CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207589Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207589
Priority or Standard	Standard
Submit Date(s)	December 18, 2014
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Division / Office	DDDP/ODEIII
Reviewer Name(s)	Patricia C. Brown, MD
Review Completion Date	September 16, 2015
Established Name	Calcipotriene and betamethasone dipropionate
(Proposed) Trade Name	Enstilar® Foam
Therapeutic Class	Psoriasis agent
Applicant	LEO Pharma, Inc.
Formulation(s)	Foam
Dosing Regimen	Once daily
Indication(s)	Topical treatment of plaque psoriasis
Intended Population(s)	Adults 18 years of age and older

Template Version: March 6, 2009

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends an approval action for the current NDA 207589, Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%, for the topical treatment of plaque psoriasis in patients 18 years of age and older.

This recommendation is contingent upon successful completion of labeling negotiations with the applicant.

1.2 Risk Benefit Assessment

The applicant, LEO Pharma, Inc., has submitted a 505(b)1 New Drug Application for Enstilar ® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%. Enstilar® Foam is a (b) (4) of the approved product Taclonex® Ointment (NDA 021852). (b) (4). In the United States the ointment formulation was approved January 2006.

To demonstrate findings of efficacy, the applicant conducted a Phase 3 pivotal trial, LP0053-1001 and a Phase 2 trial, LEO 90100-7. Trial LP0053-1001 was a national, multi-center, prospective, randomized, double-blind, 2-arm, parallel group, 4-week, vehicle-controlled study in subjects with stable plaque psoriasis on the body (trunk and/or limbs). Trial LEO 90100-7 was a Phase 2 national, multi-center, prospective, randomized, double-blind, 3-arm, parallel group, 4-week, active-controlled study in subjects with stable plaque psoriasis on the body (trunk and/or limbs) and scalp. For both of these trials, subjects must have had an IGA score of at least mild, with 2-30% BSA involvement at baseline. In LEO 90100-7 there was also a requirement also for at least 10% scalp involvement as well as the 2-30% BSA involvement of trunk and limbs. Subjects applied study product once daily for up to 4 weeks.

In both trials, the protocol-specified primary efficacy endpoint was the proportion of subjects with 'treatment success' on the trunk and limbs at Week 4. Treatment success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

In Trial LEO 90100-7, Enstilar® Foam was statistically superior to both the betamthasone dipropionate monad ($p = 0.047$) and the calcipotriene monad ($p < 0.001$). In Trial LP0053-1001, Enstilar® foam was statistically superior to vehicle foam ($p < 0.001$).

The principal evaluation of safety for Enstilar® Foam for the indication, topical treatment of plaque psoriasis in adults 18 years of age and older, was based on trials that included treatment regimens of once daily for up to 4 weeks in subjects treating psoriasis vulgaris on the body, excluding face, axillae, and groin. The pooled safety trials are LP0053-1001 pivotal (US), LEO 90100-35 (Phase 2 investigator blinded, 4 arm, vehicle and active controlled), and LEO 90100-7 (Phase 2, double blinded, 3 arm active controlled). Additional important safety information is available from trial LEO 901100-30, assessment of effects on HPA axis and calcium metabolism.

No deaths were reported in any of the seven trials in the clinical development program; LP0053-1001 pivotal (Phase 3, 2-arm vehicle controlled), LEO 90100-35 (Phase 2, 4-arm, vehicle and active controlled), LEO 90100-7 (Phase 2, 3-arm, active controlled), LEO 90100-30 MUSE open-label, LP0053-69 Vasoconstriction, LP0053-66 dermal safety, and LEO 90100-01 psoriasis plaque test. In the pooled safety studies, a total of 6 non-fatal serious adverse events (SAE's) were reported in 5 subjects; Enstilar® Foam (3 SAEs/3 subjects 0.5%) and Taclonex® Ointment (3 SAEs/2 subjects 1.5%). In the Enstilar® Foam group SAEs were hypersensitivity/urticaria, bipolar disorder, and substance-induced psychotic disorder. Hypersensitivity/urticaria was considered possibly related to treatment with Enstilar® Foam.

In the pool of controlled trials, for Enstilar® Foam, adverse drug reactions occurring at a rate greater than in foam vehicle included; application site pruritus (0.4), application site irritation (0.2), skin irritation (0.2), folliculitis (0.2), application site discoloration, hypercalcemia (0.2), urticaria (0.2), and exacerbation of psoriasis (0.2).

The effects of Enstilar® Foam on the HPA axis and on calcium metabolism were examined in trial LEO 90100-30. HPA axis suppression was evaluated in adult subjects (N=35) with moderate to severe plaque psoriasis with a mean body surface area involvement of 17.5% and mean scalp involvement of 50.2%. Treatment consisted of once daily application of Enstilar® Foam on the scalp and body for 4 weeks. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL was not observed in in any subjects after 4 weeks of treatment.

For this 505(b)(1) application, based on the data submitted from the seven trials in the clinical development program, safety and efficacy of Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% have been established for the topical treatment of plaque psoriasis in patients 18 years of age and older.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At this time, a postmarketing Risk Evaluation and Mitigation Strategy (REMS) is not recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarket Requirement:
For pediatric patients ages 12 to (b) (4) years, information is needed about systemic exposure and safety after exposure to Enstilar® Foam applied to the body and scalp. Deferred pediatric studies in pediatric patients ages 12 to (b) (4) years will be conducted as required by PREA.

A proposal for a PMR, based upon the Agreed iPSP is as follows:

> Conduct an open-label trial to assess the effect on calcium metabolism of Enstilar® Foam in 100 evaluable pediatric subjects aged 12 years to 16 years and 11 months with plaque psoriasis of the scalp and body. Pharmacokinetics (PK) of Enstilar Foam and assessment of hypothalamic-pituitary axis (HPA) suppression will be conducted in a subset of at least 30 subjects with at least moderate psoriasis under maximal use conditions

Postmarket Commitment:
In the NDA submission, the applicant describes a vasoconstriction (VCA) trial conducted to assess the potency classification of Enstilar® Foam. Upon review, this trial was determined to be inadequate.
A proposal for a PMC is as follows:

> Conduct a single point vasoconstriction assay (VCA) with adequate bracketing using visual assessment to determine the topical corticosteroid potency classification of Enstilar® Foam.

2 Introduction and Regulatory Background

2.1 Product Information

The applicant, LEO Pharma, Inc., has submitted a 505(b)1 New Drug Application for Enstilar ® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%. The objective of the current NDA is to provide data to support approval for the marketing of Enstilar® Foam for topical treatment of plaque psoriasis (of the body) in patients 18 years of age and older.

Enstilar® Foam contains a fixed combination of calcipotriene 50 mcg/g and betamethasone 0.5 mg/g (as dipropionate). It is noted that calcipotriol is identical to calcipotriene. Calcipotriol is the International Non-proprietary Name and calcipotriene is the US Adopted Name (USAN). Calcipotriol is a synthetic vitamin D3 analogue and betamethasone dipropionate is a synthetic corticosteroid.

Enstilar® Foam is a white to off-white opalescent liquid in a pressurized aluminum spray can with a continuous valve and actuator. At administration the product is a white to off-white foam after evaporation of the propellants (dimethyl ether and butane). Each gram of foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone) in a base of white petrolatum, polypropylene glycol stearyl ether, mineral oil, all-rac-alphatocopherol, and butylhydroxytoluene. Enstilar® Foam is a (b) (4) of the approved ointment product (NDA 021852 Taclonex). (b) (4)

According to the applicant, on administration most of the propellants evaporate quickly, leaving a foam with active substances and propellant residues on the skin. Apart from the propellants, no new excipients have been added to Enstilar® Foam as compared with Taclonex® ointment.

The container closure system consists of an aluminum can equipped with a valve and an actuator enabling delivery of the drug product in multiple directions, except for the horizontal.

Enstilar® Foam is available in aluminum cans of 60 grams and a unit of two cans, each containing 60 grams.

The applicant proposed indication is "topical treatment of plaque psoriasis in adults 18 years of age and older."

Proprietary Name:
The Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk, reviewed the proposed proprietary name, Enstilar, and concluded that is conditionally acceptable. This was communicated in the Agency letter to applicant dated August 12, 2015. The applicant's correspondence regarding the proposed proprietary name was dated May 29, 2015.

2.2 Tables of Currently Available Treatments for Proposed Indications

FDA approved topical products available for the topical treatment of psoriasis of the body include the following: (This is not an exhaustive listing and excludes calcipotriene and betamethasone dipropionate):

Table 1: Topical Treatments for Psoriasis of the Body

Treatment	Formulations	Indication	ages
Steroids (sampling)			
Desonide	Cream .05% Ointment .05% Lotion .05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	
Hydrocortisone butyrate	Cream 0.1% Ointment 0.1% Solution 0.1%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	
Fluticasone propionate	Cream 0.05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	3 months and older
	Ointment .005%	same	adults
Fluocinonide	Cream 0.1%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	12 years and older
Clocortolone pivalate	Cream 0.1%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	
Halcinonide	Cream 0.1% Ointment 0.1%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	
Halobetasol propionate	Cream 0.05% Ointment 0.05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	12 and older
Clobetasol propionate	Foam 0.05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	12 and older
	Lotion 0.05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	18 and older
	Spray 0.05%	Moderate to severe plaque psoriasis up to 20% BSA	18 and older
Non-steroids			
Calcitriol	Ointment, 3mcg/g	Mild to moderate plaque psoriasis	18 and older
Tazarotene	Cream .05% Cream 0.1%	Plaque psoriasis	18 and older*
	Gel 0.05% Gel 0.1%	Stable plaque psoriasis of up to 20% BSA	12 and older**

Source: Reviewer's Table updated from Drugs @ FDA accessed July 7, 2015.

* Safety and efficacy of tazarotene cream have not been established in patients with psoriasis under the age of 18 years (Current Product Labeling: Pediatric Use Section)

** Safety and efficacy of tazarotene gel have not been established in pediatric patients under the age of 12 years (Current Product Labeling: Pediatric Use Section)

2.3 Availability of Proposed Active Ingredient(s) in the United States

Table 2: Availability of Proposed Active Ingredients in the United States

Generic Name and Formulation	Brand Name	Applicant/	NDA/ANDA Number	FDA Approval Date
Calcipotriene foam, 0.005%	Sorilux	Stiefel Laboratories, Inc	22563	10/6/2010
Calcipotriene ointment, 0.005%	generic	Glenmark Generics	90633	3/24/2010
Calcipotriene cream, 0.005%	Dovonex & generics	Leo Pharma & Tolmar	20554, 200935	7/22/1996
Calcipotriene solution, 0.005%	generics	Fougera Pharms, Tolmar, G and W Labs Inc Pharma, Nycomed US	77029, 78305,78468	3/3/1997
Calcipotriene 0.005% and Betamethasone 0.064% ointment	Taclonex	Leo Pharma	21852	1/9/2006
Calcipotriene 0.005% and Betamethasone 0.064% solution	Taclonex Topical Suspension	Leo Pharma	22185	5/9/2008
Betamethasone dipropionate 0.05% ointment, augmented	Diprolene & generics	Merck Sharp Dohme, Actavis, Fougera, Taro	18741, 74304, 75373, 76753	7/27/1983
Betamethasone dipropionate 0.05% lotion, augmented	Diprolene & generics	Merck Sharp Dohme, Fougera, Taro	19716, 77111,77477	8/1/1988
Betamethasone dipropionate 0.05% cream, augmented	Diprolene AF & generics	Merck Sharp Dohme, Fougera, Glenmark, Perrigo, Taro, Tolmar	19555, 76215,78930,76592,76543,76603	4/27/1987
Betamethasone dipropionate 0.05% gel, augmented	generic	Taro, Fougera	76508, 75276	12/2/2003

Source: Reviewer's table updated from Drugs @ FDA accessed July 7, 2015.

2.4 Important Safety Issues with Consideration to Related Drugs

The adverse event profile for each of the active ingredients (calcipotriene hydrate and betamethasone) is well documented.

Adverse reactions associated with vitamin D analogues, such as calcipotriene, include both local and systemic effects. According to approved product labeling, the most common local adverse reactions associated with calcipotriene containing products are; application site erythema, application site pain, skin irritation, pruritus, rash, dermatitis, worsening of psoriasis, and contact dermatitis (Adverse Reactions Sections: SORILUX™ Foam and Dovonex® cream). Systemic absorption of vitamin D analogues can produce hypercalcemia and hypercalciuria.

Adverse reactions with topical corticosteroids also include both local and systemic effects. Common local adverse effects include atrophy, striae, tealngiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, hypertrichosis, and miliaria. Systemic adverse reactions reported with topical corticosteroids include, among others; HPA axis suppression, Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus.

For Taclonex® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Topical Suspension, adverse reactions that occurred in greater than or equal to 1 % of subjects treated with drug product (for scalp psoriasis) and at a rate higher than in those treated with vehicle were folliculitis and burning sensation of skin. Other less common reactions (trials for scalp psoriasis and body psoriasis) included acne, exacerbation of psoriasis, eye irritation, pustular rash, rash, and folliculitis. In a 52-week study (psoriasis of scalp), adverse reactions that were reported by greater than 1% of subjects treated with Taclonex® Topical Suspension were pruritus, psoriasis, erythema, skin irritation, and folliculitis.

For Taclonex® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Ointment, adverse reactions that occurred in greater than or equal to 1 % of subjects treated with drug product and at a rate higher than in those treated with vehicle included scaly rash. In a 52-week study with use "as needed," adverse reactions that were reported by greater than 1% of subjects treated with Taclonex® Ointment were pruritus, psoriasis, skin atrophy, folliculitis, burning sensation, skin depigmentation, ecchymosis, erythema, and hand dermatitis. Adverse reactions associated with Taclonex® Ointment, identified post-approval, include pustular psoriasis and rebound effect.

Hypercalcemia and hypercalciuria have been observed with use of Taclonex ® Topical Suspension and Ointment. In a study of 32 subjects treated with Taclonex Scalp® Topical Suspension and Taclonex® Ointment on the body, adrenal suppression was identified in 5 of 32 subjects (15.6%) after 4 weeks of treatment (Approved product labeling Taclonex ® Topical Suspension and Ointment, Sections 6 Adverse Reactions and 5 Warnings and Precautions).

Taclonex® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Ointment and Scalp Topical Suspension are pregnancy category C products.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Enstilar® Foam is a foam formulation of the vitamin D3 derivative calcipotriol 50 mcg/g and the potent corticosteroid betamethasone 0.5 mg/g (as dipropionate).
The applicant states that "…the foam formulation has been developed to supplement existing ointment and gel formulations and to provide an efficacious product with improved user-friendliness (convenience of application and ease of use) for the treatment of psoriasis vulgaris" (plaque psoriasis). Commercial IND 114,063 for development of the foam was opened March 28, 2012.

A Pre-IND meeting was held March 7, 2012 to discuss the planned development program for LEO 90100 (to be Enstilar® Foam). Discussion supported conduct of an appropriately designed phase 2 study to demonstrate contribution of the monads which could lead to a Phase 3 clinical trial without monad arms.

- If seeking an approval for both body and scalp psoriasis, clinical trials should be designed to demonstrate the safety and efficacy of the product in each indication. It would seem reasonable to conduct a clinical trial in each indication.
- Dosage form proposed, foam, is reasonable based on sample received.
- Agency agreed in general with proposed plan to evaluate markers of calcium homeostasis in Phase 2 trials LEO 90100-7 and LEO 90100-35 [albumin-corrected serum calcium and calcium: creatinine ratios (from spot urine samples)] and LEO 90100-30 [Serum calcium, albumin, phosphate, alkaline phosphatase; Plasma parathyroid hormone (PTH); Urine (24 hour collection) for calcium-, phosphate-, and creatinine excretion (calculated calcium: creatinine and phosphate: creatinine ratios)]. Consider measuring 25-OH Vitamin D levels at baseline.
- For MUSE trial, Agency recommended enrollment of subjects with psoriasis vulgaris involving the trunk, limbs and scalp together to qualify as maximal use conditions. Applicant requested to provide a criteria for the percentage BSA of the scalp involvement in the final protocol (e.g. at least 30 % of the scalp and, in total 15-30 % of the body surface area).
- Applicant to consider performing a Vasoconstrictor Assay (VCA) to evaluate the vasoconstrictor properties of the proposed product (b) (4) (b) (4).
- It appeared reasonable that available UV/visual spectra data, in conjunction with the safety testing performed with Taclonex® Ointment would provide sufficient justification to support a request for a waiver of phototoxicity and photoallergy studies.
- The primary efficacy variable should be defined as a Physician's Global Assessment (PGA) score of 0 or 1 (representing "Clear" or "Almost Clear") with at least 2 grades reduction from the base line. An appropriate baseline score on the PGA is needed to adequately asses the final PGA measurement.
- The applicant stated that they would revise their proposed (b) (4) to a 5-point PGA scale.

On March 28, 2012 the applicant opened the IND with two Phase 2 protocols:

- LEO 90100-7: A Phase 2 study comparing treatment with LEO 90100 (Enstilar® Foam) with betamethasone dipropionate in LEO 90100 vehicle and calcipotriol in LEO 90100 vehicle in subjects with psoriasis vulgaris.
    - A 3-arm, double-blind, randomized, 4-week trial in 300 subjects with psoriasis vulgaris on the trunk and/or limbs and scalp (100 subjects per arm) comparing the efficacy of LEO 90100 with its monads.
- LEO 90100-35: A Phase 2 study comparing treatment with LEO 90100 with calcipotriol plus betamethasone ointment, LEO 90100 vehicle and ointment vehicle in subjects with psoriasis vulgaris.
    - A 4-arm, investigator-blinded, randomized, 4 week trial in 400 subjects with psoriasis vulgaris on the trunk and/or limbs comparing the efficacy of LEO 90100 with LEO 90100 vehicle, Taclonex Ointment, and Taclonex Ointment vehicle.

Comments regarding the above two protocols were sent to the applicant in a letter dated June 1, 2012 and included the following:

- The contribution of the monads could be demonstrated in an appropriately designed Phase 2 trial. While trial LEO 90100-7 will compare the safety and efficacy of LEO 90100 with its individual components, it will be difficult to interpret the findings without including a LEO 90100 vehicle arm into the design.

An End of Phase 2 Meeting was scheduled for May 15, 2013. After review of the Premeeting Communication, dated May 9, 2013 and consisting of Agency responses to questions in the briefing package, the applicant determined that the responses were sufficient and the meeting was cancelled. Principal Agency comments include the following:

- The Agency agreed that an adequate and well-controlled Phase 2 trial demonstrating that each active moiety makes a contribution to the claimed effects of the combination product and that the combination is safe and effective for the proposed population requiring such concurrent therapy, together with one Phase 3 trial comparing LEO 90100 to vehicle, would be acceptable to support an NDA.
- The proposed primary efficacy endpoint of the proportion of subjects who achieve “treatment success” (“clear” or “almost clear” for subjects with at least moderate disease at baseline, “clear” for subjects with mild disease at baseline) according to the IGA at Week 4 and the 5-point Investigator’s Global Assessment of Disease Severity (IGA) are acceptable.
- A vasoconstrictor (VCA) trial is not required. However, to better characterize the new formulation the Agency recommended conducting a VCA trial. The Agency noted that proposed comparators for the VCA trial would be inadequate to clearly identify the potency class of the proposed foam formulation. The Agency recommended that the applicant ensure adequate bracketing for the VCA trial.

An end of Phase 2 CMC meeting occurred June 19, 2013. The objective of this meeting was for the applicant to obtain feedback on their late development program for commercial manufacture. Areas of comment included commercial batch size, batch size for primary stability batches, the filling site, information needed to support a site change, leakage rate of propellants, amount of residual propellants in the discharged foam, intended storage orientation for the primary batches in the ICH stability study, extractable/leachable testing, and recommendation for conduct of an in-use stability study.

An Advice letter was sent to the applicant on August 30, 2013 regarding the applicant's response to the Agency's written EOP2 comments and a new Phase 3 protocol entitled, "A phase 3 trial comparing once daily treatment with LEO 90100 calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) with vehicle in subjects with psoriasis vulgaris." The letter included comments about when to investigate center-to-center variability and the need to prespecify complete details about multiple imputation.

A pre-NDA meeting occurred March 26, 2014. Principal points of discussion included the following:

- Regarding pooling of data, the Agency stated that efficacy data intended to establish an efficacy claim should be presented for each trial separately and that for the integrated summary of efficacy (ISE), the applicant may pool the efficacy data. At the Agency's request, the applicant agreed to provide a safety data analysis (including local safety and laboratory data) from the vehicle controlled trials.
- The applicant's proposed strategy for statistical analysis of primary and secondary efficacy endpoints was found to be reasonable.
- The applicant proposed a plan, for establishing a "bridge" for LEO 90100 to safety data for the two approved calcipotriene/BDP products which included:
    - Safety data for LEO 90100 and Taclonex ® ointment from Phase 2 trial LEO 90100-35
    - Comparative vasoconstriction data (LP0053-69)
    - Systemic exposure data from the Maximum Use Systemic Exposure trial (LEO 90100-30) compared with historical data from similar trials with Taclonex® Ointment and Taclonex® Topical Suspension
    - Adverse event data from short term trials with LEO 90100 (Enstilar® Foam), Taclonex® Ointment and Taclonex® Topical Suspension
    - Comparative safety data from long-term clinical trials with Taclonex® Ointment and Taclonex® Topical Suspension
- The Agency agreed that a long term safety study will not be required as a Post Marketing Requirement provided that the outcome of the bridging analysis supports the conclusion that the currently available long term safety data for Taclonex® Ointment and Taclonex® Topical Suspension can be extrapolated to provide sufficient information on the long term safety of LEO 90100 (Enstilar® Foam).

