least moderate disease severity (according to Investigators Global Assessment [IGA]) on the trunk, limbs and scalp were enrolled. Drug was applied to all affected areas once daily (excluding skin folds, face and genitals) and the treatment lasted for 28 days with a maximum weekly application of 120 g. Figure 7shows a schematic representation of the trial design.

Figure 7: Schematic representation of trial design



Approximately 3 to 7 days (Visit SV2) before Visit 1 (Day 0), baseline Adreno-corticotrophic Hormone (ACTH)-challenge test and the albumin-corrected serum calcium tests were conducted so that the results were available for final subject eligibility check prior to treatment initiation. The subjects were advised to maintain the intake of calcium-rich nutrients (number of servings) which were recorded for the three days prior to and during the 24-hour urine collection at SV2 and at Visit 3 (Day 28).

At Day 28 (Visit 3) the ACTH-challenge test and PK sampling were performed along with haematology, biochemistry and urinalysis laboratory sampling. There were 2 follow-up visits after the treatment completion, out of these the second follow-up visit was scheduled to take place 28 days after the follow-up ACTH challenge test at Visit 3. Specifically, subjects that showed serum cortisol concentrations of ≤ 18 µg/dL at 30 minutes after the ACTH challenge at Visit 3 were to be re-tested.

Disposition of subjects: A total of 57 adult male and female subjects were screened and 37 subjects were found eligible and enrolled. Two subjects were withdrawn from treatment after 14 days (at/after Visit 2) and following are the details:

- Subject 1023 – Withdrawn due to failure to meet eligibility criterion for serum cortisol following ACTH challenge at baseline. The applicant has mentioned that

somehow this exclusion was not noted until 14 days into the trial and the applicant did a follow-up cosyntropin stimulation test.

- Subject 1028 – Withdrawn due to prohibited concomitant medication anti-depressant Cipralex (escitalopram) for anxiety. The subject was withdrawn from the trial at Visit 2.

Remaining 35 subjects completed the trial. Two subjects attended a follow-up visit and they were:

- Subject 1023 – This subject was withdrawn from the study at Day 14 due to failure to meet eligibility criterion for serum cortisol following ACTH challenge at baseline, was retested 28 days after the end of the treatment.
- Subject 1074 - Has a follow-up on adverse event (AE).

Demographics of the population:

	Safety Analysis Set (n=37)	
Sex	**Number of subjects**	**%**
Male	20	54.1
Female	17	45.9
Total	37	100.0

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	Safety Analysis Set (n=37)
Age (years)	
Mean	48.0
SD	14.1
Median	49.0
Minimum	21
Maximum	76
Number	37

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	Safety Analysis Set (n=37)	
Race	**Number of subjects**	**%**
WHITE	30	81.1
BLACK OR AFRICAN AMERICAN	2	5.4
ASIAN	1	2.7
AMERICAN INDIAN OR ALASKA NATIVE	1	2.7
OTHER	3	8.1
Total	37	100.0

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Other = Italian, Portuguese, and East Indian Cross-reference: EoT Table 1-8

Disease severity: The applicant included subjects with moderate to severe psoriasis with total involvement of 15-30% of the body surface area (BSA) and 30% scalp involvement.

IGA at baseline

	Safety Analysis Set (n=37)	
IGA	**Number of subjects**	**%**
Moderate	28	75.7
Severe	9	24.3
Total	37	100.0

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Extent of psoriasis at baseline

Investigator's assessment of extent	Safety Analysis Set (n=37)
Psoriasis involvement on trunk and limbs (%BSA)	
Mean	17.5
SD	4.6
Median	16.0
Minimum	12
Maximum	28
Number	37
Psoriasis involvement on scalp (%BSA)	
Mean	3.4
SD	1.6
Median	3.0
Minimum	2
Maximum	9
Number	37
Total Psoriasis involvement (%BSA)	
Mean	20.9
SD	4.6
Median	19.0
Minimum	16
Maximum	30
Number	37
Psoriasis involvement on Scalp (%Scalp)	
Mean	50.2
SD	23.2
Median	40.0
Minimum	30
Maximum	100
Number	37

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Reviewer comments: *For adult subjects with psoriasis, the maximal use PK trial has usually included subjects with at least 20% BSA and at least 25% scalp involvement. In this study the mean % BSA on the body was 17.5% and median was 16% (range 12-28%)*

and the mean scalp involvement was 50.2% and the median was 40% (range 30-100%). The mean total BSA treated was 20.9% and range was from 16 - 30%.

It is noted that the % BSA was lower than what is usually requested for a maximal use PK trial in psoriasis, however, it is worth noting that the % scalp involvement was higher than the minimum involvement requested in a maximal use PK trial in subjects with psoriasis. Hence in the opinion of this reviewer, the design of the maximal use PK trial in terms of body surface used for drug application, though not ideal, is reasonable.

Drug usage: The study limited the total dose to 120 g per week. Table 6 provides actual drug use information.

Table 6: Drug use per week

Drug Usage (g/week)	LEO 90100 (n=37)
Baseline to Visit 2	
Mean	56.6
SD	27.1
Median	51.7
Minimum	5.4
Maximum	102
Number	34
Visit 2 to End of Trial	
Mean	60.4
SD	29.5
Median	58.3
Minimum	21.3
Maximum	117
Number	33
Baseline to End of Trial	
Mean	61.8
SD	27.7
Median	61.0
Minimum	13.5
Maximum	113
Number	32

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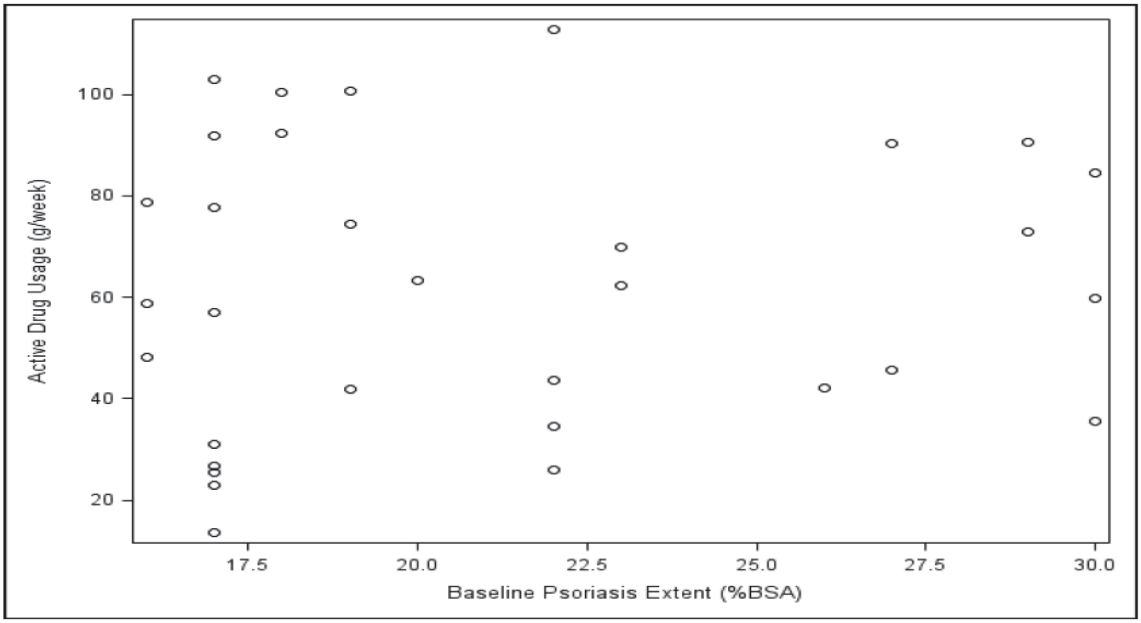
The total amount of study medication used by each subject per week versus body area treated (in terms of % BSA at baseline) is illustrated in Figure 8. From this figure, there appears to be no clear pattern in the relationship between individual BSA at baseline and the average weekly amount of LEO 90100 used.