- The Agency stated that a multi-point vasoconstriction assessment will not be acceptable for providing any comparison between different dosage forms. The Agency requested that the applicant include in the NDA single point visual assessment data at 2 hours following 16 hours of study medication application to clearly identify the potency class of LEO 90100 (Enstilar® Foam).
  - (b) (4)

2.6 Other Relevant Background Information

Daivobet® ointment was first approved in Denmark in March 2001 and was approved in the United States January 2006 under the trade name Taclonex® Ointment. The clinical development program for the topical suspension, containing the same active substances in the same concentrations, began in 2001. An NDA (22185) for treatment of psoriasis of the scalp was submitted on June 28, 2007 and on May 9, 2008, the FDA approved Daivobet ® gel under the trade name Taclonex Scalp® Topical Suspension for "topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults 18 years and older." Daivobet® gel was also approved for the treatment of scalp psoriasis in several countries in the European Union in August 2008 and subsequently in Canada (November 2008) and Australia (July 2010). The indication was extended to include non-scalp areas of the body in the European Union in July 2009 and in the US, under the name Taclonex® Topical Suspension, on October 17, 2012. On August 29, 2014 the indication for Taclonex® Topical Suspension was extended, fulfilling a PMR, to include topical treatment of plaque psoriasis of the scalp in patients age 12 to 17 years.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Department of Scientific Investigations (DSI) inspections were requested for a total of 2 sites (Trial LP0053-1001) with the following rationales:

Site US15: Jane Lee MD, in Edison, New Jersey

- The applicant admitted that an efficacy assessment (mPASI) was not conducted according to the protocol. The site also had a fairly high number of subjects, 26.

Site US26: Stephen Tyring MD, in Houston, Texas

- The site had many protocol deviations with all of them for subjects treated with Enstilar® Foam. In addition, the response rate to Enstilar was, on average, the lowest of all the clinical sites.

Inspection results: (DSI Clinical Inspection Summary, dated August 28, 2015)
Site US15: Jane Lee, MD

> "The final classification of Dr. Lee's inspection was Voluntary Action Indicated (VAI). Because of Dr. Lee's failure to properly conduct assessments of psoriatic area involvement according to protocol specifications for use in calculation of subjects' m-PASI scores, the review division should consider excluding this site's m-PASI study data from the efficacy analysis. Notwithstanding an isolated failure to obtain a safety laboratory assessment for a single subject, the clinical investigator's assessment of safety appeared to be otherwise adequate and safety data as reported appears to be reliable."
>
> More detail from Inspection Summary:
> "…the clinical investigator did not properly assess the extent of psoriatic involvement of the arms, trunk, and legs as specified in the Investigator's Assessment of Extent and Severity of Clinical Signs (protocol Section 10.7.3 Clinical Assessment). The clinical investigator performed these assessments incorrectly for 25 of the 26 subjects enrolled in the study."

Site US26: Stephen Tyring, MD

> "The final classification of Dr. Tyring's inspection was Voluntary Action Indicated (VAI) resulting from two instances of inadequate records and one protocol deviation. Other than these isolated observations, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication."

3.2 Compliance with Good Clinical Practices

As stated by the applicant: "All trials were conducted in accordance with Good Clinical Practice (GCP) and in compliance with ICH guidance on GCP (Committee of Proprietary Medicinal Products,CPMP/ICH/135/95) and 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312. All subjects gave written informed consent before participating in any trial. All protocols were given appropriate ethical review before commencing and were conducted in accordance with ethical principles derived from the Declaration of Helsinki."

3.3 Financial Disclosures

The applicant submitted form FDA 3454 for trials LEO 90100-01, LEO 90100-7, LEO 90100-30, LEO 90100-35, LP0053-66, LP0053-69, and LP0053-1001 which included a list of 140 investigators. For 139 of these investigators there was certification that there were no financial interests to disclose.

For one investigator, (b) (6), with disclosable financial interests a form FDAS 3455 was provided. This investigator participated in trial LP0053-1001, LEO 90100 (Enstilar® Foam) compared to vehicle in subjects with psoriasis vulgaris. The form detailed consultancy and honoraria for professional lectures totaling $81,352.50 that the investigator had received from the sponsor of the covered trial.

In the opinion of this reviewer, the presence of this investigator with the above disclosable financial interests does not raise questions about integrity of study data, and by extension, the approvability of the application. The study design involved in trial LP0053-1001, randomized and double- blinded, would have made data alteration difficult. In addition, according to the applicant, all data were subject to 100% Source Data Verification and the trial was independently monitored by a Clinical, Research Organization, (b) (6). Trial LP0053-1001 was conducted at 28 investigational sites and enrolled 426 subjects. (b) (6) enrolled (b) (6) subjects.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see Quality Assessment, dated September 1, 2015 by the Quality Review Team with Yichun Sun, Ph.D, as application technical lead, Branch V, Division of New Drug Products, II

Drug substance: There are two active pharmaceutical ingredients used in the drug product (Calcipotriene and Betamethasone Dipropionate (b) (4)), namely Calcipotriene and Betamethasone Dipropionate. Calcipotriene hydrate is a synthetic vitamin D3 analog. Betamethasone dipropionate is a synthetic corticosteroid. Both of the drug substances are chemically synthesized. CMC information of the drug substances is referred to DMFs. Both of the DMFs have been reviewed and found adequate in supporting their use in the NDA.

Drug product: The drug product, Enstilar® (Calcipotriene and Betamethasone Dipropionate) Foam, is a vitamin D analogue and corticosteroid combination product. It is a (b) (4) of the approved ointment product (NDA 021852 Taclonex). (b) (4) Each can contains 60 g of the (b) (4). The foam product is prepared by (b) (4)

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. The development of in vitro release test (IVRT) of Calcipotriol and Betamethasone Dipropionate from Taclonex® ointment has been carried out. However, it was not possible, despite extensive efforts, to develop and validate an IVRT method to demonstrate the sameness between Taclonex® ointment batches due to high variability of the in vitro release rates of Calcipotriol and Betamethasone Dipropionate. Therefore, the applicant's position that an IVRT specification is not feasible to be implemented as a quality control tool at release and during stability studies is acceptable. The expiration dating period of 24 months is recommended for the drug product when stored at 20 - 25°C based on the 12-month long-term and 6- month accelerated stability data obtained from 3 registration batches of the drug product.

Recommendation and Conclusion on Approvability
The applicant of this NDA has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug product.

However, the facility reviewers have not made a final "Acceptable" recommendation on the facilities involved.

Also, the issues on labels/labeling are not completely resolved at this time.

Therefore, from the OPQ perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125(b)(6),(13) until the above issues are satisfactorily resolved.

List of Deficiencies To Be Communicated
A. Drug Substance: None.
B. Drug Product: None.
C. Process/Facility: Final "Approval" recommendation has not been made.
D. Biopharmaceutics: None.
E. Microbiology: None.
F. Label/Labeling
The following are deficiencies that need to be resolved:

1. "Highlights" Section
   - Proprietary and established name, dosage form and dosage administration should be modified to include (b) (4).

ENSTILAR® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%

- "Dosage forms and strengths" should be as follows: Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone)

2. #16 How supplied/storage and Handling
   - Include 1 X 60 gram for NDC 50222-302-60
3. # 17 should include the manufacturer/distributor as per 21 CFR 201.1
4. Immediate Container Label:
   - The expiration date is not displayed on the label, however it is to be included on the bottom of the can.
   - The Strength expressed should contain statement indicating that the expressed strength is after propellant evaporation (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))
5. Carton Labeling
   - Bar Code per 21 CFR 201.25(c)(2) is not displayed for NDC 50222-302-60 carton.
   - "See package insert for dosage information" is not included on carton and in violation of (21 CFR 201.55).

Note: As of September 15, 2015, the Office of Process and Facilities in OPQ has provided an overall acceptable recommendation for all the facilities of the NDA.

4.2 Clinical Microbiology

There were no significant efficacy/safety issues since Enstilar® Foam is not an antimicrobial product.

4.3 Preclinical Pharmacology/Toxicology

Please see Pharmacology/Toxicology Review (dated 7/07/2015) by Norman A. See, PhD.

From the pharmacology/toxicology review, Integrated Summary and Safety Evaluation:

"LEO 90100 (proposed tradename "Enstilar® Foam") consists of calcipotriene 0.005% and betamethasone dipropionate 0.064%, in (b) (4) a pressurized mixture of propellants and administered as a spray. The propellant (a mixture of dimethyl ether and butane) quickly evaporates following application. The product that remains on the skin post-evaporation is essentially indistinguishable from Taclonex Ointment, which was approved under NDA 21-852 on 09-JAN-2006. The conditions of exposure (including concentrations of APIs, route of exposure, quantity applied per day, percent of the body surface area and portions of the skin exposed,

duration of exposure, indication, and patient population) proposed under NDA 207589 are essentially identical to those that are associated with NDA 21-852. NDA 207589 includes letters from LEO Pharma A/S that authorize reference to data associated with NDA 21-852 and IND 62,993 (Taclonex Ointment), and NDA 22-185 and IND 67,835 (Taclonex Topical Suspension). The proposed exposures to the APIs (calcipotriene and betamethasone dipropionate) and excipients that remain post-evaporation of the propellants have been fully qualified under NDA 21-852 and NDA 22-185. As discussed … the proposed exposures to the propellants are considered to be qualified."

Changes to proposed labeling as recommended by the pharmacology/toxicology reviewer are presented as follows: additions are shown **bold underline** and deletions are shown ~~strikethrough~~.

8.1 Pregnancy
Teratogenic Effects: Pregnancy Category C

~~Animal reproduction studies have not been conducted with Enstilar® Foam. Enstilar® Foam contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically. There are no adequate and well-controlled studies in pregnant women. Enstilar® Foam should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.~~

[redacted]

The above applicant proposed section has been reordered to produce the following Agency recommended wording:

There are no adequate and well-controlled studies in pregnant women. Pregnant women were excluded from the clinical studies conducted with Enstilar® Foam. Enstilar® Foam should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with Enstilar® Foam. Enstilar® Foam contains calcipotriene that has been shown to be fetotoxic and betamethasone dipropionate that has been shown to be teratogenic in animals when given systemically.

The remainder of section 8.1 is as proposed by the applicant:

Teratogenicity studies with calcipotriene were performed by the oral route in rats and rabbits. In rabbits, increased maternal and fetal toxicity were noted at a dosage of 12mcg/kg/day (144 mcg/m^2/day); a dosage of 36 mcg/kg/day (432 mcg/m^2/day) resulted in a significant increase in the incidence of incomplete ossification of the pubic bones

and forelimb phalanges of fetuses. In a rat study, a dosage of 54 mcg/kg/day (324 mcg/m^2/day) resulted in a significantly increased incidence of skeletal abnormalities (enlarged fontanelles and extra ribs). The enlarged fontanelles are most likely due to the effect of calcipotriene upon calcium metabolism. The estimated maternal and fetal noadverse effect levels (NOAEL) in the rat (108 mcg/m^2/day) and rabbit (48 mcg/m^2/day) derived from oral studies are lower than the estimated maximum topical dose of calcipotriene in man (460 mcg/m^2/day).

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

Betamethasone dipropionate has been shown to be teratogenic in mice and rabbits when given by the subcutaneous route at doses of 156 mcg/kg/day (468 mcg/m^2/day) and 2.5 mcg/kg/day (30 mcg/m^2/day), respectively. Those dose levels are lower than the estimated maximum topical dose in man (about 5,950 mcg/m^2/day). The abnormalities observed included umbilical hernia, exencephaly and cleft palate.
Two oral peri-and post-natal development studies were conducted with rats:

Pregnant Wistar rats were dosed daily with calcipotriene at exposures of 0, 6, 18, or 54 mcg/kg/day from gestation day 15 through day 20 postpartum. No remarkable effects were observed on any parameter, including survival, behavior, body weight, litter parameters, or the ability to nurse or rear pups.

Betamethasone dipropionate was evaluated for effects when orally administered to pregnant rats from gestation day 6 through day 20 postpartum at dosages of 0, 100, 300, and 1000 mcg/kg/day. Mean maternal body weight was significantly reduced on gestation day 20 in animals dosed at 300 and 1000 mcg/kg/day. The mean duration of gestation was slightly, but statistically significantly, increased at 100, 300, and 1000 mcg/kg/day. The mean percentage of pups that survived to day 4 was reduced in relation to dosage. On lactation day 5, the percentage of pups with a reflex to right themselves when placed on their back was significantly reduced at 1000 mcg/kg/day. No effects on the ability of pups to learn were observed, and the ability the offspring of treated rats to reproduce was not affected.

12.1 Mechanism of Action

Enstilar® Foam combines the pharmacological effects of calcipotriene hydrate as a synthetic vitamin D3 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.**

The above section of labeling is the same as current labeling for Taclonex® Ointment and Taclonex® Topical Suspension.

(b) (4)

[redacted]

4.4 Clinical Pharmacology

Please see Clinical Pharmacology Review (dated 8/24/15) by Chinmay Shukla, Ph.D., DCP-3. The reader is also referred to section 7.4.5, Special Safety Studies/Clinical Trials, for further discussion of the maximal use PK trial LEO90100-30.

4.4.1 Mechanism of Action

See section 12.1 under pharmacology/toxicology proposed labeling. What is proposed by the clinical pharmacology reviewer is the same.

4.4.2 Pharmacodynamics

Vasoconstriction (VCA) trial: The VCA trial conducted by the applicant was determined to be not acceptable (b) (4) [redacted]

(b) (4)

[redacted]

(b) (4)

Comment from Clinical Pharmacology Reviewer: *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.*

The information from the VCA trial is not required for approval and is recommended to be obtained post-approval.

HPA axis suppression and effect on calcium metabolism: In the maximal use PK trial (LEO 90100-30), 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.

12.2 Pharmacodynamics

Changes to applicant proposed labeling are presented as follows; additions are shown **bold underline** and deletions are shown ~~strikethrough~~.

(b) (4)

(b) (4)

Effects on Calcium Metabolism

(b) (4) effects of once daily application of Enstilar Foam on the scalp and body for 4 weeks on calcium metabolism (b) (4) Enstilar Foam (b) (4) elevated serum (b) (4) calcium levels outside the normal range were (b) (4) observed in (b) (4) subjects.

(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.

4.4.3 Pharmacokinetics

As stated by the clinical pharmacology reviewer: "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 C_{max} and AUC_{last} for betamethasone 17-propionate were 147.9 ± 224.0 pg/mL and 683.6 ± 910.6 pg*h/mL."

Based on the results of the maximal use PK trial (LEO 90100-30) the pharmacology reviewer proposes the following labeling:

12.3 Pharmacokinetics
Absorption

The **pharmacokinetics (PK)** (b) (4) of Enstilar® Foam in psoriasis 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 (b) (4)

(b) (4) 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,** (b) (4) The maximal plasma concentrations (C_{max}) **and area under the concentration curve until the last measured time point (AUC_{last})** (b) (4) **for** calcipotriene **were** (b) (4) 55.9 pg/mL **and 82.5 pg*h/mL, respectively;** and **the mean ± SD C_{max} and AUC_{last} for MC1080 was** (b) (4) **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** (b) (4) 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** (b) (4) pg/mL and **683.6 ± 910.6 pg*h/mL** (b) (4), 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 (b) (4) **primary** metabolite.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Protocol #	Type of trial	Trial Design	Subject Population/ # of sites	Test products/dosage regimen	Subjects in group: randomized/ completed	Diagnosis/ treatment duration
LP0053-1001	Safety and efficacy	Phase 3 multi-center, double-blinded, vehicle controlled, 2-arm, randomized, parallel group	Age 18 and older 27 US	1. Enstilar® foam 2. Foam vehicle Once daily	323/313 103/99 Total: 426/412	Psoriasis vulgaris on body Up to 4 weeks
LEO 90100-35	Safety and efficacy	Phase 2, multi-center, investigator blinded, active and vehicle controlled, 4-arm, randomized, parallel group	Age 18 and older 35 US	1. Enstilar® foam 2. Taclonex ointment 3. Foam vehicle 4. Ointment vehicle Once daily	141/136 135/127 49/47 51/48 Total: 376/358	Psoriasis vulgaris on body Up to 4 weeks
LEO 90100-7	Safety and efficacy	Phase 2, multi-center, double-blinded, 3-arm, active controlled randomized, parallel group	Age 18 and older 28 US	1. Enstilar® 2. Betamethasone 3. Calcipotriol Once daily	100/94 101/94 101/93 Total:302/281	Psoriasis vulgaris on body and scalp Up to 4 weeks
LEO 901100-30	MUSE	Open label, non-controlled HPA axis test, Ca++ metabolism, PK	Age 18 and older 8 Canada	Enstilar Once daily	37 exposed 35 completed	Extensive psoriasis vulgaris, trunk, limbs, scalp Up to 4 weeks
LP0053-69	Vasoconstriction	Randomized, investigator-blinded, single-dose, intra-individual comparison	Age 18 to 50 1 France	1. Enstilar 2. Dermoval/ Dermovate cream 3. Taclonex ointment 4. Synalar ointment 5. BDP in Enstilar vehicle 6. Enstilar foam vehicle	35/35	Healthy subjects Single dose
LP0053-66	Dermal safety trial	Randomized, double-blind, intra-individual comparison	Age 18 to 65 1 France	1. Enstilar 2. Enstilar Foam vehicle 3. white petrolatum	218/214	Healthy subjects 16 applications

Protocol #	Type of trial	Trial Design	Subject Population/ # of sites	Test products/dosage regimen	Subjects in group: randomized/ completed	Diagnosis/ treatment duration
LEO 90100-01	Psorias -is plaque test	Randomized, Investigator blinded, Active & Vehicle controlled, repeat dose, intra-individual comparison	Age 18 or above 1 France	1. Enstilar 2. Taclonex ointment 3. BDP 4. Enstial foam vehicle	24/24	Psoriasis vulgaris on body 4 weeks

Source: Applicant's NDA, from Module 5, 5.2, adapted from Tabular Listing of All Clinical Studies

5.2 Review Strategy

Trials, LP0053-1001 (Phase 3 pivotal) and LEO 90100-7 (Phase 2 to demonstrate effect of Enstilar foam against monads) are reviewed in detail for efficacy. The applicant also conducted a supportive Phase 2 trial, LEO 90100-35, which is discussed briefly regarding efficacy. The applicant pooled the results of the three following trials which are reviewed in detail or safety:

- LP0053-1001 pivotal (Phase 3, 2-arm vehicle controlled)
- LEO 90100-35 (Phase 2, 4-arm, vehicle and active controlled)
- LEO 90100-7 (Phase 2, 3-arm, active controlled)

The safety data from these trials is pooled because the inclusion criteria are generally similar, the drug is applied to psoriasis vulgaris on the body (and the scalp also for trial LEO 90100-7), the treatment period is 4 weeks as proposed for marketing, and the trials are either vehicle or active controlled.

Special safety studies are discussed in section 7.4.5 and include:

- LEO 901100-30 (assessment of effects on HPA axis and calcium metabolism): This trial was not included in pooled trials because it was not controlled and subjects had extensive disease.
- LP0053-66 (assessment of skin irritation potential and sensitization potential): This trial was not included in pooled trials because it was performed in healthy subjects.

5.3 Discussion of Individual Studies/Clinical Trials

Pivotal Phase 3 Trial

The pivotal phase 3 trial had a two arm design, with vehicle control.

Title: "LEO 90100 compared to vehicle in subjects with psoriasis vulgaris: A phase 3 trial comparing once daily treatment with LEO 90100 calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) with vehicle in subjects with psoriasis vulgaris"

Objectives:
Primary
To compare the efficacy of treatment with LEO 90100 (Enstilar® Foam) to that of treatment with vehicle for up to 4 weeks in subjects with psoriasis vulgaris

Secondary
To compare the safety of treatment with LEO 90100 (Enstilar® Foam) to that of treatment with vehicle for up to 4 weeks in subjects with psoriasis vulgaris

Subject Population:
The trial population was to include male and female subjects of any race or ethnicity and was chosen to include subjects ≥ 18 years of age with psoriasis vulgaris on the trunk and/or limbs of at least mild severity according to the Investigator's Global Assessment of Disease Severity (IGA) and amenable to topical therapy with up to 90 g of trial medication per week.

Protocol #: LP0053-1001

Study Sites:
Trial LP0053-1001 was conducted at 27 investigational sites in the United States and had 27 principal investigators. The first subject was enrolled June 17, 2013 and the last subject completed October 2, 2013.