Figure 8: Average Weekly Use of LEO 90100 versus Extent of Psoriasis



Reviewer comments: *Provided below (Table 7) is the amount of formulation used in the Phase 3 trial (LP0053-1001) and compared to this the amount of formulation used in the maximal use PK trial is higher.*

Table 7: Average weekly amount of the medication used in the Phase 3 trial

Interval Amount (grams per week)	LEO 90100 (n=323)	Vehicle (n=103)
Baseline to week 1		
Mean	29.9	32.9
SD	21.9	23.5
Median	22.5	25.5
Minimum	0.9	2.7
Maximum	97.3	87.7
Number	314	101
Week 1 to week 2		
Mean	28.5	32.6
SD	23.1	24.1
Median	20.4	23.4
Minimum	0.0	2.0
Maximum	121.5	89.0
Number	309	100
Week 2 to week 4		
Mean	30.2	32.7
SD	23.0	25.5
Median	24.1	23.7
Minimum	0.0	0.0
Maximum	106.4	100.4
Number	295	97
Total treatment period		
Mean	29.8	32.1
SD	21.2	23.6
Median	24.3	23.1
Minimum	2.1	2.5
Maximum	89.7	87.7
Number	293	98

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Treatment compliance: Over the total treatment period, 26 subjects were fully compliant and applied the medication once daily every day. The remaining 11 subjects each missed between one and two applications during the study.

HPA axis suppression results: See section 2.3.4.

Effect on calcium metabolism: See Section 2.3.5.

PK results: See Section 2.3.3.

Clinical Efficacy: Clinical efficacy was assessed as the percentage of subjects with 'controlled disease' (i.e. clear or almost clear) according to the IGA on the trunk and limbs at Day 28 (Visit 3). The percentage of subjects with 'controlled disease' at Day 28 (Visit 3) was 48.6% at Day 28 (Visit 3) and 45.9% at the end of treatment (Table 8). Table 9 shows the summary of number of subjects with regards to disease severity at each visit and at end of treatment (LOCF). Controlled disease (IGA) at each visit and at end of treatment (LOCF) is shown in Table 9..

Table 8: Summary of efficacy by Visits

	LEO 90100 (n=37)	
Controlled Disease According to IGA	**Number of subjects**	**%**
SV2/DAY -7 TO -3		
Non-controlled	37	100
Total	37	100
VISIT 1/DAY 0		
Non-controlled	37	100
Total	37	100
VISIT 2/DAY 14		
Controlled	4	10.8
Non-controlled	33	89.2
Total	37	100
VISIT 3/DAY 28		
Controlled	17	48.6
Non-controlled	18	51.4
Total	35	100
EOT		
Controlled	17	45.9
Non-controlled	20	54.1
Total	37	100

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Table 9: Summary of number of subjects and disease severity at each visit

	LEO 90100 (n=37)	
IGA	**Number of subjects**	**%**
SV2/DAY -7 TO -3		
Moderate	29	78.4
Severe	8	21.6
Total	37	100
VISIT 1/DAY 0		
Moderate	28	75.7
Severe	9	24.3
Total	37	100
VISIT 2/DAY 14		
Almost clear	4	10.8
Mild	26	70.3
Moderate	6	16.2
Severe	1	2.7
Total	37	100
VISIT 3/DAY 28		
Clear	2	5.7
Almost clear	15	42.9
Mild	13	37.1
Moderate	5	14.3
Total	35	100
EOT		
Clear	2	5.4
Almost clear	15	40.5
Mild	15	40.5
Moderate	5	13.5
Total	37	100

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Brief Summary of Adverse Events: The adverse events (AEs) in the max use PK trial were few. After study treatment had started, 4 (10.8%) subjects reported 6 AEs. There were no deaths and no serious adverse events (SAEs), discontinuations of investigational product due to an AE, or other significant adverse events were reported. There was one severe adverse event (erythema) which was considered by the Investigator to be probably related to treatment (an adverse drug reaction). All the remaining AEs reported in this trial were of mild or moderate intensity and assessed by the Investigator as not related to study treatment. Mostly local AEs were reported which included dryness, erythema and burning.