Principal Inclusion Criteria:
- Clinical diagnosis of psoriasis vulgaris of at least 6 months duration involving the trunk and/or limbs and amenable to treatment with a maximum of 90 g of study medication per week
- Psoriasis vulgaris on the trunk and/or limbs (excluding psoriasis on the genitals and skin folds) involving 2 to 30% of the Body Surface Area (BSA)
- An Investigator's Global Assessment of disease severity (IGA) of at least mild on the trunk and/or limbs at Day 0 (Visit 1)
- A modified PASI (m-PASI) score of at least 2 on the trunk and/or limbs at Day 0 (Visit 1)
- A target lesion of a minimum of 5 cm at its longest axis and preferably not located on the extensor surface on an elbow or knee, scoring at least 1 for each of redness, thickness and scaliness, and at least 4 in total by the Investigator's Assessment of Severity of the Target Lesion
- Females of childbearing potential must have a negative pregnancy test at Day 0

(Visit 1) and I must agree to use a highly effective method of birth control during the study.

Principal Exclusion Criteria:

- Systemic treatment with biological therapies with a possible effect on psoriasis vulgaris within the following time periods prior to randomization:
  - etanercept – within 4 weeks prior to randomization
  - adalimumab, infliximab – within 8 weeks prior to randomization
  - ustekinumab – within 16 weeks prior to randomization
  - other products – within 4 weeks/5 half-lives prior to randomization (whichever is longer)
- Systemic treatment with all other therapies with a possible effect on psoriasis vulgaris (e.g., corticosteroids, retinoids, methotrexate, cyclosporin and other immunosuppressants) within 4 weeks prior to randomization
- Subjects who have received treatment with any non-marketed drug substance (i.e. a drug which has not yet been made available for clinical use following registration) within 4 weeks/5 half-lives (whichever is longer) prior to randomization
- PUVA therapy within 4 weeks prior to randomization
- UVB therapy within 2 weeks prior to randomization
- Topical anti-psoriatic treatment on the trunk and limbs (except for emollients) within 2 weeks prior to randomization
- Topical treatment on the face, scalp and skin folds with corticosteroids or vitamin D analogues or prescription shampoos within 2 weeks prior to randomization
- Planned excessive exposure of treated area(s) to either natural or artificial sunlight
- Planned initiation or changes to concomitant medication that could affect psoriasis vulgaris (e.g. beta blockers, antimalarial drugs, lithium, ACE inhibitors)
- Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis
- Subjects with any of the following on the treatment area:
  - viral (e.g. herpes or varicella) lesions, fungal and bacterial skin infections, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, icthyosis, ulcers and wounds.
  - other inflammatory skin disorders (e.g. seborrheic dermatitis or contact dermatitis)
- Known or suspected:
  - disorders of calcium metabolism associated with hypercalcemia
  - severe renal insufficiency or severe hepatic disorders
  - hypersensitivity to component(s) of the investigational products
- Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.

Study Design and Plan:
This was a multi-center, prospective, randomized, double-blinded, 2-arm, parallel group Phase 3 trial comparing once daily treatment with LEO 90100 to once daily treatment with vehicle in subjects with psoriasis vulgaris. After an informed consent was signed, the subjects entered a washout phase (if needed) for up to 4 weeks prior to randomization. Eligible subjects were randomized in a 3:1 ratio to receive once daily treatment for up to 4 weeks with either LEO 90100 or vehicle foam. The randomization of subjects was stratified according to site.

Subjects were instructed to apply the investigational product once daily to all areas affected with psoriasis. The face, skin folds and genitals were not to be treated with the Investigational Product or assessed as part of the efficacy analysis.

Four visits were scheduled during the treatment phase: Day 0 (Visit 1), Day 7 (±2 days) (Visit 2), Day 14 (±2 days) (Visit 3) and Day 28 (±2 days) (Visit 4). If an ongoing adverse event occurred (which was possibly related or probably related to the investigational drug), the albumin-corrected serum calcium was above the reference range or any laboratory parameter was abnormal and clinically significant at the last treatment visit, then subjects were reassessed during the 2 week follow-up period.

Subjects who experienced an adverse event which requires the discontinuation of treatment remained in the trial and were assessed at all subsequent trial visits according to the trial schedule. The subject was to be evaluated until the adverse event resolved or the etiology was identified and the adverse event stabilized.

If the investigator assessed that a site was “clear” according to IGA at Visits 2 or 3 then the subject was directed to stop the treatment of the cleared area. Subjects were to resume treatment if they observed recurrence according to their own judgment.

Product Application:
Enstilar Foam and foam vehicle were provided as cans containing 30 grams of aerosol formulation.

Subject Treatment Instructions included the following (among others):

- Apply the study medication to psoriasis on the trunk, arms and legs once daily using your finger tips
- Apply the study medication on the affected areas only and rub in gently and completely. Avoid contact with the face, eyes, lips and mucous membranes (e.g. inside the mouth, inside the nose)
- Wash your hands thoroughly with mild soap and water after each application
- If you have psoriasis on the face, genitals or skin folds (armpits, groin, under the breasts and between the buttocks), do not use the study medication here. Your study doctor will provide you with other medication for these areas. Any such medication you receive for these areas must not be used anywhere else

- Do not use more than 3 cans of medication per week
- Do not bandage, cover or wrap the treated areas
- Avoid excessive exposure of treated areas to either natural or artificial sunlight (including tanning beds, sun lamps, etc.)
- Keep the study medication out of sight and reach of children and pets
- Shake well before use

The maximum amount of product applied per week, 90 grams, will be reflected in labeling. [Similar instructions regarding maximum amount of product to be applied were also used in trials LEO 90100-35 (Phase 2, 4-arm, vehicle and active controlled) and trial LEO 90100-7 (Phase 2, 3-arm, active controlled)].

Product Used/Treatment Compliance:
Subjects were provided with a diary at visits 1-3 to record adherence to the once daily treatment regimen during the visit interval.

Prior to secondary packaging, but following individual unit labelling, 10 cans were weighed by the CMO and the average used as an estimate of the known filled weight for each can. All returned cans which were dispensed to a subject were weighed by the CMO to determine the amount of the investigational product used per treatment phase visit interval for each subject.

Table 3: Flow Chart – Trial LP0053-1001

Phase	Screening	Treatment						Follow-up if required
Visit	SV[a]	V1	Day 3	Day 5	V2	V3	V4[g]	FU[f][p]
Week	Up to -4	0	subject diary[l]	subject diary[l]	1	2	4	6
Visit window (days)	Up to -28	0			7±2	14±2	28±2	+14±2
Informed consent[b]	(x)	x						
Subject demographics	(x)	x						
In-/exclusion criteria	(x)	x						
Concurrent diagnoses	(x)	x						
Concomitant medication	(x)	x			x	x	x	x
Relevant medical history	(x)	x						
Physical examination	(x)	x						
Vital signs		x					x	
Pregnancy test[c]		x					x	
Investigator's Global Assessment of Disease Severity		x			x	x	x	
Investigator's Assessment of BSA Involvement		x			x	x	x	
Investigator's Assessment of Extent and Severity of Clinical Signs (m-PASI)		x			x	x	x	
Investigator's Assessment of the Severity of the Target Lesion (Redness, Thickness, Scaliness)		x			x	x	x	
Clinical Photography[o]		x[n]			x[j]		x[j]	
Local Safety and Tolerability Assessment		x			x	x	x	
Adverse Event(s)[e]		x			x	x	x	x
Laboratory sampling; biochemistry[h]		x					x	x[d][i]
Laboratory sampling; 25-OH Vitamin D		x						
Laboratory sampling;		x					x	x[i]

Phase	Screening	Treatment						Follow-up if required
Visit	SV[a]	V1	Day 3 subject diary[l]	Day 5 subject diary[l]	V2	V3	V4[g]	FU[f][p]
Week	Up to -4	0			1	2	4	6
Visit window (days)	Up to -28	0			7±2	14±2	28±2	+14±2
Spot Urinalysis[h]								
Patient's Global Assessment of Disease Severity		x			x	x	x	
Subject's Assessment of Itch by use of a Visual Analogue Scale (VAS)		x	x	x	x	x	x	
Subject's Assessment of Itch-Related Sleep Loss by use of a Visual Analogue Scale (VAS)		x	x	x	x	x	x	
Subject Diary; Provided		x			x	x		
Subject Diary; Collected					x[m]	x[m]	x[m]	
Quality of Life Questionnaire; DLQI		x			x	x	x	
Quality of Life Questionnaire; EQ-5D-5L		x					x	
Randomisation		x						
Subject Treatment Instructions		x						
Dispensing of trial medication		x			x	x		
Compliance check[m]					x	x	x	
Return of trial medication					x	x	x	
End of treatment Form[k]							x	

a) A washout period of up to 4 weeks was completed if the subject was treated or had recently been treated with anti-psoriatic treatments or other relevant medication, as defined by the exclusion criteria. Items denoted by brackets were reviewed at a Screening Visit prior to commencing a washout, to assess if the subject was otherwise eligible. Such items were checked for any change in eligibility status at Visit 1 after the washout was completed.

b) Informed consent was signed both by subject and (sub)investigator (medically qualified) before any trial related procedures were carried out. For subjects requiring a washout period, informed consent was

Phase	Screening	Treatment						Follow-up if required
Visit	SV[(a)]	V1	Day 3 subject diary[(l)]	Day 5 subject diary[(l)]	V2	V3	V4[(g)]	FU[(f)(p)]
Week	Up to -4	0			1	2	4	6
Visit window (days)	Up to -28	0			7±2	14±2	28±2	+14±2

completed prior to washout.

c) For women of child-bearing potential, a pregnancy test was performed at Visit 1 and Visit 4 (or at the last on-treatment visit)
d) If albumin-corrected serum calcium was above the reference range at the last on-treatment visit, a follow up test was performed.
e) AEs were collected from the date of signing the informed consent form, i.e. during the washout period
f) If an adverse event (serious or non-serious) classified as possibly or probably related to the trial treatment or not assessable in relation to the trial treatment was on-going at the last on-treatment visit.
g) For subjects prematurely withdrawn from treatment, the final efficacy assessments scheduled for Visit 4 were completed at the last on-treatment visit.
h) If a laboratory result was abnormal and judged as clinically significant, the (sub)investigator was to follow-up as clinically appropriate (this could involve requesting repeat samples).
i) If any laboratory parameter was abnormal and judged as clinically significant by the (sub)investigator at the last on treatment visit, a follow-up visit was performed.
j) Clinical photography to include target lesion only
k) If the subject was not randomised or did not complete the treatment period, the End of Trial form wascompleted as appropriate.
l) Conducted as self-assessment by the subject and recorded in the diary provided at Visit 1.
m) To supplement the compliance check made at Visit 2 to Visit 4, a subject diary was completed daily during each visit interval.
n) Clinical photography included target lesion and full body anterior and posterior images.
o) Clinical photography was a voluntary additional procedure for a subset of the studied population.
p) Where the (sub)investigator considered it appropriate, the follow-up visit was performed as a telephone contact.

Source: Applicant's NDA Module 5.3.5.1, Clinical Study Report LP0053-1001, pp 42-44.

Blinding:
The trial was a double-blind trial. The packaging and labelling of the investigational products contained no evidence of their identity. The applicant states that it was not considered possible to differentiate between the investigational products solely by sensory evaluation. Consequently, according to the applicant, the subjects and the (sub) investigators remained unaware of the individual treatment assignment during the conduct of the clinical trial.

Treatment codes were not broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject had been made and documented.

Efficacy Analysis:
The treatment areas to be assessed were the trunk and limbs.

At all treatment visits (Visit 1 to Visit 4) the (sub) investigator made a global assessment of the disease severity of the psoriasis vulgaris on the trunk and limbs by use of the 5-point scale presented in the following table. This assessment represented the average lesion severity on the trunk and limbs. The assessments were based on the condition of the disease at the time of evaluation, and not in relation to the condition at any previous visit.

Table 4: Investigator's Global Assessment of Disease Severity

Clear	Plaque thickening = no elevation or thickening of normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present)
Almost clear	Plaque thickening = none or possible thickening but difficult to ascertain whether there is a slight elevation above normal skin level Scaling = none or residual surface dryness and scaling Erythema = light pink coloration
Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions Erythema = light red coloration
Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
Severe	Plaque thickening = marked or very marked elevation typically with hard or sharp edges Scaling = non-tenacious or thick tenacious scale, covering most or all of the lesions Erythema = very bright red coloration; extreme red coloration; deep red coloration

Source: Applicant's NDA Module 5.3.5.1, Clinical Study Report LP0053-1001, Table 5-5, p 47.

Investigator's Assessment of the Extent and Severity of Clinical Signs (Redness, Thickness, Scaliness)

At all treatment visits (Visit 1 to Visit 4) the (sub) investigator made assessments of the extent and severity of clinical signs of the subject's psoriasis vulgaris.

The extent of psoriatic involvement was recorded for each of the three areas (arms, trunk and legs) using the following scale:

0 = no involvement
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

The severity of the psoriatic lesions in each of the three areas was recorded for each of the clinical signs of redness, thickness, and scaliness. For each clinical sign, a single score, reflecting the average severity of all psoriatic vulgaris lesions on a given body region, was determined according to the scale in the following table:

Table 5: Severity Score for Redness, Thickness, and Scaliness

Redness	0	=	none (no erythema)
	1	=	mild (faint erythema, pink to very light red)
	2	=	moderate (definite light red erythema)
	3	=	severe (dark red erythema)
	4	=	very severe (very dark red erythema)
Thickness	0	=	none (no plaque elevation)
	1	=	mild (slight, barely perceptible elevation)
	2	=	moderate (definite elevation but not thick)
	3	=	severe (definite elevation, thick plaque with sharp edge)
	4	=	very severe (very thick plaque with sharp edge)
Scaliness	0	=	none (no scaling)
	1	=	mild (sparse, fine-scale lesions, only partially covered)
	2	=	moderate (coarser scales, most of lesions covered)
	3	=	severe (entire lesion covered with coarse scales)
	4	=	very severe (very thick coarse scales, possibly fissured)

Source: Applicant's NDA Module 5.3.5.1, Clinical Study Report LP0053-1001, Table 5-6, p 48.

Investigator's Assessment of the Severity of the Target Lesion (Redness, Thickness, Scaliness)

At Visit 1, the (sub) investigator selected a target lesion per protocol. The target lesion had to be a minimum of 5 cm at its longest axis and preferably not located on the extensor surface of an elbow or knee. Location was recorded in the CRF as trunk, limb excluding elbow/knee, elbow or knee, and in more detail in the subject medical records to allow identification of the target lesion at subsequent visits.

At Visits 1 to 4, the (sub) investigator assessed the severity of the target lesion for each clinical sign (redness, thickness, scaliness) according to the same scale as for the Investigator's Assessment of the Severity of Clinical Signs (Redness, Thickness, Scaliness); see Table 5 above. At Visit 1, the scoring of the target lesion must have been at least 1 for each of the three categories, and at least 4 in total.

Investigator's Assessment of the Body Surface Area (BSA) Involvement of Psoriasis Vulgaris on Trunk and Limbs

At all treatment phase visits (Visit 1 to Visit 4) the (sub) investigator assessed the extent of the subject's psoriatic involvement on the trunk and limbs. The total psoriatic involvement on the trunk and limbs (excluding skin folds and genitals) was recorded as a percentage of the total BSA, estimating that the surface of the subject's full, flat palm (including the five digits) correlated to approximately 1% of the total BSA. The purpose was to obtain an estimate of the area on the trunk and limbs to be treated with investigational product for each subject.

Safety Assessments:
Safety Population: All subjects randomized and exposed to study medication

The assessment of local safety and tolerability consisted of signs assessed by the (sub) investigator and symptoms reported by the subject.

At Visits 1 to 4, the (sub) investigator assessed application site reactions for the following signs: perilesional erythema, perilesional oedema, perilesional dryness, and perilesional erosion. The subject assessed the symptoms of application site burning or pain.

For perilesional erythema, oedema, dryness and erosion, the area for the (sub) investigator to assess was the perilesional area, defined as the band of skin within two (2) cm from the border of the psoriatic lesion, i.e. not the lesion itself, at any given time.

The assessed signs had to be present in this area, but could extend beyond it in a continuous manner.

The area for the subject to assess application site burning or pain was the lesional and perilesional area. The reported symptoms had to be present in this area, but could extend beyond it in a continuous manner.

For each sign and symptom the highest (worst) skin reaction score across all treatment areas was coded by use of the 4-point scale presented in the following two tables:

Table 6: Investigator Assessment of Skin Reaction Score

	0 = absent	1 = mild	2 = moderate	3 = severe
Perilesional erythema:	No perilesional erythema	Slight, barely perceptible perilesional erythema	Distinct perilesional erythema	Marked, intense perilesional erythema
Perilesional oedema:	No perilesional oedema	Slight, barely perceptible perilesional oedema	Distinct perilesional oedema	Marked, intense perilesional oedema
Perilesional dryness:	No perilesional dryness	Slight, barely perceptible perilesional dryness	Distinct perilesional dryness	Marked, intense perilesional dryness
Perilesional erosion:	No perilesional erosion	Slight, barely perceptible perilesional erosion	Distinct perilesional erosion	Marked, intense perilesional erosion

Source: Applicant's NDA Module 5.3.5.1, Clinical Study Report LP0053-1001, Table 5-8, p 52.

Table 7: Subject Assessment of Skin Reaction Score

	0 = absent	1 = mild	2 = moderate	3 = severe
Application site burning or pain:	No burning or pain after application	Slight, barely perceptible burning or pain after application	Distinct burning or pain after application	Marked, intense burning or pain after application

Source: Applicant's NDA Module 5.3.5.1, Clinical Study Report LP0053-1001, Table 5-8, p 52.

The (sub) investigator explained the categories of the scale to the subject and the subject told the (sub) investigator which category to mark.

Laboratory:
A urine pregnancy test was performed at Visit 1 prior to randomization and at the last on-treatment visit (Visit 4 unless early withdrawal) in female subjects of child-bearing potential.

A sample of venous blood and a spot urine sample were taken on Day 0 (Visit 1/baseline) and on Day 28 (Visit 4). These were analyzed by a central laboratory. and Parameters analyzed included the following:

Table 8: Serum Biochemistry and Urinalysis

Serum Biochemistry		**Urinalysis (spot urine sample)**	
Calcium[a]	Visit 1 and 4	Calcium[b]	Visit 1 and 4
Albumin[a]	Visit 1 and 4	Creatinine[b]	Visit 1 and 4
25-hydroxy vitamin D	Visit 1	-	-

Source: Applicant's NDA Module 5.3.5.1, Clinical Study Report LP0053-1001, Table 5-10, p 53.

If any of the laboratory results were abnormal and judged as clinically significant, the (sub) investigator followed-up with the subject as clinically appropriate (this could have involved requesting repeat samples). Likewise, if the albumin-corrected serum calcium result was above the reference range at the last on-treatment visit, a follow-up visit was performed for repeat sampling Laboratory values evaluated by the (sub) investigator as clinically significant were to be regarded as AEs).

6 Review of Efficacy

Efficacy Summary

To demonstrate findings of efficacy, the applicant conducted a Phase 3 pivotal trial, LP0053-1001 and a Phase 2 trial, LEO 90100-7. Trial LP0053-1001 was a national, multi-center, prospective, randomized, double-blind, 2-arm, parallel group, 4-week, vehicle-controlled study in subjects with stable plaque psoriasis of at least mild severity on the body (trunk and/or limbs). Trial LEO 90100-7 was a Phase 2 national, multi-center, prospective, randomized, double-blind, 3-arm, parallel group, 4-week, active-controlled study in subjects with stable plaque psoriasis of at least mild severity on the body (trunk and/or limbs) and scalp. For both of these trials, subjects must have had an IGA score of at least mild, involving 2-30% BSA at baseline. It should be noted that the

requirement of 2-30% BSA in Trial LP0053-1001 included the trunk and limbs whereas in LEO 90100-7 there was a requirement also for at least 10% scalp involvement as well as the 2-30% BSA trunk and limbs.

In addition, data from trial LEO 90100-35 was submitted as supportive of efficacy. This was a Phase 2 national, multi-center, prospective, randomized, investigator-blind, 2-arm, parallel group, 4-week, active and vehicle-controlled study in subjects with stable plaque psoriasis of at least mild severity (IGA of at least 2, BSA 2-30%) on the body (trunk and/or limbs).

In regard to demographics, for trials LP0053-1001 and LEO 90100-7 (the principal trials in support of efficacy) the mean age was similar among the treatment groups and ranged from 46 to 51 years. For trial LEO 90100-7 gender was generally balanced across treatment groups. For trial LP0053-1001 there was a higher proportion of male subjects in the Enstilar® (63%) as compared with the vehicle foam arm (48%). Race and ethnicity were generally balanced across treatment groups. Baseline disease characteristics were balanced across treatment groups. The majority of subjects (73 to 77%) had moderate disease at baseline and among the remaining subjects 11 to 16% had mild disease at baseline. Mean BSA (trunk/limbs) ranged from 6.7 to 8 % across treatment arms. Baseline mean m-PASI (trunk/limbs) ranged from 7.2 to 7.9.

In both trials, the protocol-specified primary efficacy endpoint was the proportion of subjects with “treatment success” on the trunk and limbs at Week 4. Treatment success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

In Trial LEO 90100-7, Enstilar® Foam was statistically superior to both the BDP monad ($p = 0.047$) and the calcipotriene monad ($p < 0.001$). In Trial LP0053-1001, Enstilar® foam was statistically superior to vehicle foam ($p < 0.001$). The response rate for Enstilar® foam was lower in Trial LEO 90100-7 (45%) compared to Trial LP0053-1001 (53%).

For the trial supportive of efficacy, LEO 90100-35, primary efficacy endpoint at Week 4, Enstilar® foam was found to be statistically superior ($p = 0.025$) to Taclonex® ointment. However, it should be noted that the comparison between Enstilar® foam and vehicle foam was not pre-specified in the protocol and therefore is a post-hoc analysis.

Results for the primary endpoint were examined in subpopulations for trials LP0053-1001 and LEO 90100-7 and the response rate for Enstilar® Foam was found generally to be similar across age, gender, and race subgroups.

Regarding data integrity, the applicant reported that a center in trial LP0053-1001 (US15; Dr. Jane Lee) did not perform assessments as specified in the protocol. A sensitivity analysis was performed where all subjects from this center were removed

from primary efficacy analysis.. The results were similar with and without center #15 and the center did not affect overall efficacy findings..

In conclusion, the efficacy of the Enstilar® Foam combination product compared with the component monads and vehicle was established for the topical treatment of plaque psoriasis of the body at 4 weeks.

6.1 Indication

The applicant has proposed that the indication be; "…topical treatment of plaque psoriasis in adults 18 years of age and older." For the purposes of labeling, the patient population will be specified as "patients" rather than "adults" because under some circumstances adults could be interpreted as subjects 17 years of age and older. In the CFR (21 CFR § 201.57) the pediatric age group is defined to be from birth to 16 years of age.

6.1.1 Methods

To demonstrate findings of efficacy, the applicant conducted a phase 3 pivotal trial, LP0053-1001 and a phase 2 trial, LEO 90100-7. The applicant also conducted a supportive phase 2 trial, LEO 90100-35. These trials are further described in the following table:

Table 9: Trials Used to Evaluate Efficacy

Protocol #	Type of trial/ sites	Trial Design	Subject Population	Test products/dosage regimen	Subjects in group: randomized /completed	treatment duration
LP0053-1001	Safety and efficacy 27 US	Phase 3 multi-center, double-blinded, vehicle controlled, 2-arm, randomized, parallel group	age 18 and older psoriasis vulgaris (body) IGA ≥ 2 2-30% BSA m-PASI ≥ 2 (body)	1. Enstilar® foam 2. Foam vehicle Once daily	323/313 103/99 Total: 426/412	Up to 4 weeks
LEO 90100-7	Safety and efficacy 28 US	Phase 2, multi-center, double-blinded, 3-arm, active controlled randomized, parallel group	age 18 and older Psoriasis vulgaris (body and scalp) IGA ≥ 2 2-30 % BSA ≥ 10 % of scalp m-PASI ≥ 2 (body)	1. Enstilar® 2. Betamethasone 3. Calciptriol Once daily	100/94 101/94 101/93 Total:302/ 281	Up to 4 weeks

Protocol #	Type of trial/ sites	Trial Design	Subject Population	Test products/dosage regimen	Subjects in group: randomized /completed	treatment duration
Supportive **LEO 90100-35**	Safety and efficacy 35 US	Phase 2, multi-center, investigator blinded, active and vehicle controlled, 4-arm, randomized, parallel group	age 18 and older Psoriasis vulgaris (body) IGA ≥ 2 2-30 % BSA m-PASI ≥ 2 (body)	1. Enstilar® foam 2. Taclonex ointment 3. Foam vehicle 4. Ointment vehicle Once daily	141/136 135/127 49/47 51/48 Total: 376/358	Up to 4 weeks

Source: Applicant's NDA, from Module 5, adapted from 5.2 Tabular Listing of all Clinical Studies and from 5.3.5.1 Clinical Study Reports LP0053-1001 section 7.1, LEO 90100-35 section 10.1, LEO 90100-7 section 10.1.

It is noted that trial LEO 90100-35 was investigator blinded. Also for this trial the comparison between Enstilar® Foam and vehicle foam was not pre-specified in the protocol and is therefore a post-hoc analysis.

6.1.2 Demographics

The mean age was similar among the treatment groups and ranged from 46 to 51 years. For trial LEO 90100-7 gender was generally balanced across treatment groups. For trial LP0053-1001 there was a higher proportion of male subjects in the Enstilar® (63%) as compared with the vehicle foam arm (48%). Race and ethnicity were generally balanced across treatment groups.

Table 10: Demographics ITT

	Trial LEO 90100-7			Trial LP0053-1001	
	Enstilar® Foam (N=100)	BDP in Vehicle (N=101)	Calcipotriene in Vehicle (N=101)	Enstilar® Foam (N=323)	Vehicle Foam (N=103)
Age					
Mean (SD)	47.4 (14.8)	49.0 (14.4)	50.7 (14.7)	51.2 (13.9)	46.0 (13.2)
Median	49.0	50.0	51.0	52.0	46.0
Range	20 - 81	20 - 85	21 - 85	18 - 87	19 - 79
Gender					
Male	53 (53.0%)	56 (55.4%)	61 (60.4%)	204 (63.2%)	49 (47.6%)
Female	47 (47.0%)	45 (45.6%)	40 (39.6%)	119 (36.8%)	54 (52.4%)
Race					
White	93 (93.0%)	83 (82.2%)	92 (91.1%)	276 (85.4%)	90 (87.4%)
Black	6 (6.0%)	8 (7.9%)	4 (4.0%)	24 (7.4%)	6 (5.8%)
Asian	1 (1.0%)	5 (5.0%)	3 (3.0%)	10 (3.1%)	3 (2.9%)

Other	0	5 (5.0%)	2 (2.0%)	13 (4.0%)	4 (3.9%)
Ethnicity					
Hispanic or Latino	23 (23.0%)	20 (19.8%)	22 (21.8%)	85 (26.3%)	22 (21.4%)
Not Hispanic or Latino	77 (77.0%)	81 (80.2%)	79 (78.2%)	238 (73.7%)	81 (78.6%)

Source: Statistical review NDA 207589, Table 6, p. 10

Baseline disease characteristics were balanced across treatment groups. The majority of subjects (73 to 77%) had moderate disease at baseline. Among the remaining subjects 11 to 16% had mild disease at baseline. Mean BSA (Trunk/limbs) ranged from 6.7 to 8 % across treatment arms. Baseline mean m-PASI (trunk/limbs) ranged from 7.2 to 7.9. See following table.

Table 11: Baseline Disease Characteristics

	Trial LEO 90100-7			Trial LP0053-1001	
	Enstilar® Foam (N=100)	BDP in Vehicle (N=101)	Calcipotriene in Vehicle (N=101)	Enstilar® Foam (N=323)	Vehicle Foam (N=103)
IGA (Trunk/Limbs)					
2 - Mild	11 (11.0%)	16 (15.8%)	14 (13.9%)	50 (15.5%)	15 (14.6%)
3 - Moderate	77 (77.0%)	75 (74.3%)	78 (77.2%)	244 (75.5%)	75 (72.8%)
4 - Severe	12 (12.0%)	10 (9.9%)	9 (8.9%)	29 (9.0%)	13 (12.6%)
% BSA (Trunk/Limbs)					
Mean (SD)	6.7 (4.9)	7.6 (6.3)	7.2 (5.6)	7.4 (6.4)	8.0 (7.0)
Median	5.0	5.0	5.0	5.0	5.0
Range	2 - 28	2 - 28	2 - 27	2 - 30	2 - 30
m-PASI (Trunk/Limbs)					
Mean (SD)	7.9 (4.5)	7.2 (3.9)	7.7 (4.4)	7.4 (4.8)	7.9 (6.6)
Median	6.7	6.3	6.4	6.0	6.1
Range	2 - 28	2.1 - 19.8	2.1 - 25.6	2 - 36.6	2 - 47.4

Source: Statistical review NDA 207589, Table 6, p. 10.

6.1.3 Subject Disposition

Subject withdrawal was generally balanced across treatment groups but was mildly higher in trial LEO 90100-7.

Table 12: Subject Disposition

	Trial LEO 90100-7			Trial LP0053-1001	
	Enstilar® Foam (N=100)	BDP in Vehicle (N=101)	Calcipotriene in Vehicle (N=101)	Enstilar® Foam (N=323)	Vehicle Foam (N=103)
Discontinued	6 (6.0%)	7 (6.9%)	8 (7.9%)	10 (3.1%)	4 (3.9%)
Adverse Event	2	0	2	0	0
Lost to Follow-Up	2	5	5	7	1
*Other**	2	0	0	1	1
Voluntary	0	2	1	2	2

Source: Statistical review NDA 207589, Table 5, p. 9.

*For trial LEO 90100-7, Enstilar® Foam arm, "other" reasons for withdrawal included:

1. Subject completed visit 4 eight days after visit 3. The subject was inadvertently scheduled early.
2. Subject is noncompliant – visit 4 has been rescheduled and subject no showed every time.

(From Clinical Study report LEO 90100-7, Appendix 16.2.1: Discontinued Subjects)

*For trial LP0053-1001, Enstilar® Foam arm, the "other" reason for withdrawal was:

- Subject had to return to college sooner than expected.

*For trial LP0053-1001, Vehicle foam arm, the "other" reason for withdrawal was:

- Subject stated he was moving to Canada for work and will not be able to continue in the trial.

(From Clinical Study report LP0053-1001, Appendix 2.1: Discontinued Subjects)

6.1.4 Analysis of Primary Endpoint(s)

The intent-to-treat (ITT) population was defined as all randomized subjects. This was the primary analysis population. The per-protocol population (PP) was defined as the ITT population minus those subjects who; received no treatment with trial medication, provided no efficacy data following start of treatment, were known to have taken the wrong trial medication throughout the treatment phase, and/or who did not fulfill the disease defining inclusion criteria.

In both trials, the protocol-specified primary efficacy endpoint was the proportion of subjects with 'treatment success' on the trunk and limbs at Week 4. Treatment success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

The following table shows results for the primary efficacy endpoint at Week 4 for both trials in the ITT population:

Table 13: Primary Efficacy Results at Week 4 (ITT, LOCF[1], MI[2])

	Enstilar® Foam	Betamethasone dipropionate in Vehicle Foam	Calcipotriene in Vehicle Foam	Vehicle Foam
Trial LEO 90100-7	(N=100)	(N=101)	(N=101)	-
Treatment Success[3] Rate	45 (45.0%)	31 (30.7%)	15 (14.9%)	-
P-value[4]	-	0.047	<0.001	-
Trial LP0053-1001	(N=323)	-	-	(N=103)
Treatment Success[3] Rate[5]	172.1 (53.3%)	-	-	4.9 (4.8%)
P-value[4]	-	-	-	<0.001

(1) Missing data for Study 7 was imputed using last observation carried forward (LOCF).
(2) Missing data for Study 1001 was imputed using multiple imputation (MI).
(3) Treatment success is defined as an IGA score of 0 or 1 with at least 2-grade improvement from baseline.
(4) P-value based on a CMH test stratified by pooled centers.
(5) Rates displayed are the averages over the 1000 imputed datasets.
Source: Statistical Review NDA 207589, Table 7, p. 11.

In Trial LEO 90100-7, Enstilar® foam was statistically superior to both the BDP monad ($p = 0.047$) and the calcipotriene monad ($p < 0.001$). In Trial LP0053-1001, Enstilar® foam was statistically superior to vehicle foam ($p < 0.001$). The response rate for Enstilar® foam was lower in Trial LEO 90100-7 (45%) compared to Trial LP0053-1001 (53%).

Results in the PP population were similar to those in the ITT population. However, according to the statistical reviewer, the comparison between Enstilar® foam and the BDP monad was no longer statistically significant ($p = 0.104$). The statistical reviewer states that this could be due to the decrease in sample size.

Table 14: Primary Efficacy Results at Week 4 (PP)

	Enstilar® Foam	BDP in Vehicle Foam	Calcipotriene in Vehicle Foam	Vehicle Foam
Trial LEO 90100-7	(N=79)	(N=86)	(N=81)	-
Treatment Success[1] Rate	37 (46.8%)	29 (33.7%)	13 (16.0%)	-
P-value[2]	-	0.104	<0.001	-
Trial LP0053-1001	(N=302)	-	-	(N=96)
Treatment Success[1] Rate	162 (53.6%)	-	-	4 (4.2%)
P-value[2]	-	-	-	<0.001

(1) Treatment success is defined as an IGA score of 0 or 1 with at least 2-grade improvement from baseline.
(2) P-value based on a CMH test stratified by pooled centers.
Source: Statistical review NDA 207589, Table 8, p. 11.

6.1.5 Analysis of Secondary Endpoints(s)

The two trials, LEO 90100-7 and LP0053-1001, had differing protocol-specified secondary endpoints. For trial LEO 90100-7, the protocol specified one secondary endpoint, the proportion of subjects with treatment success on the trunk and limbs at Week 1. For trial LP0053-1001, the protocol specified two secondary endpoints, m-PASI at Week 1 and m-PASI at Week 4. Because the secondary endpoints were different between the two trials and the applicant is not seeking labeling claims for the secondary endpoints, analysis of the secondary endpoints will not be discussed further.

6.1.6 Other Endpoints

Other endpoints were not analyzed.

6.1.7 Subpopulations

For both trials, LEO 90100-7 and LP0053-1001, the response rate for Enstilar Foam was generally similar across age, gender, and race subgroups.

Table 15: Primary Efficacy Results at Week 4 by Age, Gender, Race and Baseline Disease Severity for Trial LEO 90100- 7 (ITT, LOCF[1])

Subgroup (N_E, N_{BDP}, N_C)	Enstilar® Foam (N=100)	BDP in Vehicle (N=101)	Calcipotriene in Vehicle (N=101)
Age			
< 65 (88, 88, 81)	44.3%	28.4%	13.6%
≥ 65 (12, 13, 20)	50.0%	46.2%	20.0%
Gender			
Male (53, 56, 61)	43.4%	28.6%	18.0%
Female (47, 45, 40)	46.8%	33.3%	10.0%
Race			
White (93, 83, 92)	45.2%	30.1%	14.1%
Non-White (7, 18, 9)	42.9%	33.3%	22.2%
IGA			
2 – Mild (11, 16, 14)	45.5%	18.8%	0%
3 – Moderate (77, 75, 78)	49.4%	32.0%	19.2%
4 – Severe (12, 10, 9)	16.7%	40.0%	0%

(1) Missing data for Study 7 was imputed using last observation carried forward (LOCF).
Source: Statistical Review NDA 207589, Table 15, p. 15.

Table 16: Primary Efficacy Results at Week 4 by Age, Gender, Race and Baseline Disease Severity for Trial LP0053-1001 (ITT, MI[1])

Subgroup (N_E, N_V)	Enstilar® Foam (N=323)	Vehicle Foam (N=103)
Age		
< 65 (260, 93)	52.5%	5.3%
≥ 65 (63, 10)	56.5%	0%
Gender		
Male (204, 49)	56.8%	5.9%
Female (119, 54)	47.3%	3.7%
Race		
White (276, 90)	53.8%	4.3%
Non-White (47, 13)	50.0%	7.7%
IGA		
2 – Mild (50, 15)	30.2%	0.2%
3 – Moderate (244, 75)	59.8%	5.2%
4 – Severe (29, 13)	37.9%	7.7%

(1) Missing data for Study 1001 was imputed using multiple imputation (MI).
(2) Rates displayed are the averages over the 1000 imputed datasets.
Source: Statistical Review NDA 207589, Table 16, p. 15.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Clinical data regarding dosing was not provided in the current submission. Information regarding exposure-response relationships was submitted and reviewed in the original application.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Analyses of persistence of efficacy and/or tolerance were not performed.

6.1.10 Additional Efficacy Issues/Analyses

In trial LP0053-1001, the applicant states (clinical study report LP0053-1001 p. 78) that one site (Site US15 - Jane Lee MD) reported a protocol deviation wherein the site could not confirm that the scores given for the m-PASI assessments conformed to the directions specified in the consolidated clinical study protocol. "It was identified that the errors in clinical judgment were isolated to the extent calculation in the m-PASI transformation and were not implicated in any other investigator assessments. The site recruited several subjects and hence completed multiple randomization blocks. Any effect was therefore expected to be balanced between LEO 90100 and the vehicle

group with a limited impact on the results of the trial. Nevertheless, before unblinding, LEO decided to perform and report the outcome of sensitivity analyses excluding Site US15 for all PASI endpoints…"

This issue is expected to have little impact on labeling for Enstilar® Foam since secondary endpoints involving m-PASI scores are not included in labeling. (In addition OSI inspection results did not indicate anomalies in IGA assessment.)

However, to be certain that errors in efficacy assessment, if present in IGA assessment, would not affect trial results, the statistical reviewer conducted a sensitivity analysis where all subjects from center #15 were removed. The results were similar with and without center #15 and the center did not affect the overall efficacy conclusion.

7 Review of Safety

Safety Summary

The principal evaluation of safety for Enstilar® Foam, indication topical treatment of plaque psoriasis in adults 18 years of age and older, was based on trials that included subjects treating psoriasis vulgaris on the body, excluding face, axillae, and groin. The trials included in the pooled safety database are LP0053-1001 pivotal (US), LEO 90100-35 (Phase 2 investigator blinded, 4 arm, vehicle and active controlled), and LEO 90100-7 (Phase 2, double blinded, 3 arm active controlled). Additional safety information is available from trial LEO 901100-30, assessment of effects on HPA axis and calcium metabolism, not included in the pooled studies due to differences in trial design. All of the trials named above were conducted with the final-to-be-marketed formulation.

An additional analysis of pooled safety data from the two vehicle-controlled trials was performed. This pool includes all safety data from trial LP0053-1001 and two treatment arms of (Enstilar® foam and foam vehicle) from trial LEO 90100-35. The pool of vehicle controlled trials included 616 subjects exposed to study drugs, 464 to Enstilar® Foam and 152 to foam vehicle.

Pooled Safety Database (3 Controlled Trials):
The trials in the pooled safety database were randomized, multicenter, prospective vehicle and/or active controlled clinical trials in subjects with psoriasis vulgaris on the body (and scalp also for trial LEO 90100-7). Subjects applied study product once daily for up to 4 weeks and median weekly dose was 24.78 grams for subjects treated with Enstilar® Foam. The integrated/pooled safety database includes 1,099 subjects exposed to study drugs; Enstilar® Foam (564), betamethasone dipropionate (BDP) foam (99), calcipotriol foam (99), foam vehicle (152), Taclonex® Ointment (134), and ointment vehicle (51). Subject ages ranged from 18 to 88 years and the mean age for those exposed to Enstilar® Foam was 50.5 years.

No deaths were reported in any of the seven trials; LP0053-1001 pivotal (Phase 3, 2-arm vehicle controlled), LEO 90100-35 (Phase 2, 4-arm, vehicle and active controlled), LEO 90100-7 (Phase 2, 3-arm, active controlled), LEO 90100-30 MUSE open-label, LP0053-69 Vasoconstriction, LP0053-66 dermal safety, and LEO 90100-01 psoriasis plaque test. In the pooled safety studies, a total of 6 non-fatal SAE's were reported in 5 subjects; Enstilar® Foam (3 SAEs/3 subjects 0.5%) and Taclonex® Ointment (3 SAEs/2 subjects 1.5%). In the Enstilar® Foam group SAEs were hypersensitivity/urticaria, bipolar disorder, and substance-induced psychotic disorder. Hypersensitivity/urticaria was considered possibly related to treatment with Enstilar and led to withdrawal from the trial. The other 2 SAEs were considered not related to treatment with Enstilar. One of them (substance induced psychotic disorder) led to discontinuation of treatment with trial medication. In the Taclonex® Ointment group the SAEs were bronchitis, hypertension, and bile duct stone. Two of them (bronchitis and hypertension) were experienced by the same subject. All 3 events are unlikely to be related to trial medication.

In the Enstilar® Foam group, 3 of 564 subjects (0.5%) had AEs that were recorded as a reason for permanent discontinuation of treatment with trial medication. The events were hypersensitivity/urticaria, substance-induced psychotic disorder, and irregular menstruation; each event was reported for 1 (0.2%) subject. Hypersensitivity/urticaria was assessed as possibly related to trial medication and the other 2 AEs were considered not related to trial medication. Hypersensitivity/urticaria and irregular menstruation were reported also as reasons for withdrawal from the trial.
In the calcipotriol group, 3 of 99 subjects (3%) had AEs that were recorded as a reason for permanent discontinuation of treatment with trial medication. The events were medication residue (e.g. greasy hair) (2 AEs) and contact dermatitis (1 AE) and were assessed as probably related to trial medication. One AE of medication residue and the AE of contact dermatitis were also reported as reasons for withdrawal from the trial.
In the Taclonex® Ointment group, 1 of 134 subjects (0.7%) had AEs that were recorded as a reason for permanent discontinuation of treatment with trial medication. The events, all in 1 subject, were dizziness, dyspnea, increased heart rate, and swelling of face. The events were assessed as not related to trial medication. The AE of increased heart rate was also reported as a reason for withdrawal from the trial.

In the pooled, controlled trials a total of 8 severe adverse events were reported, these included 6 events in 6 subjects (6/78 or 8% of subjects having adverse events) in the Enstilar® foam group and 2 events in one (1/14 or 7% of subjects having adverse events) in the Taclonex ® Ointment group. The severe AEs for the Enstilar® foam group include the following: cellulitis (in arm) possibly related to venipuncture, substance-induced psychotic disorder, bipolar disorder, peripheral edema (right hand swelling), psoriasis "flare", and hypersensitivity/urticaria. Of the 6 events, the latter two are considered to be possibly related to study medication and are included in proposed labeling as "exacerbation of psoriasis" and "urticaria." The severe events reported for

Taclonex® Ointment included hypertension and bronchitis, not considered to be related to study drug.