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

/s/

CHINMAY SHUKLA
08/20/2015

DOANH C TRAN
08/24/2015

EDWARD D BASHAW
08/24/2015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	207589	**Brand Name**	Enstilar
OCP Division (I, II, III, IV, V)	III	**Generic Name**	Calcipotriene and betamethasone dipropionate foam, 0.005%/0.064%
Medical Division	DDDP	**Drug Class**	Vitamin D analogue and corticosteroid combination
OCP Reviewer	Chinmay Shukla, Ph.D.	**Indication(s)**	Treatment of plaque psoriasis in adults
OCP Team Leader	Doanh Tran, Ph.D.	**Dosage Form**	Foam
Pharmacometrics Reviewer	NA	**Dosing Regimen**	Apply Foam to affected areas once daily for up to 4 weeks. Patients should not exceed a maximum weekly dose of (b) (4) g
Date of Submission	December 18, 2014	**Route of Administration**	Topical
Estimated Due Date of OCP Review	August 18, 2015	**Applicant**	Leo Pharma A/S
Medical Division Due Date	August 25, 2015	**Priority Classification**	Standard
PDUFA Due Date	October 18, 2015		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	1		Trial LEO90100-30: Maximal use PK trial
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD - Phase 1:	**X**	1		Trial LP0053-69: Vasoconstriction trial
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	To-be-marketed formulation is used in all clinical trials
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the Applicant submitted a justification that was previously agreed to before the NDA submission?	X			

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g.,	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	CDISC)?				
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
- N.A. –

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memorandum

Clinical Pharmacology Review

NDA: 207589
Compound: Calcipotriene and betamethasone dipropionate foam, 0.005%/0.064%
Indication: Treatment of psoriasis (b) (4) in adults
Applicant: Leo Pharma Inc.
Date: 12/18/2014
Reviewer: Chinmay Shukla, Ph.D.
Team Leader: Doanh Tran, Ph.D.
Related IND: 114063

Background: This NDA application is for LEO 90100 aerosol foam formulation of calcipotriene and betamethasone dipropionate (BDP), 0.005%/0.064% for once daily topical treatment of plaque psoriasis in adults. The combination is currently marketed in the US and a number of other countries worldwide in ointment and gel formulations. These products are marketed in the US under the trade name Taclonex® and in Europe under other trade names such as Daivobet®, Dovobet®, and Xamiol®. Information on US approved products is shown below:

- Taclonex® Ointment (NDA 21-852, Approval date: 01/09/2006)
  - Indication: Treatment of psoriasis in patients 12 years of age and older
- Taclonex® Scalp Topical Suspension (NDA 22-185, Approval date: 05/09/2008)
  - Indication: Treatment of scalp and body psoriasis in patients 18 years of age and older and treatment of scalp psoriasis in patients 12 to 17 years of age

The applicant for this NDA is the same as the one that owns both the Taclonex products and the indication sought is treatment of plaque psoriasis in subjects 18 years of age and older. The proposed dosing regimen will be to apply to the affected area once daily for up to 4 weeks and if control is achieved, the therapy should be discontinued. The patients will be instructed not to exceed a maximum weekly dose of (b) (4) g.

Regulatory: Since the same applicant markets two approved combination products of calcipotriene and betamethasone dipropionate, 0.005%/0.064% (Taclonex® ointment and Taclonex® scalp topical suspension), this application will follow a 505(b)(1) regulatory pathway.

Clinical program: The most relevant clinical trials include one maximal use pharmacokinetic (PK) trial, one vasoconstriction trial, and one Phase 3 trial. Figure 1 shows the summary of the clinical development program to support this application.

Figure 1: Overview of the clinical development program

Adequate and well-controlled efficacy and safety trials

Phase 3
Pivotal trial
LP0053-1001 (US)
426 patients
Randomised, double-blind, 2-arm:
1) LEO 90100
2) Foam vehicle

Once daily, 4-week
Body

Phase 2
Proof-of-concept trial
LEO 90100-7 (US)
302 patients
Randomised, double-blind, 3-arm:
1) LEO 90100
2) Betamethasone dipropionate
3) Calcipotriol

Once daily, 4-week
Body and scalp

Supportive efficacy and safety trial

Phase 2
Comparative trial vs Daivobet®
Ointment
LEO 90100-35 (US)
376 patients
Randomised, investigator-blind, 4-arm:
1) LEO 90100
2) Daivobet® ointment
3) Foam vehicle
4) Ointment vehicle