In the pooled controlled trials, at least one adverse event was reported by 78 (13.8%) of subjects in the Enstilar® Foam group, 13 (13.1%) in the BDP group, 10 (10.1%) in the calcipotriol group, 14 (10.4%), in the Taclonex® Ointment group, 13 (8.6%) in the foam vehicle group, and 2 (3.9%) in the ointment vehicle group. For the pooled safety trials, in those exposed to Enstilar® Foam, the most common adverse event was nasopharyngitis, reported for 6 (1.1%) subjects. Other adverse events experienced by ≥2 subjects in the Enstilar ® group, and at a rate greater than vehicle, were increased blood pressure 3 (0.5%) subjects, nausea 3 (0.5%) subjects, application site pruritus 2 (0.4%) subjects, contusion 2 (0.4%) subjects, excoriation 2 (0.4%) subjects, flank pain 2 (0.4%) subjects, and hordeolum 2 (0.4%) subjects.

Adverse drug reactions were not seen in 1% or greater of subjects for any investigational drug product; Enstilar® Foam, BDP foam, calcipotriol foam, foam vehicle, Taclonex ointment, or ointment vehicle. In the pool of controlled trials, for Enstilar® Foam, adverse drug reactions occurring at a rate greater than in foam vehicle included; application site pruritus (0.4), application site irritation (0.2), skin irritation (0.2), folliculitis (0.2), application site discoloration, hypercalcemia (0.2), urticaria (0.2), and exacerbation of psoriasis.

The analysis of pooled safety data from the two vehicle-controlled trials was supportive of findings from the pool of 3 controlled trials.

Of subjects exposed to Enstilar® Foam, in the pool of 3 controlled trials, 97 were aged 65 and older and 21 were aged 75 and older. Clinically significant differences in safety of Enstilar® Foam between subjects in these age ranges versus younger subjects were not seen.

Trial LEO 901100-30 (assessment of effects on HPA axis and calcium metabolism):
The effects of Enstilar® Foam on the HPA axis and on calcium metabolism were examined in trial LEO 80185-G24. HPA axis suppression was evaluated in adult subjects (N=35) with moderate to severe plaque psoriasis with a mean body surface area involvement of 17.5% and mean scalp involvement of 50.2%. Treatment consisted of once daily application of Enstilar® Foam on the scalp and body for 4 weeks. The mean ± SD weekly amount of formulation used was 61.8 ± 27.7 grams. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL was not observed in in any subjects after 4 weeks of treatment. The effects on calcium metabolism of once daily application of Enstilar® Foam on the scalp and body for 4 weeks were also examined. There was no change in mean serum or urinary calcium levels. Following once daily application of Enstilar® Foam on the scalp and body, elevated serum or urinary calcium levels outside the normal range were not observed in

any subjects. No SAEs, discontinuation of investigational product due to AEs or other significant AEs were reported in this trial.

A dermal safety study was performed in support of this application, evaluating the skin irritation potential and sensitization potential of Enstilar® Foam and the foam vehicle after repeated applications to the skin of healthy subjects. Under the conditions of the study, Enstilar® Foam showed no potential for sensitization and repeated applications revealed limited potential for irritancy.

The applicant is waived from conduct of phototoxicity and photoallergy studies on the basis that, apart from propellants, no new excipients have been added to Enstilar® Foam as compared to Taclonex® Ointment and UV/VIS spectra obtained for Taclonex® Ointment and Enstilar® Foam before and after evaporation of the propellants are very similar. The phototoxic and photoallergenic potential of Taclonex® Ointment, which absorbs light in the 290-700 nm range, has been evaluated in healthy volunteers (trial MCB 0101 FR and trial MCB 0204 FR, respectively). No phototoxic or photoallergic reactions were observed.

Long Term Safety Assessment:
The applicant did not conduct any long term studies with Enstilar® Foam for the indication of topical treatment of non-scalp psoriasis. Please see section 7.7 of this review for further discussion of long term safety.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 17: Principal Clinical Trials Used to Evaluate Safety

Protocol #	Type of trial	Trial Design	Subject Population/ # of sites	Test products/dosage regimen	Subjects in group: randomized/ completed	Diagnosis/ treatment duration
LP0053-1001	Safety and efficacy	Phase 3 multi-center, double-blinded, vehicle controlled, 2-arm, randomized, parallel group	Subjects age 18 and older 27 US	1. Enstilar® foam 2. Foam vehicle Once daily	323/313 103/99 Total: 426/412	Psoriasis vulgaris on body Up to 4 weeks

Protocol #	Type of trial	Trial Design	Subject Population/ # of sites	Test products/dosage regimen	Subjects in group: randomized/ completed	Diagnosis/ treatment duration
LEO 90100-35	Safety and efficacy	Phase 2, multi-center, investigator blinded, active and vehicle controlled, 4-arm, randomized, parallel group	Subjects age 18 and older 35 US	1. Enstilar® foam 2. Taclonex ointment 3. Foam vehicle 4. Ointment vehicle Once daily	141/136 135/127 49/47 51/48 Total: 376/358	Psoriasis vulgaris on body Up to 4 weeks
LEO 90100-7	Safety and efficacy	Phase 2, multi-center, double-blinded, 3-arm, active controlled randomized, parallel group	Subjects age 18 and older 28 US	1. Enstilar® 2. Betamethasone 3. Calciptriol Once daily	100/94 101/94 101/93 Total:302/281	Psoriasis vulgaris on body and scalp Up to 4 weeks

Source: Applicant's NDA, from Module 5, adapted from 5.2 Tabular Listing of all Clinical Studies and from 5.3.5.1 Clinical Study Reports LP0053-1001 section 7.1, LEO 90100-35 section 10.1, LEO 90100-7 section 10.1

For the integrated summary of safety, the applicant pooled the results of the three following trials:

- LP0053-1001 pivotal (Phase 3, 2-arm vehicle controlled)
- LEO 90100-35 (Phase 2, 4-arm, vehicle and active controlled)
- LEO 90100-7 (Phase 2, 3-arm, active controlled)

In addition an analysis of pooled safety data from the two vehicle-controlled trials was performed at the request of the FDA. This pool includes all safety data from trial LP0053-1001 and two treatment arms of (Enstilar® foam and foam vehicle) from trial LEO 90100-35.

Deaths, serious adverse events, discontinuation due to adverse events and clinically important adverse events were considered from all clinical studies.

7.1.2 Categorization of Adverse Events

In all seven trials, the reported AEs were coded using MedDRA. AEs reported for the three controlled trials were coded according to MedDRA version 15.0 (Trials LEO 90100-7 and LEO 90100-35) or version 16.0 (Trial LP0053-1001). For the integrated analysis of safety, all AEs reported for the three controlled trials were re-coded according to MedDRA version 15.1. AEs reported for the non-pooled trials were coded according to MedDRA version 6.1 (Trial LEO 90100-01 plaque test) and version 15.1

(Trials LEO 90100-30 MUSEand LP0053-66 dermal safety). There were no AEs reported in Trial LP0053-69 (vasoconstriction). The categorization to preferred terms appears appropriate.

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

AEs were classified according to MedDRA SOC and preferred term in each of the seven trials.

AE tabulations consist of treatment-emergent AEs (TEAEs) only. TEAEs were defined as events that occurred after the first application of trial medication or events that occurred before the first application of trial medication and increased in intensity while on trial medication.

As stated by the applicant, AEs were reported on the body in Trials LP0053-1001 and LEO 90100-35 and on the body and scalp in Trial LEO 90100-7. For the analysis of safety for the pooled controlled trials, all TEAEs including those reported on the scalp in Trial LEO 90100-
7 were summarized; for the vehicle-controlled trials, all TEAEs reported on the body in Trial LP0053-1001 and for two treatment arms (LEO 90100 and foam vehicle) in Trial LEO 90100-35 were summarized.

The intensity (mild, moderate, or severe) of AEs and lesional/perilesional AEs were tabulated by pooled treatment group. If there were several records of intensity for the same event (preferred term) for a subject, the intensity was taken as the worst ever record of the AE for that subject.

If there were several records of causal relationship for the same event (preferred term) for a subject, causal relationship was taken from the last report of the event. According to the applicant, that was when the investigator was in possession of most information and so best able to judge causal relationship.

7.2 Adequacy of Safety Assessments

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

In the pooled controlled trials, 1099 subjects were exposed to study drugs; 564 Enstilar® Foam, 99 betamethasone foam, 99 calcipotriol foam, 152 foam vehicle, 134 Taclonex Ointment, 51 Taclonex ointment vehicle.

Table 18: Number of Subjects Exposed in Pooled Controlled Trials

Treatment	Safety Population			
	Total	LEO 53 -1001	L90100-35	90100-7
	Subjects (%)	Subjects (%)	Subjects (%)	Subjects (%)
LEO 90100 (Enstilar® Foam)	564 (100)	323 (57.3)	141 (25)	100 (17.7)
Betamethasone foam	99 (100)			99 (100)
Calcipotriol foam	99 (100)			99 (100)
Foam vehicle	152 (100)	103 (67.8)	49 (32.2)	
Taclonex ointment	134 (100)		134 (100)	
Ointment vehicle	51 (100)		51 (100)	

Source: Applicant's NDA from module 2.7.4, Summary of Clinical Safety, adapted from Table 5, p 35.

In the pooled vehicle-controlled trials, 616 subjects were exposed to study drugs, 464 Enstilar Foam, 152 foam vehicle.

Table 19: Number of Subjects Exposed in Pooled Vehicle-Controlled Trials.

Treatment	Safety Population		
	Total	LEO 53 -1001	L90100-35
	Subjects (%)	Subjects (%)	Subjects (%)
LEO 90100 (Enstilar)	464 (100)	323 (76.4)	141 (23.6)
Foam vehicle	152 (100)	103 (67.8)	49 (32.2)

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, adapted from Table 5, p 35.

Duration of exposure:
In the pooled controlled trials, mean duration of exposure across age categories, sexes, races, and ethnic groups was generally similar. The mean duration of exposure for Enstilar® Foam was 4.0 weeks.

Table 20: Duration of Exposure to Study Treatment (Pooled Controlled Trials)

Exposure	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Mean	4.0	4.0	4.1	4.0	3.9	4.0
SD	0.7	0.6	0.8	0.6	0.9	0.8
Minimum	0.1	0.6	0.7	0.1	0.1	0.1
Maximum	8.4	5.6	6.9	6.3	5.0	5.0
Number	564	99	99	152	134	51
Subject-treatment	2269	393	402	612	526	202

weeks						

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 8, p 42.

In the pooled vehicle-controlled trials, mean duration of exposure across age categories, sexes, races, and ethnic groups was generally similar. The mean duration of exposure for Enstilar Foam and Foam vehicle was 4.0 weeks.

Table 21: Duration of Exposure to Study Treatment (Vehicle-Controlled Trials)

Exposure	Enstilar Foam	Foam Vehicle
	N = 464	N = 152
Mean	4.0	4.0
SD	0.6	0.6
Minimum	0.1	0.1
Maximum	8.4	6.3
Number	462	152
Subject-treatment weeks	1858	612

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 9, p 43.

Amount of study medication used

In the pooled controlled trials, the amount of study drug used was calculated by subtracting the weight of the returned used containers (either cans or tubes) from the mean weight of the total set of full containers dispensed. For foam cans, the total amount of trial medication used was adjusted by a correction factor of 0.41 to subtract the propellant gases.

The mean total amount of study medication used was 125.34 grams in the Enstilar® Foam group, 145.45 grams in the betamethasone foam group, 145.75 grams in the calcipotriol foam group, 129.96 grams in the foam vehicle group, 128.35 grams in the Taclonex ointment group, and 117.98 grams in the ointment vehicle group.

Table 22: Total Amount of Study Drug Used (Pooled Controlled Trials)

Exposure	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Mean	125.34	145.45	145.75	129.96	128.35	117.98
SD	89.01	92.09	91.36	95.62	90.53	92.87
Median	99.47	122.58	129.02	100.83	98.63	82.91
Minimum	8.2	4.9	6.0	8.5	1.2	14.4
Maximum	346.2	355.8	339.9	350.7	338.0	315.9
Number[2]	516	90	88	144	120	49

[2]Data is provided only for subjects who returned all dispensed containers.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, Table 12, p 14.

In the pooled vehicle-controlled trials, the mean total amount of study medication used was similar between Enstilar® Foam (123.40 grams) and foam vehicle groups (129.96 grams).

Table 23: Total Amount of Study Medication Used (Vehicle Controlled Trials)

Exposure	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Mean	123.40	129.96
SD	88.80	95.62
Median	94.53	100.83
Minimum	8.2	8.5
Maximum	346.1	350.7
Number[2]	423	144

[2]Data is provided only for subjects who returned all dispensed containers.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, Table 111, p 13.

The median weekly amount of study medication used was 24.78 grams in the Enstilar® Foam group, 30.46 grams in the betamethasone foam group, 32.32 grams in the calcipotriol foam group, 23.62 grams in the foam vehicle group, 25.66 grams in the Taclonex ointment group, and 23.19 grams in the ointment vehicle group.

Table 24: Weekly Amount of Study Drug Used (Pooled Controlled Trials)

Exposure	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Mean	30.92	35.76	35.43	23.35	31.80	29.32
SD	21.95	22.34	21.69	24.02	22.21	22.52
Median	*24.78*	*30.46*	*32.32*	*23.62*	*25.66*	*23.19*
Minimum	2.1	5.4	5.0	2.2	1.3	3.4
Maximum	89.7	89.0	84.0	87.7	87.7	77.6
Number[2]	516	90	88	144	120	49

[2]Data is provided only for subjects who returned all dispensed containers.
Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 11, p 44.

For the vehicle-controlled trials, the median weekly amount of study medication used was similar for both the Enstilar Foam (24.08 grams) and foam vehicle groups (23.62).

Table 25: Weekly Amount of Study Drug Used (Vehicle-Controlled Trials)

Exposure	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Mean	30.48	32.35
SD	22.04	24.02
Median	*24.08*	*23.62*
Minimum	2.1	2.2
Maximum	89.7	87.7
Number[2]	423	144

[2]Data is provided only for subjects who returned all dispensed containers.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of safety, Table 109, p 11.

Demographic Characteristics

Table 26: Age and BMI (Pooled Controlled Trials)

Demographic	Enstilar Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Age (years)						
Mean	50.5	49.2	51.1	45.9	50.7	52.6
SD	13.9	14.5	14.4	13.3	13.1	11.1
Median	51.0	51.0	51.0	46.0	52.0	55.0
Minimum	18	20	21	19	21	30
Maximum	87	85	85	79	88	73
Number	564	99	99	152	134	51
BMI (kg/m^2)						
Mean	31.7	31.3	30.2	32.1	30.2	30.9
SD	7.5	7.5	5.3	8.5	6.0	6.7
Median	30.1	30.6	29.2	30.3	29.4	30.0
Number	563	99	99	150	134	51

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, adapted from Table 14, p 49.

Subject ages ranged from 18 to 88 years. The mean age was 50.5 for the Enstilar® Foam group, 49.2 years for the betamethasone group, 51.1 years for the calcipotriene group, 45.9 years for the foam vehicle group, 50.7 for the Taclonex Ointment group, and 52.6 for the ointment vehicle group. The mean body mass index (BMI) was similar across treatment groups, ranging between 30.2 and 32.1 kg/m^2. The distribution of age groups was similar for the treatment groups and the majority (generally at least two thirds) of subjects were in the age categories 36 to 50 years old or 51 to 64 years old. Of subjects exposed to Enstilar® Foam, 97 were aged 65 and older and 21 were aged 75 and older.

Treatment groups exhibited a mildly higher proportion of male subjects (range 52 to 65%) as compared with female subjects (range 35 to 48 %). White subjects comprised the predominant majority of each treatment group (range 81.8% to 91.9%). Black/African American and Asian subjects accounted for a range of 3 to 9.8 % and 2 to 5.1%, respectively, of each treatment group. Hispanic or Latino subjects comprised a range of 9.8% to 24.6% for the treatment groups.

Table 27: Demographic Characteristics (Pooled Controlled Trials)

	Enstilar Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Demographic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Sex						
Male	344 (61.0)	55 (55.6)	60 (60.6)	79 (52.0)	87 (64.9)	30 (58.8)
Female	220 (39.0)	44 (44.4)	39 (39.4)	73 (48.0)	47 (35.1)	21 (41.2)
Total	564 (100)	99 (100)	99 (100)	152 (100)	134 (100)	51 (100)
Age Group						
≤ 35 years old	94 (16.7)	19 (19.2)	16 (16.2)	36 (23.7)	19 (14.2)	7 (13.7)
36 – 50 yrs old	165 (29.3)	30 (30.3)	30 (30.3)	63 (41.4)	44 (32.8)	13 (25.5)
51 – 64 yrs old	208 (36.9)	37 (37.4)	33 (33.3)	40 (26.3)	54 (40.3)	25 (49.0)
≥ 65 yrs old	97 (17.2)	13 (13.1)	20 (20.2)	13 (8.6)	17 (12.7)	6 (11.8)
< 75 years old	543 (96.3)	96 (97.0)	96 (97.0)	149 (98.0)	128 (95.5)	51 (100.0)
≥ 75 years old	21 (3.7)	3 (3.0)	3 (3.0)	3 (2.0)	6 (4.5)	0 (0)
Total	564 (100)	99 (100)	99 (100)	152 (100)	134 (100)	51 (100)
Ethnicity						
Hispanic or Latino	139 (24.6)	20 (20.2)	21 (21.2)	30 (19.7)	28 (20.9)	5 (9.8)
Not Hispanic or Latino	425 (75.4)	79 (79.8)	78 (78.8)	122 (80.3)	106 (79.1)	46 (90.2)
Race						
White	491 (87.1)	81 (81.8)	91 (91.9)	135 (88.8)	117 (87.3)	44 (86.3)
Black or African Amer.	42 (7.4)	8 (8.1)	3 (3.0)	9 (5.9)	4 (3.0)	5 (9.8)
Asian	13 (2.3)	5 (5.1)	3 (3.0)	3 (2.0)	6 (4.5)	2 (3.9)
Amer Indian or Alaska Native	5 (0.9)	1 (1.0)	0 (0)	2 (1.3)	1 (0.7)	0 (0)
Native Hawaiian or other Pacific Islander	2 (0.4)	2 (2.0)	1 (1.0)	1 (0.7)	1 (0.7)	0 (0)

	Enstilar Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Demographic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	11 (2.0)	2 (2.0)	1 (1.0)	2 (1.3)	5 (3.7)	0 (0)
Total	564 (100)	99 (100)	99 (100)	152 (100)	134 (100)	51 (100)

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, adapted from Table 15, pp 50-51.

Table 28: Age and BMI for Vehicle-Controlled Trials

	Enstilar Foam	Foam Vehicle	
Demographic	N = 464	N = 152	
Age (years)			
Mean	51.2	45.9	
SD	13.6	13.3	
Median	52.0	46.0	
Minimum	18	19	
Maximum	87	79	
Number	464	152	
BMI (kg/m^2)			
Mean	31.9	32.1	
SD	7.6	8.5	
Median	30.4	30.3	
Number	463	150	

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, adapted from Table 19, p 57.

For the vehicle-controlled trials, subject ages ranged from 18 to 87 years. The mean age was 51.2 for the Enstilar® Foam group and 45.9 years for the foam vehicle group. For both the Enstilar® Foam and vehicle foam groups, the majority (approximately two thirds) of subjects were in the age categories 36 to 50 years old or 51 to 64 years old. The mean body mass index (BMI) was similar for both the Enstilar® Foam (31.9 kg/m2) and vehicle foam groups (32.2 kg/m2. Of subjects exposed to Enstilar® Foam 85 were aged 65 and older and 17 were aged 75 and older.

The Enstilar® Foam group included a higher proportion of male subjects (67.2%) than women (37.3%). In the foam vehicle group the proportion of male and female subjects was close to even (52% and 48%, respectively). White subjects comprised the predominant majority of each treatment group (Enstilar® Foam 85.8% and vehicle foam 88.8%). Black/African American and Asian subjects accounted for 7.8% and 5.9% and 2.6% and 2.0%, respectively, Enstilar and vehicle foam groups. Hispanic or Latino subjects comprised 25.0 % and 19.7% of the Enstilar® and vehicle foam groups.

By comparison the US population (as of 2013, 1 year estimate) was 76.2% White, 13.8% Black or African American, 6% Asian, 1.7% American Indian and Alaska Native, 0.4% Native Hawaiian and Other Pacific Islander, 5.2% other race. A total of 17.1% of the population was Hispanic (of any race) and 82.9% were not Hispanic or Latino.[1]

Table 29: Demographic Characteristics Vehicle-Controlled Trials

	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Demographic	n (%)	n (%)
Sex		
Male	291 (62.7)	79 (52.0)
Female	173 (37.3)	73 (48.0)
Total	464 (100)	152 (100)
Age Group		
≤ 35 years old	68 (14.7)	36 (23.7)
36 – 50 yrs old	139 (30.0)	63 (41.4)
51 – 64 yrs old	172 (37.1)	40 (26.3)
≥ 65 yrs old	85 (18.3)	13 (8.6)
< 75 years old	447 (96.3)	149 (98.0)
≥ 75 years old	17 (3.7)	3 (2.0)
Total	464 (100)	152 (100)
Ethnicity		
Hispanic or Latino	116 (25.0)	30 (19.7)
Not Hispanic or Latino	348 (75.0)	122 (80.3)
Race		
White	398 (85.8)	135 (88.8)
Black or African American	36 (7.8)	9 (5.9)
Asian	12 (2.6)	3 (2.0)
American Indian or Alaska Native	5 (1.1)	2 (1.3)
Native Hawaiian or other Pacific Islander	2 (0.4)	1 (0.7)
Other	11 (2.4)	2 (1.3)
Total	464 (100)	152 (100)

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, adapted from Table 20, p 58.

[1] U. S. Census Bureau, 2013 American Community Survey, Table DP05 - ACS Demographic and Housing Estimates, 2013 American Community Survey 1-Year Estimates.

7.2.2 Explorations for Dose Response

Explorations for Dose response were not performed in the current submission

7.2.3 Special Animal and/or In Vitro Testing

Special animal and/or In Vitro testing was not performed in the current submission.

7.2.4 Routine Clinical Testing

The routine clinical testing was designed to assess the safety and efficacy of use of daily application for up to 4 weeks.

7.2.5 Metabolic, Clearance, and Interaction Workup

Assessment of drug-drug interactions was not performed in the current submission.

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

The applicant's efforts to detect adverse events that are associated with the drug classes of each active ingredient (calcipotriene and betamethasone dipropionate) were adequate in the development program, in regard to local safety, collection of adverse event data, and the potential for systemic effects (calcium metabolism and/or the HPA axis).

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in any of the seven trials; LP0053-1001 pivotal (Phase 3, 2-arm vehicle controlled), LEO 90100-35 (Phase 2, 4-arm, vehicle and active controlled), LEO 90100-7 (Phase 2, 3-arm, active controlled), LEO 90100-30 MUSE open-label, LP0053-69 vasoconstriction, LP0053-66 dermal safety, and LEO 90100-01 psoriasis plaque test.

7.3.2 Nonfatal Serious Adverse Events

In the controlled trials:

- In the Enstilar group (calcipotriene and betamethasone foam): 3 of 564 subjects (0.5%) had a total of 3 serious adverse events (SAEs). These were hypersensitivity/urticaria, bipolar disorder, and substance-induced psychotic disorder. Hypersensitivity/urticaria was considered possibly related to treatment with Enstilar and led to withdrawal from the trial. The other 2 SAEs were considered not related to treatment with Enstilar. One of them (substance induced psychotic disorder) led to discontinuation of treatment with trial medication.
- In the Taclonex ointment group (calcipotriene and betamethasone): 2 of 134 subjects (1.5%) had a total of 3 SAEs. These were bronchitis, hypertension, and bile duct stone. Two of them (bronchitis and hypertension) were experienced by the same subject. All 3 events were assessed by the investigator as not related to trial medication.

No SAEs were reported in the MUSE trial (LEO 90100-30), the vasoconstriction trial (LP0053-69), or the exploratory psoriasis plaque test trial (LEO 90100-01).

One SAE (rectal hemorrhage) was reported after application of LEO 90100 in the dermal safety trial (LP0053-66). The event was assessed by the investigator as not related to treatment, and led to withdrawal from the trial.

In the vehicle-controlled trials:

- In the Enstilar group: 2 of 464 subjects (0.4%) experienced 2 SAEs. These were bipolar disorder, and substance-induced psychotic disorder. As noted previously, the latter 2 SAEs were considered not related to treatment with Enstilar.
- In the foam vehicle group: no SAEs were reported (0 out of 152).

Details of Case of Interest:
From the controlled trials, one SAE, hypersensitivity, was considered possibly related to treatment and occurred in a subject receiving Enstilar Foam in trial LEO 90100-7.

Event of Hypersensitivity: Subject LEO90100_7 0001_23_7
The subject was a 40 year old male randomized to Enstilar Foam, beginning treatment May 21, 2012. The subject had no relevant medical history and was not receiving concomitant medications at trial entry. On (b) (6) the subject experienced urticaria and took aspirin 162 mg. The following morning, (b) (6), the subject woke up with swollen lips and eyelids. In the emergency room he was treated for an allergic reaction; mild shortness of breath, mild trouble swallowing, and slight swelling of tongue. The subject received intravenous methylprednisolone 125 mg, diphenhydramine 50 mg, ranitidine 50 mg, and famotidine 20 mg. The subject was discharged from the ER within 3 hours of being triaged. The subject received the last study treatment on June 3, 2012 and discontinued the trial due to this event. The

adverse event was resolved June 4, 2012. The investigator considered the event to be of severe intensity and possibly related to study medication.

This case is confounded by the fact that the subject took aspirin and subsequently was noted to have mild shortness of breath, mild trouble swallowing, and slight swelling of tongue. Current OTC labeling for aspirin states that aspirin may cause a severe allergic reaction which may include; hives, shock, facial swelling, asthma (wheezing). For the purposes of labeling, this event will be included as "urticaria" since the primary event appears to be urticaria and the details of the case are not adequate to label it as hypersensitivity.

Table 30: Serious Adverse Events (Pooled Controlled Trials)

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infections & Infestations						
Bronchitis	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
SOC total	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
Immune system disorders						
Hypersensitivity	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SOC total	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psychiatric disorders						
Bipolar disorder	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Substance-induced psychotic disorder	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SOC total	2 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders						
Hypertension	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
SOC total	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
Hepatobiliary disorders						
Bile duct stone	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
SOC total	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
Total number of SAEs[2]	3	0	0	0	3	0
Total number of subjects	3 (0.5)	0 (0)	0 (0)	0 (0)	2 (1.5)	0 (0)

[1] Classification according to MedDRA version 15.1

[2] Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 33, pp 99-100.

Table 31: Serious Adverse Events Vehicle-Controlled Trials

System Organ Class (SOC)	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Preferred Term[1]	n (%)	n (%)
Psychiatric disorders		
Bipolar disorder	1 (0.2)	0 (0)
Substance-induced psychotic disorder	1 (0.2)	0 (0)
SOC total	2 (0.4)	0 (0)
Total number of SAEs[2]	2	0
Total number of subjects	2 (0.4)	0 (0)

[1] Classification according to MedDRA version 15.1

[2] Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, Table 145, p 29.

7.3.3 Dropouts and/or Discontinuations

In the pooled safety trials:

- In the Enstilar® Foam group (calcipotriene and betamethasone dipropionate): 3 of 564 subjects (0.5%) had AEs that were recorded as a reason for permanent discontinuation of treatment with trial medication. The events were hypersensitivity/urticaria, substance-induced psychotic disorder, and irregular menstruation; each event was reported for 1 (0.2%) subject. Hypersensitivity/urticaria (narrative discussed above) was assessed by the investigator as possibly related to trial medication and the other 2 AEs were considered not related to trial medication. Hypersensitivity/urticaria and irregular menstruation were reported also as reasons for withdrawal from the trial.
- In the calcipotriol group: 3 of 99 subjects (3%) had AEs that were recorded as a reason for permanent discontinuation of treatment with trial medication. The events were medication residue – e.g. greasy hair (2 AEs) and contact dermatitis (1 AE) and were assessed as probably due to trial medication. One AE of medication residue and the AE of contact dermatitis were also reported as reasons for withdrawal from the trial.

- In the Taclonex® Ointment group: 1 of 134 subjects (0.7%) had AEs that were recorded as a reason for permanent discontinuation of treatment with trial medication. The events, all in 1 subject, were dizziness, dyspnea, increased heart rate, and swelling of face. The events were assessed as not related to trial medication. The AE of increased heart rate was also reported as a reason for withdrawal from the trial.

Table 32: Adverse Events Leading to Permanent Discontinuation of Investigational Product (Pooled Controlled Trials)

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Immune system disorders						
Hypersensitivity	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SOC total	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psychiatric disorders						
Substance-induced psychotic disorder	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SOC total	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders						
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
SOC total	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
Respiratory, thoracic and mediastinal disorders						
Dyspnea	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
SOC total	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
Skin & subcutaneous tissue disorders						
Dermatitis, contact	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)
Swelling, face	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
SOC total	0 (0)	0 (0)	1 (1.0)	0 (0)	1 (0.7)	0 (0)
Reproductive system & breast disorders						
Menstruation irregular	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SOC total	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders & administration site conditions						
Medication residue*	0 (0)	0 (0)	2 (2.0)	0 (0)	0 (0)	0 (0)
SOC total	0 (0)	0 (0)	2 (2.0)	0 (0)	0 (0)	0 (0)
Investigations						
Heart rate increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
SOC total	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
Total number of adverse events[2]	3	0	3	0	4	0
Total number of	3 (0.5)	0 (0)	3 (3.0)	0 (0)	1 (0.7)	0 (0)

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
subjects						

* "Greasy hair"
[1] Classification according to MedDRA version 15.1
[2] Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 34, pp 102,103.

Table 33: Adverse Events Leading to Permanent Discontinuation of Investigational Product (Vehicle-Controlled Trials)

System Organ Class (SOC)	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Preferred Term[1]	n (%)	n (%)
Psychiatric disorders		
Substance-induced psychotic disorder	1 (0.2)	0 (0)
SOC total	1 (0.2)	0 (0)
Total number of withdrawals[2]	1	0
Total number of subjects	1 (0.2)	0 (0)

[1] Classification according to MedDRA version 15.1
[2] Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, Table 146, p 30.

Case Narratives of Interest for subjects withdrawing from trials:
Hypersensitivity/urticaria: Subject: LEO90100_7_0001_23_07: Narrative discussed above.

Event of medication residue: Subject: LEO90100_7_ 0017_01_07
Treatment: Calcipotriol
Subject was a 63 year old female who started treatment with calcipotriol on August 78, 2012. The subject had no relevant medical history and was receiving no concomitant

medications at study entry. On Day 1 of treatment, the subject experienced greasy hair. The event was considered to be of mild intensity and to be probably related to treatment by the investigator. A week later, at the next clinic visit, the event was considered resolved. The subject last applied study treatment on August 12, 2012 and discontinued the study due to this event.

Contact dermatitis: Subject: LEO90100_7_0008_40_07
Treatment: Calcipotriol
Subject was a 62 year old female who started treatment with calcipotriol on June 13, 2012. The subject had no relevant medical history and was receiving no concomitant medications at study entry. On Day 25 of treatment the subject experienced irritant dermatitis which lasted for 12 days. The event was assessed as moderate in severity and probably related to study medication. The subject last applied study medication on July 7, 2012 and discontinued the trial due to this event.

Heart rate increased: Subject LEO90100_35_0003_17_35
Treatment: Taclonex ® Ointment
The subject is a 47-year-old man who started treatment with calcipotriol plus BDP ointment on June 21, 2012. The subject had a medical history of stab wound to the liver. Concomitant medication included albuterol, ibuprofen and nicorette. On June 21, 2012 the subject experienced increased heart rate. Trial medication was discontinued on the same day and the subject was withdrawn from the trial due to the event. The subject recovered on June 22, 2012. The investigator considered the event to be not related to the trial medication.

This reviewer notes that other events listed for this subject include dizziness, shortness of breath, and cheek swelling. The events are listed as beginning on June 21, 2012 and the subject is noted to have recovered on June 22, 2012. In the CRF the subject is noted to have applied study medication and to have had an approved discontinuation due to adverse events.

7.3.4 Significant Adverse Events

In the pooled controlled trials (LP0053-1001, LEO 90100-7, LEO 90100-35) a total of 8 severe adverse events were reported, these included 6 events in 6 subjects (6/78 or 8% of subjects having adverse events) in the Enstilar® Foam group and 2 events in one (1/14 or 7% of subjects having adverse events) in the Taclonex® Ointment group.

The severe AEs reported for subjects exposed to Enstilar® Foam included the following:
Trial LP0053-1001
1) Cellulitis (in arm), possibly related to venipuncture in subject with history of type 2 diabetes, assessed as not related to study medication. This reviewer agrees with this assessment.

2) Substance-induced psychotic disorder, assessed as not related to study medication. This reviewer agrees with this assessment.
3) Bipolar disorder in subject with prior history of same. This was assessed as not related to study medication. This reviewer agrees with this assessment.
4) Psoriasis flare/exacerbation assessed as possibly related. This reviewer agrees with this assessment.
5) Peripheral edema (right hand swelling) on day 26 of treatment, treated with fexofenadine hydrochloride 180 mg and 1 application of triamcinolone. The event outcome was reported as resolving and the subject's treatment with trial medication was completed according to protocol one day later. This event was assessed as not related to study medication and this reviewer agrees.
Trial LEO 90100-7
6) Event of hypersensitivity/urticaria, assessed as possibly related to study medication. This event was discussed under the heading, nonfatal serious adverse events 7.3.2

The severe AEs reported for subjects exposed to Taclonex® Ointment included the following:
Trial LEO 90100-35:
1) Hypertension and bronchitis in same subject, with prior history of hypertension. On the 6th day of treatment the subject experienced hypertension and a bronchial infection and was hospitalized. The subject was lost to follow-up. The events were assessed as not related to trial medication and this reviewer agrees.

For the current submission, further details of events that may be related to study medication are presented below:

Trial LP0053-1001
Subject CRF number: 011_27: Event of "Psoriasis flare"
The subject is a 27 year old male who was treated with Enstilar® Foam once daily from July 9, 2013 to August 5, 2013. The subject was diagnosed with psoriasis 14 years ago. Areas affected included arms, trunk and legs and genitals. Past treatment history included topical steroids and vitamin D either as monotherapy or fixed combination. Current medical conditions included drug hypersensitivity (amoxicillin) and seasonal allergy. No improvement or only minor improvements of the subject's psoriasis were noted during the trial: the subject had 21% BSA involvement at baseline, 24% at Week 2, 20% at Week 3, and 21% at Week 4 (end of treatment). The investigator's assessment of disease severity was 'moderate' at all visits. The subject used in total 330.2 g LEO 90100 over 4 weeks of treatment (on average 82.6 g/week). On a follow-up visit (Aug 26, 2013) scheduled due to flank pain, which was ongoing at Visit 4, the subject reported a flare of psoriasis; the start date according to CRF was Aug 22, 2013 (i.e. 17 days after completion of treatment with LEO 90100), but according to progress notes an earlier start date, approximately 1 week after discontinuation of treatment with LEO 90100 was likely. Specifically, the subject developed redness (initially over ribs,

then spreading to stomach, chest, and arms), some cracking, and bleeding. After trying lotion, he developed 'dead, wet skin' with foul smell under the armpits. The subject was seen again on Aug 27, 2013: scalp psoriasis with cracks and bleeding on the head, thorax 90% involved, anterior and posterior with scales that diffusely shed with movement, arms 85% involved, legs 21% involvement. The subject looked 'less sick'. The subject received hydroxyzine 25 mg on Aug 26, 2013 for itch/sleeplessness. The outcome of the event(s) was reported as not recovered/not resolved at the follow–up visit on Aug 27, 2013. Causality per investigator: possibly related.

For the purposes of labeling, this event will be described as exacerbation of psoriasis since no pre-specified definition of "flare" was established in the trial protocol.

Trial LEO 90100-7:
Subject CRF number: 0001_23: Event of Hypersensitivity/urticaria
This event was discussed under the heading, nonfatal serious adverse events 7.3.2

Other Trials:

A) In trial LEO90100-30 (MUSE Trial) one severe AE was reported, erythema of the skin.

Subject CRF number: 1074
The subject was a 47 year old female treated with Enstilar® Foam once daily from Jan 29, 2013 to Feb 26, 2013 to psoriasis lesions on body and scalp. Medical history included fibromyalgia and chronic low back pain. As of Feb 15, 2013 concomitant medications included only paracetamol. On February 1, 2013, 3 days after starting treatment, the subject experienced severe erythema on the non-scalp region of the body (exact location not specified). The event was reported from the local safety and tolerability assessments at Visit 2 (Day 14) on Feb 12, 2013 where the investigator scored erythema as 'severe'; all other signs (dryness, erosion, edema) and symptoms reported by subject (burning and pain) were scored as 'absent'. On the next visit, Visit 3 (Day 28) on Feb 26, 2013, the investigator scored erythema as 'moderate'; all other signs and symptoms were 'absent'. The subject had 'moderate' disease (IGA) and total 16% BSA involvement (13% body + 3% scalp) at Visit 1 (Day 0), 'mild' (IGA) and total 7% BSA involvement (6% body + 1% scalp) at Visit 2 (Day 14), and 'almost clear' (IGA) and 2 %BSA involvement (2% body + 0% scalp) at Visit 3 (Day 28). The event was reported as resolved on the follow-up visit on Mar 13, 2013 (15 days after completion of treatment with LEO 90100). Treatment with trial medication was completed according to protocol. Causality as per investigator: probably related. This reviewer agrees with this assessment.

B) In trial LP0053-66 (dermal safety trial- combined dermal irritation and contact sensitization), 3 severe AEs were reported:
1) Rectal hemorrhage occurred in a 56 year old woman who was treated with investigational products from Sept 30, 2013 to Oct 2, 2013. On Sept 26, the subject was attacked by her ex-partner and suffered cranial, abdominal, thoracic, and perineal

trauma. On (b) (6) the subject was hospitalized due to proctorrhagia. Causality was assessed as not related to study drugs. This reviewer agrees with this assessment.
2) The subject was a 32 year old woman with a medical history of herpes labialis. Treatment with investigational products began Oct 14, 2013. Left facial paralysis (moderate intensity) and a severe headache were reported Oct 28, 2013. The subject received prednisolone 60 mg and acyclovir 1000mg. Treatment with investigational products was prematurely discontinued on Oct 29, 2013 because the subject required treatment with anti-inflammatory drugs (i.e. an exclusion criterion emerging during trial). The outcome of the event, headache, was reported as resolved on the same date. Causality per investigator: not related. This reviewer agrees with this assessment.
3) The subject was a 26 year old man treated with investigational products from Oct 14, 2013 to Nov 4, 2013 and on Nov 20, 2014 during the induction and challenge phases, respectively. On 25-Oct-2013, the subject experienced severe folliculitis on the site treated with Enstilar® Foam. Due to the adverse event, the application of Enstilar ® Foam was relocated to a new site on Oct 30, 2013 (Day 17 of trial treatment) and treatment with all investigational products was completed according to protocol. The event was reported as resolved on 16-Nov-2013. Causality per investigator: probably related. This reviewer agrees with this assessment.

7.3.5 Submission Specific Primary Safety Concerns

There are no new specific safety concerns regarding the current submission. Approved product labeling for Taclonex® Topical Suspension (August, 2014) lists folliculitis and burning sensation of skin as adverse reactions that occurred in $\geq$ 1% of subjects (with scalp psoriasis) treated with Taclonex® Topical Suspension and at a rate higher than in subjects treated with vehicle. Other less common reactions included acne, exacerbation of psoriasis, eye irritation, and pustular rash. In a 52-week study, adverse reactions that were reported by greater than 1% of subjects treated with Taclonex® Topical Suspension were pruritus, psoriasis, erythema, skin irritation, and folliculitis. For subjects with psoriasis of the body, less common adverse reactions (<1% but >0.1%) were rash and folliculitis.

Hypercalcemia and hypercalciuria have been observed with use of Taclonex® Topical Suspension. In a study of 32 subjects treated with Taclonex® Topical Suspension and Taclonex® Ointment on the body, adrenal suppression was identified in 5 of 32 subjects (15.6%) after 4 weeks of treatment.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 34: Overview of Events for the Controlled Trials

	Enstilar® Foam n = 564	BDP foam n = 99	Calcipotriol foam n = 99	Foam Vehicle n = 152	Taclonex Oint n = 134	Oint vehicle n = 51
Event	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**	**Subjects (%)**
Adverse event	78 (13.8%)	13 (13.1%)	10 (10.1%)	13 (8.6%)	14 (10.4%)	2 (3.9%)
Adverse drug reaction*	15 (2.7%)	7 (7.1%)	6 (6.1%)	2 (1.3%)	4 (3.0%)	-
Lesional/perilesional adverse events†	14 (2.5%)	5 (5.1%)	4 (4.0%)	3 (2.0%)	5 (3.7%)	-

* ADRs were defined as AEs for which the investigator had not described the causal relationship to trial medication as not related.
† A lesional/perilesional AE was defined as an AE located ≤2 cm from the border of lesion(s) treated with the trial medication; a distant AE was an AE located >2 cm from the lesion border.
Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, adapted from Table 24, p 66.

In the pooled controlled trials, at least one adverse event was reported by 78 (13.8%) of subjects in the Enstilar® Foam group, 13 (13.1%) in the BDP group, 10 (10.1%) in the calcipotriol group, 14 (10.4%), in the Taclonex® Ointment group, 13 (8.6%) in the foam vehicle group, and 2 (3.9%) in the ointment vehicle group.

For Enstilar ®, in the pooled vehicle-controlled trials, at least one adverse event was reported by 67 (14.4%) of subjects in the Enstilar® Foam group compared with 13 (8.6%) subjects in the vehicle group.