Once daily, 4-week
Body

Safety, pharmacokinetic and pharmacodynamic trials

MUSE trial
LEO 90100-30 (Canada)
37 patients
Open, non-controlled
HPA axis test
Calcium metabolism, PK
LEO 90100

Once daily, 4-week
Body and scalp

Vasoconstriction trial
LP0053-69 (France)
35 healthy subjects

Randomised, investigator-blind, intra-individual comparison

Dermal safety trial
LP0053-66 (France)
218 healthy subjects

Combined dermal irritation and contact sensitisation

Randomised, double-blind, intra-individual comparison

Exploratory plaque trial

LEO 90100-01 (France)
24 patients
Psoriasis plaque test
1) LEO 90100
2) Daivobet® ointment
3) Betamethasone dipropionate
4) Foam vehicle

Once daily, 4-week
Body

Clinical pharmacology trials: The applicant has conducted a maximal use PK trial which assessed the plasma concentrations of BDP and its metabolite betamethasone 17-propionate as well ascalcipotriol and its metabolite MC1080. This trial also assessed the potential for HPA axis

suppression and effects on calcium metabolism in subjects with 15-30% body surface area (BSA) involved in 37 adult subjects with psoriasis on the body and scalp. Table 1 provides summary of the Clinical Pharmacology Trials submitted with this application.

Table 1: Summary of Clinical Pharmacology trials

Type of Trial	Trial ID Trial Status, Type of Report	Trial Design	FSFV/LSLV Sites; No. & Location	No. of Subjects Treated/completed Median Age (range), Sex	Diagnosis Main Inclusion Criteria	IPs; Dose, Route & Regimen	Duration of Treatment	Primary Endpoint(s)
MUSE	LEO 90100-30 Completed, full CSR	Open, non-controlled, multi-centre, single-group	04-Jun-2012 02-May-2013 8 sites in Canada	37/35 49.0 (21 to 76) years 20M/17F	Psoriasis vulgaris, body + scalp 15-30% of BSA with ≥30% of the scalp involved	LEO 90100 Once daily on all lesions on the body + scalp	4 weeks	Subjects with serum cortisol concentration of ≤18 mcg/dl 30 minutes after ACTH-challenge at Day 28 Change from baseline to Day 28 in albumin-corrected serum calcium, 24-hour urinary calcium excretion, and urinary calcium:creatinine ratio
Vasocon-striction	LP0053-69 Completed, full CSR *and* Completed Addendum CSR	Randomised, investigator-blinded, single dose, single centre, intra-individual comparison	13-Sep-2013 03-Oct-2013 1 site in France	35/35 36.0 (21 to 49) years 14M/21F	Healthy adults	LEO 90100 Daivobet® ointment Dermoval®/ Dermovate® cream Synalar® ointment BDP Foam vehicle Single application of each IP on selected test sites	1 day (single dose)	Visual assessment of skin blanching (visual score) expressed by the AUC_{0-32h} by treatment site

ACTH = adrenocorticotropic hormone; AUC = area under the concentration time curve; BDP = betamethasone dipropionate; BSA = body surface area; CSR = clinical study report; F = females; FSFV = first subject first visit; IP = investigational product; LSLV = last subject last visit; M = males; MUSE = Maximum use systemic exposure.

Formulation: According to the applicant the formulation consists of [redacted] (b) (4) propellants dimethyl ether and butane. Daivobet Ointment is a brand marketed in Europe and is identical in composition to the US formulation, Taclonex® Ointment. According to the applicant, all clinical trials were conducted using the to-be-marketed formulation.

Pediatric assessment: The applicant has requested a partial waiver for pediatric assessment in subjects 0 to 11 years of age and the reason to support waiver request is that the product would be unsafe in this age range [redacted] (b) (4). The applicant has also requested a deferral of assessment in subjects aged 12 to [redacted] (b) (4) years as this product is ready for Agency NDA review in adults.

Bioanalytical method validation and Bioanalysis reports: Submitted for review.

Recommendation: NDA 207589 is fileable from the Clinical Pharmacology perspective.

Comments to be sent to the Applicant: None.

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/s/

CHINMAY SHUKLA
02/03/2015

DOANH C TRAN
02/03/2015