Table 35: Overview of Events for Vehicle-Controlled Trials

	Enstilar® Foam n = 464	Foam vehicle n = 152
Event	**Subjects (%)**	**Subjects (%)**
Adverse event	67 (14.4%)	13 (8.6%)
Adverse drug reaction	11 (2.4%)	2 (1.3%)
Lesional/perilesional adverse events	12 (2.6%)	3 (2.0%)

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 131, p 3.

For the pooled controlled trials, in those exposed to Enstilar® Foam, the most common adverse event was nasopharyngitis, reported for 6 (1.1%), as well as for 1 (1.0%)

subject in the BDP group, 1 (1.0%) in the calcipotriol group, and 2 (1.5%) subjects in the Taclonex (Daivobet®) Ointment group, 0 (0.0%) in the foam vehicle group, and 0 (0.0%) in the ointment vehicle group. Other adverse events experienced by ≥2 subjects in the Enstilar group, and at a rate greater than vehicle, were increased blood pressure 3 (0.5%) subjects, nausea 3 (0.5%) subjects, application site pruritus 2 (0.4%) subjects, contusion 2 (0.4%) subjects, excoriation 2 (0.4%) subjects, flank pain 2 (0.4%) subjects, and hordeolum 2 (0.4%) subjects.

In the pooled vehicle controlled trials, adverse events experienced by ≥2 subjects in the Enstilar ® group, and at a rate greater than foam vehicle were; increased blood pressure 3 (0.6%) subjects, nausea 3 (0.6%) subjects, excoriation 2 (0.4%) subjects, flank pain 2 (0.4%) subjects, and hordeolum 2 (0.4%) subjects.

LEO Grouped Terms:
The applicant created LEO grouped terms to group together preferred terms representing the same type of reaction. The following table shows how the preferred terms were grouped.

Table 36: MedDRA Primary SOC, Preferred Term and Leo Defined Grouped Term

MedDRA primary SOC	MedDRA preferred term	LEO defined grouped term
Infections and infestations	Abscess Groin abscess	Abscess
Skin and subcutaneous tissue disorders	Alopecia Alopecia effluvium	Alopecia
General disorders and administration site conditions Skin and subcutaneous tissue disorders	Application site irritation Skin irritation	Application site irritation
General disorders and administration site conditions Skin and subcutaneous tissue disorders	Application site pruritus Pruritus	Application site pruritus
Ear and labyrinth disorders Nervous system disorders	Vertigo Dizziness	Dizziness
Vascular disorders	Flushing Hot flush	Flushing
Investigations Vascular disorders	Blood pressure increased Hypertension	Hypertension
General disorders and administration site conditions Infections and infestations	Influenza like illness Influenza	Influenza
Cardiac disorders Investigations	Tachycardia Heart rate increased	Tachycardia
Infections and infestations	Tinea cruris Tinea infection	Tinea

Source: Applicant's NDA from Module 5, 5.3.5.3, Statistical Report Integrated Analysis of Safety, Table 2, p 7.

Using LEO-defined groupings, for the pooled controlled trials, events experienced by ≥2 subjects in the Enstilar® Foam group were nasopharyngitis 6 (1.1%) subjects), hypertension 4 (0.7%) subjects, and nausea 3 (0.5%) subjects. The following were reported for 2 (0.4%) subjects each; application site irritation, application site pruritus, contusion, excoriation, flank pain, flushing, hordeolum, and influenza.

For the pooled vehicle-controlled trials, using LEO-defined groupings, events experienced by ≥2 subjects in the Enstilar® Foam group were nasopharyngitis 6 (1.3%) subjects), hypertension 4 (0.9%) subjects, and nausea 3 (0.6%) subjects. The following

were reported for 2 (0.4%) subjects each; application site irritation, application site pruritus, excoriation, flank pain, flushing, hordeolum, and influenza.

Drug-Related Adverse Events

Adverse drug reactions were defined as those adverse events (AEs) where the investigator had not excluded a causal relationship to study medication (i.e. the relationship was not described as 'not related').

Adverse drug reactions were not seen in 1% or greater of subjects for any investigational drug product; Enstilar® Foam, BDP foam, calcipotriol foam, foam vehicle, Taclonex® Ointment, or ointment vehicle.

Table 37: Adverse Drug Reactions in any Treatment Group by SOC and PT for Controlled Trials

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infections and infestations						
Folliculitis	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Staphylococcal infection	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)
Tinea infection	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)
Immune system disorders						
Hypersensitivity	1 (0.2)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders						
Buccal mucosal roughening	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin & subcutaneous tissue disorders						
Alopecia	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psoriasis	1 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
Skin irritation	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Alopecia effluvium	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)
Pruritus	0 (0)	1 (1.0)	0 (0)	0 (0)	2 (1.5)	0 (0)
Dermatitis, contact	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)
General disorders & administration site conditions						
Application site pain	3 (0.5)	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.7)	0 (0)
Application site pruritus	2 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Application site discoloration	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Application site irritation	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Application site reaction	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Medication residue*	0 (0)	3 (3.0)	2 (2.0)	0 (0)	0 (0)	0 (0)
Application site erosion	0 (0)	0 (0)	1 (1.0)	1 (0.7)	0 (0)	0 (0)
Application site erythema	0 (0)	0 (0)	1 (1.0)	1 (0.7)	0 (0)	0 (0)
Application site edema	0 (0)	0 (0)	1 (1.0)	1 (0.7)	0 (0)	0 (0)
Application site dryness	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (0.7)	0 (0)
Investigations						
Blood calcium increased	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Urine calcium/creatinine ratio increased	1 (0.2)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)
Total number of drug reactions[2]	15	8	10	5	5	0
Total number of subjects	15 (2.7)	7 (7.1)	6 (6.1)	2 (1.3)	4 (3.0)	0 (0)

* "Greasy hair"
[1] Classification according to MedDRA version 15.1
[2] Different adverse drug reactions within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 50, pp 73-75.

In the pool of controlled trials, for Enstilar® Foam, adverse drug reactions occurring at a rate greater than in foam vehicle included; application site pruritus (0.4), application site irritation (0.2), skin irritation (0.2), folliculitis (0.2), application site discoloration, hypercalcemia (0.2), hypersensitivity/urticaria (0.2), psoriasis rebound effect/exacerbation (0.2), application site reaction (0.2), alopecia (0.2), and buccal mucosal roughening (0.2).

For the purposes of labeling, application site reaction and buccal mucosal roughening will not be included because the terminology is imprecise. Alopecia will not be included because it occurred in the context of product application to the scalp and the indication being sought in this submission is psoriasis of the body.

For the pool of vehicle-controlled trials, for Enstilar® Foam, adverse drug reactions occurring at a rate greater than in foam vehicle included; application site pruritus (0.4),

application site irritation (0.2), skin irritation (0.2), folliculitis (0.2), application site discoloration, hypercalcemia (0.2), and application site reaction (0.2). See following table.

Table 38: Adverse Drug Reactions in any Treatment Group by SOC and PT for Vehicle-Controlled Trials

System Organ Class (SOC)	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Preferred Term[1]	n (%)	n (%)
Infections and infestations		
Folliculitis	1 (0.2)	0 (0)
Skin & subcutaneous tissue disorders		
Psoriasis	1 (0.2)	0 (0)
Skin irritation	1 (0.2)	0 (0)
General disorders & administration site conditions		
Application site pain	2 (0.4)	1 (0.7)
Application site pruritus	2 (0.4)	0 (0)
Application site discoloration	1 (0.2)	0 (0)
Application site irritation	1 (0.2)	0 (0)
Application site reaction	1 (0.2)	0 (0)
Application site erosion	0 (0)	1 (0.7)
Application site erythema	0 (0)	1 (0.7)
Application site edema	0 (0)	1 (0.7)
Application site dryness	0 (0)	1 (0.7)
Investigations		
Blood calcium increased	1 (0.2)	0 (0)
Total number of drug reactions[2]	11	5
Total number of subjects	11 (2.4)	2 (1.3)

[1] Classification according to MedDRA version 15.1

[2] Different adverse drug reactions within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 50, pp 73-75.

Local Adverse Events

For the pooled controlled trials (LP0053-1001, LEO 90100-7, and LEO 90100-35) adverse events (AEs) were described as lesional/perilesional (local) if ≤ 2 cm from the border of lesion(s) treated with investigational product. Adverse events were described as distant if > 2 cm from the border of lesion(s) treated with investigational product.

Table 39: (Local) Lesional/perilesional AEs for Enstilar Foam at a rate greater than for Foam Vehicle (Controlled Trials)

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infections and infestations						
Impetigo	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skin & subcutaneous tissue disorders						
Alopecia	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psoriasis	1 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)
Skin irritation	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sunburn	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders & administration site conditions						
Application site pruritus	2 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Application site discoloration	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Application site irritation	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Injury, poisoning & procedural complications						
Excoriation	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total number of adverse events[2,3]	14	6	7	6	7	0
Total number of subjects	14 (2.5)	5 (5.1)	4 (4.0)	3 (2.0)	5 (3.7)	0 (0)

[1] Classification according to MedDRA version 15.1
[2] Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
[3] This table does not show all lesional/perilesional adverse events.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 52, pp 81-83.

The proportion of subjects with lesional/perilesional adverse events was similar between the Enstilar® Foam (2.5%) and foam vehicle (2.0%) groups, and was slightly less than

seen in the BDP foam (5.1%), calcipotriol foam (4.0%), and Taclonex ointment (3.7%) groups.

In the pool of controlled trials, for Enstilar® Foam, lesional/perilesional AEs occurring at a rate greater than in foam vehicle included; application site pruritus (0.4%), application site irritation (0.2%), skin irritation (0.2%), application site discoloration (0.2%), psoriasis rebound effect/exacerbation (0.2%), alopecia (0.2%), impetigo (0.2%), sunburn (0.2%) and excoriation (0.2%).

Local Adverse Events (Pooled Vehicle-Controlled Trials)
In the pool of vehicle controlled trials, for Enstilar foam, lesional/perilesional AEs occurring at a rate greater than in foam vehicle included; application site pruritus (0.4%), application site irritation (0.2%), skin irritation (0.2%), application site discoloration (0.2%), psoriasis 'rebound effect'/exacerbation (0.2%), impetigo (0.2%), sunburn (0.2%) and excoriation (0.2%).

Table 40: Local (Lesional/perilesional) AEs in any Treatment Group by SOC and PT for Vehicle-Controlled Trials

System Organ Class (SOC)	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Preferred Term[1]	n (%)	n (%)
Infections and infestations		
Impetigo	1 (0.2)	0 (0)
Skin & subcutaneous tissue disorders		
Psoriasis	1 (0.2)	0 (0)
Skin irritation	1 (0.2)	0 (0)
Sunburn	1 (0.2)	0 (0)
General disorders & administration site conditions		
Application site pain	3 (0.6)	2 (1.3)
Application site pruritus	2 (0.4)	0 (0)
Application site discoloration	1 (0.2)	0 (0)
Application site irritation	1 (0.2)	0 (0)
Application site dryness	0 (0)	1 (0.7)
Application site erosion	0 (0)	1 (0.7)
Application site erythema	0 (0)	1 (0.7)
Application site edema	0 (0)	1 (0.7)
Injury, poisoning & procedural complications		
Excoriation	1 (0.2)	0 (0)

System Organ Class (SOC)	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Preferred Term[1]	n (%)	n (%)
Total number of adverse events[2]	12	6
Total number of subjects	12 (2.6)	3 (2.0)

[1] Classification according to MedDRA version 15.1
[2] Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, adapted from Table 32, p 95.

7.4.2 Laboratory Findings

Clinical laboratory evaluations (except for urine pregnancy testing) were not performed in trials:
1) LEO 90100-01 (psoriasis plaque test)
2) LP0053-66 (Combined cumulative Irritation Potential and Repeat Insult Patch Test)
3) LP0053-69 (Vasoconstriction Study)

For the controlled trials (LP0053-1001, LEO 90100-7, LEO 90100-35)

- 25-hydroxy vitamin D was measured at baseline only
- Albumin-corrected serum calcium levels and urinary calcium:creatinine ratio in spot urine samples were assessed at baseline and Week 4

Clinical laboratory evaluations were also performed in the MUSE trial (LEO 90100-30). Please see section 7.4.5 for further discussion.

Albumin-corrected serum calcium
The applicant has defined threshold levels for concern for a clinically significant change based on the CTCAE v4.0 for grading of specific clinical laboratory results. The low threshold level for the albumin corrected serum calcium was '<2.0 mmol/L' and the high threshold level was '>2.9 mmol/L'. *Note: This reviewer finds these thresholds to be acceptable.*

Controlled Trials:
Albumin-corrected serum calcium:

Mean albumin-corrected serum calcium was similar across the treatment groups at Baseline and Visit 4 and mean changes from baseline were small (range -0.020 to 0.010 mmol/L across the groups and visits). The majority of subjects in all treatment groups had albumin-corrected serum calcium values within the normal reference range (2.15 to 2.55 mmol/L) at baseline and Week 4. A few subjects demonstrated shifts; a shift from normal at baseline to a high value at Week 4 was reported for 3 subjects in the Enstilar foam group and 1 in the Taclonex® ointment group. Of the 3 cases in the Enstilar foam group, all returned to normal or to low at follow up. None of these values crossed the threshold defined above for clinically significant elevation of albumin corrected calcium, > 2.9 mmol/L

Table 41: Albumin Corrected Serum Calcium - Subjects Having a Shift from Normal at Baseline to High at Week 4 Controlled Trials

Subject	Age	Gender	Race	Visit	Albumin corrected serum Ca (mmol/L)	Reference range
Enstilar foam: Trial LP0053 1001						
13 003 13	71	F	White	Baseline	2.40	2.15 – 2.55
				Week 4	2.58 H	2.15 – 2.55
				Follow-up	2.35	2.15 – 2.55
06 009 06	74	F	White	Baseline	2.25	2.15 – 2.55
				Week 4	2.63 H	2.15 – 2.55
				Follow-up	2.13 L	2.15 – 2.55
15 017 15	57	F	Asian	Baseline	2.38	2.15 – 2.55
				Week 4	2.60 H	2.15 – 2.55
				Follow-up	2.35	2.15 – 2.55
Taclonex oint: Trial LEO90100 35						
0009 29 35	71	M	White	Baseline	2.45	2.15 – 2.55
				Week 4	2.58 H	2.15 – 2.55

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 67, pp 71-72.

One of these cases was reported as an adverse event of mild intensity, possibly related to trial medication. This was for subject 003 13, on Enstilar foam in trial LP0053 1001, duration of event 15 days, intensity mild, 26 days since first dose, no action taken with study drug, outcome was recovered.

25-Hydroxy Vitamin D Controlled Trials

Table 42: 25-hydroxy Vitamin D at Baseline Controlled Trials

	Enstilar Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Vitamin D	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
low	441 (80.0)	82 (86.3)	87 (91.6)	120 (80.5)	121 (93.1)	44 (89.8)
normal	109 (19.8)	13 (13.7)	8 (8.4)	29 (19.5)	9 (6.9)	5 (10.2)
high	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	551 (100.0)	95 (100.0)	95 (100.0)	149 (100.0)	130 (100.0)	49 (100.0)

Source: Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 18, p 57.

At baseline, the majority (80.0 to 93.1%) of subjects had low 25-hydroxy vitamin D levels.

Regarding baseline vitamin D status, mean albumin-corrected serum calcium was similar across the treatment groups at Baseline and Visit 4 and mean changes from baseline to Visit 4 were small across the groups. See following tables.

Table 43: Change from Baseline to Week 4 in Albumin-Corrected Serum Calcium (mmol/L) by Baseline 25-Hydroxy Vitamin D Classification - Low (Controlled Trials)

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Vitamin D classification						
Low						
Baseline/# of subjects	439	81	84	120	120	43
Mean	2.298	2.280	2.310	2.296	2.308	2.310
SD	0.089	0.083	0.086	0.093	0.080	0.081
Minimum	2.05	1.93	2.10	2.10	2.15	2.15
Maximum	2.83	2.43	2.63	2.70	2.55	2.45
Week 4/# of subjects	430	79	84	117	115	43
Mean	2.293	2.294	2.299	2.271	2.301	2.297
SD	0.094	0.076	0.086	0.079	0.084	0.079
Minimum	1.83	2.13	2.10	2.10	2.10	2.13
Maximum	2.78	2.48	2.50	2.55	2.58	2.45
Change from Baseline/ # of subjects	428	78	81	117	115	42
Mean	-0.006	0.016	-0.013	-0.024	-0.006	-0.013
SD	0.093	0.095	0.081	0.086	0.081	0.096

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Vitamin D classification						
Minimum	-0.45	-0.20	-0.20	-0.35	-0.23	-0.30
Maximum	0.38	0.40	0.15	0.20	0.20	0.18

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 69, pp 81-83.

Table 44: Change from Baseline to Week 4 in Albumin-Corrected Serum Calcium (mmol/L) by Baseline 25-Hydroxy Vitamin D Classification – Normal & High (Controlled Trials)

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Vitamin D classification						
Normal						
Baseline/# of subjects	109	13	8	29	9	5
Mean	2.314	2.356	2.274	2.313	2.300	2.338
SD	0.092	0.088	0.070	0.099	0.054	0.090
Minimum	2.10	2.18	2.15	2.10	2.20	2.20
Maximum	2.80	2.55	2.35	2.50	2.35	2.43
Week 4/# of subjects	104	12	8	27	8	5
Mean	2.308	2.323	2.313	2.317	2.296	2.282
SD	0.086	0.085	0.094	0.094	0.113	0.054
Minimum	2.13	2.18	2.13	2.18	2.05	2.20
Maximum	2.75	2.48	2.45	2.53	2.40	2.35
Change from Baseline/ # of subjects	104	12	8	27	8	5
Mean	-0.006	-0.029	0.039	-0.007	0.003	-0.056
SD	0.075	0.077	0.060	0.074	0.092	0.056
Minimum	-0.20	-0.20	-0.03	-0.12	-0.15	-0.13
Maximum	0.15	0.07	0.13	0.18	0.12	0.00
High						
Baseline/# of subjects	1					
Mean	2.200					
Week 4/# of subjects	1					

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Vitamin D classification						
Mean	2.300					
High						
Change from Baseline/ # of subjects	1					
Mean	0.100					

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 69, pp 81-83.

Shifts in albumin-corrected serum calcium from normal at baseline to high at Week 4 were seen only in subjects with low 25-hydroxy vitamin D at baseline: 3 subjects in the Enstilar® Foam and 1 in the Taclonex® Ointment group.

There was no association seen between the average weekly amount of trial medication used and changes in albumin-corrected serum calcium levels from baseline to Week 4 for any of the pooled treatment groups. Usage ranges included Enstilar® Foam (2.1 – 89.7 g/week), BDP foam (5.4 – 89.0 g/week), calcipotriol foam (5.0 – 84.0 g/week), foam vehicle (2.2 – 87.7 g/week), Taclonex ointment (1.3 – 87.7 g/week), and ointment vehicle (3.4 – 77.6 g/week) [ranges from Table 11 and listings Table 66, Module 2.7.4 p. 44 and Module 5.5.5.3 pp10-70.]

Vehicle-Controlled Trials

Albumin-corrected serum calcium:

Mean albumin-corrected serum calcium was similar across both pooled treatment groups at Baseline and Visit 4 and mean changes from baseline were small, -0.005 and -0.020 mmol/L, in Enstilar foam and foam vehicle groups respectively. The majority of subjects in both treatment groups had albumin-corrected serum calcium values within the normal reference range (2.15 to 2.55 mmol/L) at baseline and Week 4. For albumin-corrected serum calcium, a shift from normal at baseline to a high value at Week 4 was reported for 3 subjects in the Enstilar foam group. Of the 3 cases in the Enstilar foam group, all returned to normal or to low at follow up. None of these values crossed the threshold defined above for clinically significant elevation of albumin corrected calcium, > 2.9 mmol/L.

Table 45: Subjects Having a Shift from Normal at Baseline to High at Week 4 Vehicle-Controlled Trials

Subject	Age	Gender	Race	Visit	Albumin corrected serum Ca (mmol/L)	Reference range
Enstilar foam: Trial LP0053 1001						
13 003 13	71	F	White	Baseline	2.40	2.15 – 2.55
				Week 4	2.58 H	2.15 – 2.55
				Follow-up	2.35	2.15 – 2.55
06 009 06	74	F	White	Baseline	2.25	2.15 – 2.55
				Week 4	2.63 H	2.15 – 2.55
				Follow-up	2.13 L	2.15 – 2.55
15 017 15	57	F	Asian	Baseline	2.38	2.15 – 2.55
				Week 4	2.60 H	2.15 – 2.55
				Follow-up	2.35	2.15 – 2.55

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 67, pp 71-72.

25-Hydroxy Vitamin D Vehicle-Controlled Trials

Table 46: 25-hydroxy Vitamin D at Baseline Vehicle-Controlled Trials

	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Vitamin D	n (%)	n (%)
low	352 (77.0)	120 (80.5)
normal	104 (22.8)	29 (19.5)
high	1 (0.2)	0 (0)
Total	457 (100.0)	149 (100.0)

Source: Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 23, p 61.

A preponderance of subjects either had low (77.0% in the Enstilar® Foam group and 80.5% in the foam vehicle group) or normal levels of 25-hydroxy vitamin D at baseline (22.8% in the Enstilar® Foam group and 19.5% in the foam vehicle group). Only one remaining subject had high 25-hydroxy vitamin D levels at baseline.

Mean and median changes in albumin-corrected serum calcium were small and similar between the Enstilar® Foam and foam vehicle groups, regardless of whether 25-hydroxyvitamin D at baseline was low, normal, or high.

The three subjects in the Enstilar® Foam group who had shifts from normal at baseline to high albumin-corrected serum calcium at Week 4 (LOCF) had low 25-hydroxy vitamin D at baseline.

There was no association seen between the average weekly amount of trial medication used and changes in albumin-corrected serum calcium levels from baseline to Week 4 for either the Enstilar® Foam or vehicle foam groups. Usage ranges included Enstilar® Foam (2.1 – 89.7 g/week) and foam vehicle (2.2 – 87.7 g/week).

Urinary calcium:creatinine ratio:

The reference range for urinary calcium:creatinine ratio is 0.255 to 8.2 mmol/g in women and 0.3 to 6.1 mmol/g in men.

Mean and median urinary calcium:creatinine ratio values were within the reference range and similar across the treatment groups at Baseline and Visit 4. Mean changes from baseline were small (range -0.191 to 0.054 mmol/L across the groups and visits). The majority of subjects in all treatment groups had urinary calcium:creatinine ratio values within the normal reference range at baseline and Week 4.

Table 47: Urinary Calcium:Creatinine Ratio Summary (Controlled Trials)

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Ca^{++}/Creatinine (mmol/g)						
Baseline/# of subjects	560	97	95	150	133	51
Mean	2.747	2.693	2.851	2.641	2.969	2.759
SD	2.949	2.310	2.768	1.980	2.487	2.095
Median	2.070	2.000	2.050	2.225	2.120	2.450
Minimum	0.17	0.17	0.32	0.12	0.22	0.15
Maximum	53.32	12.67	16.15	11.12	14.82	8.72
Week 4/# of subjects	546	95	96	146	128	49
Mean	2.819	2.597	2.898	2.420	2.730	2.584
SD	3.629	1.820	2.645	1.869	1.846	1.942
Median	2.185	2.400	2.110	1.875	2.270	2.320
Minimum	0.17	0.25	0.20	0.22	0.07	0.22
Maximum	66.67	10.47	15.00	9.12	7.82	9.22
Change from Baseline/ # of subjects	542	93	92	144	127	49
Mean	0.054	-0.038	0.018	-0.191	-0.189	-0.147
SD	2.504	2.279	2.529	1.804	1.977	2.422
Median	-0.060	0.080	0.015	-0.125	-0.150	-0.150

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Ca^{++}/Creatinine (mmol/g)						
Minimum	-15.45	-12.00	-9.65	-6.55	-8.80	-6.32
Maximum	32.85	5.00	12.18	5.40	5.30	6.85

Source: Source: Applicant's NDA from Module 2.7.4, Summary of Clinical Safety, Table 39, p 125.

Shifts from normal at baseline to a high ratio at Week 4 were seen in generally similar proportions of subjects in each pooled treatment group: 17 (17/541; 3%) subjects in the Enstilar Foam group, 1 subject (1/93; 1%) in the BDP group, 3 subjects (3/92; 3%) in the calcipotriol group, 3 subjects (3/144; 2%) in the foam vehicle group, 3 subjects (3/126; 2%) in the Taclonex® ointment group, and 1 subject (1/49; 2%) in the ointment vehicle group. See following table.

Table 48: Urinary Calcium/Creatinine Ratio - Subjects Having a Shift from Normal at Baseline to High at Week 4 Controlled Trials

Subject	Age	Gender	Race	Visit	Calcium/Creatinine ratio (mmol/g)	Reference range
Enstilar foam: Trial LEO90100 35						
0005 40 35	48	F	White	Baseline	4.300	0.22 – 8.2
				Week 4	15.950 H	0.22 – 8.2
0006 07 35	58	M	White	Baseline	5.625	0.3 – 6.1
				Week 4	11.950 H	0.3 – 6.1
0006 45 35	50	M	White	Baseline	3.975	0.3 – 6.1
				Week 4	9.375 H	0.3 – 6.1
0010 25 35	58	F	White	Baseline	0.475	0.22 – 8.2
				Week 4	33.325 H	0.22 – 8.2
Enstilar foam: Trial LP0053 1001						
001 13	68	F	White	Baseline	6.425	0.22 – 8.2
				Week 4	8.425 H	0.22 – 8.2
001 20	74	M	White	Baseline	4.900	0.3 – 6.1
				Week 4	6.200 H	0.3 – 6.1
001 21	38	M	White	Baseline	5.125	0.3 – 6.1
				Week 4	6.775 H	0.3 – 6.1

001 25	68	M	White	Baseline	4.475	0.3 – 6.1
				Week 4	7.050 H	0.3 – 6.1
002 03	44	M	White	Baseline	1.400	0.3 – 6.1
				Week 4	6.450 H	0.3 – 6.1
005 13	37	M	White	Baseline	6.050	0.3 – 6.1
				Week 4	8.750 H	0.3 – 6.1
006 06	50	F	White	Baseline	3.800	0.22 – 8.2
				Week 4	8.700 H	0.22 – 8.2
006 19	51	F	White	Baseline	4.900	0.22 – 8.2
				Week 4	8.250 H	0.22 – 8.2
008 05	51	M	Asian	Baseline	5.950	0.3 – 6.1
				Week 4	10.075 H	0.3 – 6.1
008 13	64	M	White	Baseline	2.750	0.3 – 6.1
				Week 4	6.175 H	0.3 – 6.1
008 29	60	M	White	Baseline	1.700	0.3 – 6.1
				Week 4	7.325 H	0.3 – 6.1
013 03	66	M	Amer. Indian or Alaska Native	Baseline	4.050	0.3 – 6.1
				Week 4	6.575 H	0.3 – 6.1
0202 09	53	M	Native Hawaiian or Other Pacific Islander	Baseline	5.200	0.3 – 6.1
				Week 4	7.275 H	0.3 – 6.1
BDP Foam: Trial LEO90100-7						
0010 02 07	64	M	White	Baseline	2.575	0.3 – 6.1
				Week 4	7.575 H	0.3 – 6.1
Calcipotriol foam: Trial LEO90100-7						
0006 23 07	58	M	White	Baseline	1.975	0.3 – 6.1
				Week 4	7.050 H	0.3 – 6.1
				Follow-up	4.625	0.3 – 6.1
0008 06 07	71	F	White	Baseline	2.825	0.22 – 8.2

				Week 4	15.000 H	0.22 – 8.2
0014 29 07	65	M	White	Baseline	4.875	0.3 – 6.1
				Week 4	6.525 H	0.3 – 6.1
Foam vehicle: Trial LEO90100 35						
0004 37 35	64	M	White	Baseline	4.300	0.3 – 6.1
				Week 4	6.525 H	0.3 – 6.1
Foam vehicle: Trial LP0053 1001						
002 05	46	M	White	Baseline	5.300	0.3 – 6.1
				Week 4	7.275 H	0.3 – 6.1
028 27	41	M	White	Baseline	4.200	0.3 – 6.1
				Week 4	6.300 H	0.3 – 6.1
Taclonex oint: Trial LEO90100 35						
0007 45 35	52	M	White	Baseline	1.875	0.3 – 6.1
				Week 4	6.200 H	0.3 – 6.1
0011 24 35	48	M	White	Baseline	5.775	0.3 – 6.1
				Week 4	6.750 H	0.3 – 6.1
0012 47 35	39	M	White	Baseline	6.100	0.3 – 6.1
				Week 4	6.625 H	0.3 – 6.1
Ointment vehicle: Trial LEO90100 35						
0001 24 35	60	M	White	Baseline	5.400	0.3 – 6.1
				Week 4	9.225 H	0.3 – 6.1

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 68, pp 73-80.

Baseline 25-Hydroxy Vitamin D Classification and Urinary Calcium:Creatinine Ratio
The majority of subjects (from 80.0% to 93.1%) in all pooled treatment groups had low levels of 25-hydroxy vitamin D at baseline. See Table 42 above

Table 49: Change from Baseline to Week 4 in Urinary Calcium:Creatinine Ratio (mmol/g) by Baseline 25-Hydroxy Vitamin D Classification - Low (Controlled Trials)

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Vitamin D classification						
Low						
Baseline/# of subjects	440	81	85	119	121	44
Mean	2.689	2.725	2.908	2.553	3.063	2.992

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Vitamin D classification						
SD	3.089	2.389	2.820	1.911	2.559	2.106
Week 4/# of subjects	428	79	84	117	115	42
Mean	2.870	2.718	2.758	2.353	2.727	2.782
SD	3.984	1.921	2.375	1.751	1.821	1.986
Change from Baseline/ # of subjects	427	78	82	116	115	42
Mean	0.163	0.044	-0.183	-0.140	-0.290	-0.189
SD	2.551	2.351	2.172	1.777	1.927	2.570
Median	-0.030	0.105	-0.010	-0.090	-0.170	-0.215
Minimum	-9.50	-12.00	-9.65	-6.03	-8.80	-6.32
Maximum	32.85	5.00	5.08	5.40	5.30	6.85

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 72, pp 86-88.

Mean changes in urinary calcium:creatinine ratio from baseline to Week 4 were generally small and similar across the pooled treatment groups, regardless of whether subjects had low or normal 25- hydroxy vitamin D at baseline. See Table above. An exception to the previous was a small subgroup of subjects with normal baseline 25-hydroxy vitamin D in the calcipotriol group (n=7), where the mean change was 2.483 mmol/g; the median change in this group was 0.900 mmol/g. See Table below.

Table 50: Change from Baseline to Week in Urinary Calcium:Creatinine Ratio (mmol/g) by Baseline 25-Hydroxy Vitamin D Classification – Normal & High (Controlled Trials)

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Vitamin D classification						
Normal						
Baseline/# of subjects	108	13	7	29	9	5
Mean	2.804	2.850	2.014	2.926	2.176	1.660
SD	1.865	1.997	1.454	2.292	1.468	1.493
Week 4/# of subjects	104	12	8	26	9	5
Mean	2.694	2.158	4.575	2.783	2.511	1.664
SD	1.884	1.056	4.709	2.417	1.968	1.264

	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Vitamin D classification						
Change from Baseline/ # of subjects	103	12	7	26	9	5
Mean	-0.152	-0.746	2.483	-0.298	0.336	0.004
SD	1.805	1.982	4.983	1.967	2.069	1.561
Median	-0.150	-1.125	0.900	-0.315	0.050	-0.250
Minimum	-5.95	-4.47	-1.80	-6.55	-3.47	-1.67
Maximum	4.30	2.35	12.18	5.13	3.92	2.48
High						
Baseline/# of subjects	1					
Mean	2.100					
Week 4/# of subjects	1					
Mean	2.220					
High						
Change from Baseline/# of subjects	1					
Mean	0.120					

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 72, pp 86-88.

Urinary Calcium:Creatinine Ratio Vehicle-Controlled Trials

Mean and median values for urinary calcium:creatinine ratio were within the normal ranges at baseline and Week 4 for both treatment groups . The mean urinary calcium:creatinine ratio increased slightly in the Enstilar® Foam group (0.146 mmol/g) and decreased slightly in the foam vehicle group (-0.191 mmol/g) from baseline.

Table 51: Urinary Calcium:Creatinine Ratio Summary (Vehicle-Controlled Trials)

	Enstilar® Foam	Foam Vehicle
	N = 564	N = 152
Ca^{++}/Creatinine (mmol/g)		
Baseline/# of subjects	461	152
Mean	2.740	2.641
SD	3.152	1.980
Median	2.070	2.225

	Enstilar® Foam	Foam Vehicle
	N = 564	N = 152
Ca^{++}/Creatinine (mmol/g)		
Minimum	0.17	0.12
Maximum	53.32	11.12
Week 4/# of subjects	450	146
Mean	2.903	2.420
SD	3.923	1.869
Median	2.210	1.875
Minimum	0.17	0.22
Maximum	66.67	9.12
Change from Baseline/ # of subjects	447	144
Mean	0.146	-0.191
SD	2.642	1.804
Median	0.020	-0.125
Minimum	-15.45	-6.55
Maximum	32.85	5.40

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, Table 150, p 7.

The majority of subjects in both pooled treatment groups had a normal urinary calcium:creatinine ratio at baseline and Week 4. Shifts from normal at baseline to a high ratio at Week 4 were observed in 17 subjects in the LEO 90100 group and 3 subjects in the foam vehicle group. See Table 48 previous.

Table 52: Change from Baseline to Week 4 in Urinary Calcium:Creatinine Ratio (mmol/g) by Baseline 25-Hydroxy Vitamin D Classification - Low (Vehicle-Controlled Trials)

	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Vitamin D classification		
Low		
Baseline/# of subjects	351	119
Mean	2.685	2.553
SD	3.360	1.911

	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Vitamin D classification		
Median	2.050	2.070
Minimum	0.20	0.12
Maximum	53.32	10.45
Week 4/# of subjects	343	117
Mean	2.993	2.353
SD	4.366	1.751
Median	2.220	1.850
Minimum	0.17	0.30
Maximum	66.67	7.50
Change from Baseline/ # of subjects	342	116
Mean	0.289	-0.140
SD	2.722	1.777
Median	0.070	-0.090
Minimum	-9.50	-6.03
Maximum	32.85	5.40

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 155, pp 14-16.

For subjects having low 25-hydroxy vitamin D level at baseline, the mean urinary calcium:creatinine ratio increased in the Enstilar foam group (mean change: 0.289 mmol/g) and decreased in the foam vehicle group (mean change: -0.140 mmol/g). Median change values are noted to be closer to zero and more similar between the treatment groups (0.070 mmol/g and -0.090 mmol/g, respectively).

For subjects having normal 25-hydroxy vitamin D at baseline, the urinary calcium:creatinine ratio decreased from baseline to Week 4 in both treatment groups (mean change: -0.110 mmol/g in the Enstilar foam group and -0.298 mmol/g in the foam vehicle group). See following table.

Table 53: Change from Baseline to Week 4 in Urinary Calcium:Creatinine Ratio (mmol/g) by Baseline 25-Hydroxy Vitamin D Classification – Normal & High (Vehicle-Controlled Trials)

	Enstilar® Foam	Foam Vehicle
	N = 464	N = 152
Vitamin D classification		
Normal		
Baseline/# of subjects	103	29
Mean	2.735	2.926
SD	1.856	2.292
Median	2.070	2.670
Week 4/# of subjects	99	26
Mean	2.666	2.783
SD	1.904	2.417
Median	2.200	1.950
Change from Baseline/ # of subjects	98	26
Mean	-0.110	-0.298
SD	1.792	1.967
Median	-0.110	-0.315
Minimum	-5.95	-6.55
Maximum	4.30	5.13
High		
Baseline/# of subjects	1	
Mean	2.100	
Week 4/# of subjects	1	
Mean	2.220	
High		
Change from Baseline/# of subjects	1	
Mean	0.120	

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 155, pp 14-16.

7.4.3 Vital Signs

Vital signs (blood pressure and heart rate) were collected at baseline and Week 4 in the three controlled trials (LP0053-1001, LEO 90100-7, and LEO 90100-35) and in the MUSE trial (Trial LEO 90100-30). In the vasoconstriction trial (LP0053-69), vital signs were collected at baseline and Day 2. Vital signs were not reported in the dermal safety trial (LP0053-66) or the exploratory psoriasis plaque test trial (LEO 90100-01).

For the pool of controlled trials, changes in mean and median blood pressure (systolic and diastolic) and heart rate were small and similar across treatment groups. Similar findings were noted for the pool of vehicle controlled trials (LP0053-1001, and Enstilar foam and foam vehicle arms from trial LEO 90100-35). Clinically significant changes from baseline in mean and median vital signs were not seen in the MUSE (LEO 90100-30) or the vasoconstriction trial (LP0053-69).

7.4.4 Electrocardiograms (ECGs)

Information Pertinent to Moieties (calcipotriene & betamethasone):
To support approval of Taclonex® Topical Suspension for the treatment of scalp psoriasis in adults, the applicant collected ECGs as part of the safety monitoring during Trial MBL 0404 FR. Mean changes seen in QT and QTc were assessed as not clinically significant. Both calcipotriene and betamethasone were evaluated for cardiovascular effects in nonclinical studies. No effects were seen on cardiac parameters including ECGs following oral dosing to conscious telemetered dogs or in repeated dose toxicology studies in minipigs. See Pharmacology/Toxicology Review by Norman See, Ph.D. dated 2/20/2008 for an evaluation of the preclinical data.

Current NDA (Enstilar ® Foam):
Regarding the current application, ECG's were not collected in the controlled Trials LP0053-1001, LEO 90100-7, LEO 90100-35. ECG' s were also not collected in the MUSE trial (Leo 90100-30), the dermal safety trial (LP0053-66), the vasoconstriction trial (LP0053-69), or the exploratory psoriasis plaque trial (LEO90100-01).

In the current application, Module 1.12.5, the applicant requests a waiver for the conduct of a thorough QT study. The rationale includes the following:
1) No current data indicate an effect of corticosteroids on cardiac repolarisation or an association with cardiac arrhythmias. When given as single oral dose to telemetrised dogs, betamethasone dipropionate had no effect on electrocardiograms (ECG), heart rate, or cardiac conduction times including QT interval. (See also above.)

2) Regarding calcipotriene, when given as single oral dose to telemetrised dogs, calcipotriene had no effect on ECG, heart rate, or cardiac conduction times including QT interval. (See also above.)

3) Pharmacokinetic data from the maximum use systemic exposure (MUSE) trial in subjects with extensive plaque psoriasis (LEO90100-30) demonstrated low quantifiable plasma levels of calcipotriene, and its metabolite MC1080, in only a few subjects. In this trial there was no evidence of an effect of LEO 90100 on calcium metabolism after daily topical application of LEO 90100 for up to 4 weeks, indicating no or only minimal systemic exposure.

4) There is no published literature describing an association between calcipotriene and human cardiac arrhythmias. The applicant conducted a search of LEO Pharma's post-marketing safety database (containing approximately 5800 post-marketing case reports concerning the calcipotriene-containing products) through 26 June 2014 for all marketed calcipotriene-containing products (Dovonex® cream, Dovonex® ointment, Dovonex® solution, Taclonex® Ointment, Taclonex® Topical Suspension) under the MedDRA System Organ Class (SOC) term Cardiac Disorders, and retrieved 18 case reports. The applicant further screened cases of potential cardiac arrhythmia to only include patients with a diagnosis of a specific arrhythmia. Based on this criterion, 5 case reports were identified.

The 5 cases do not give evidence of a clinically significant safety signal. The cases either do not include enough evidence, do not indicate a link between use of calcipotriene and arrhythmia, or are confounded by a preceding history of arrhythmia or comorbid condition such as hypertension or anemia and use of concomitant medications.

The Division accepts the request for a waiver to submit data from a thorough QT/QTc study on the basis of low systemic exposure and no evidence of a relevant safety signal for the moieties calcipotriene & betamethasone.

It is noted that a waiver to submit data from a thorough QT/QTc study was granted for Sorilux™ (calcipotriene) Foam, 0.005% (NDA 22-563) on the basis of low systemic exposure and no evidence of a relevant safety signal for the moiety.

7.4.5 Special Safety Studies/Clinical Trials

For the current application, the applicant conducted two special safety trials:
1) Trial LP0053-66 (dermal safety trial)
2) Trial LEO 90100-30 MUSE trial

1) LP0053-66: "A phase 1 study evaluating the skin irritation potential and sensitisation potential of LEO 90100 aerosol foam and the aerosol foam vehicle after repeated applications to the skin of healthy subjects"

Objective: The primary objective of the trial was to determine the skin irritation potential and sensitization potential of Enstilar® Foam and the foam vehicle after repeated applications on the skin of healthy subjects.

Study Design: Single-center, prospective, randomized, investigator-blinded, vehicle- and negative controlled phase 1 trial with intra-individual comparison in healthy subjects of the following test articles:

- Enstilar® Foam
- Foam vehicle
- White petrolatum; negative control

Number of healthy volunteers enrolled: 218 subjects enrolled; 214 completed the trial

Study Methodology: The trial consisted of a screening phase (up to 6 weeks), an induction phase (3 weeks), a rest phase (2 weeks), and a challenge phase (5 or 6 days).
Each subject received under semi-occlusive conditions (patches):

- Enstilar® Foam: 122mg (corresponding to 50 mg per dose after evaporation of the propellants)
- Foam vehicle: 122mg
- White petrolatum: 50 mcl

The test sites were covered by semi-occlusive patches consisting of a thin 2×2 cm piece of non-woven compress maintained on the skin surface with a 5×5 cm piece of kind removal, breathable, hypoallergenic medical tape with silicone adhesive, standard roll (Micropore Silicone 3M tape). The patch was semi-occlusive to allow the propellants in the aerosol foam to evaporate after application.

Induction Phase (Days 1 to 21):
During the 21-day induction phase, each subject received 15 applications on small test areas (4 cm^2) on the skin of each investigational product distributed as 5 applications per week (every day except weekends). Throughout the induction phase, each investigational product was applied on the same test site on the subject's middle back under semi-occlusive conditions. The dermal response was scored by a qualified evaluator using a 0 to 4 point standardized visual assessment scale (0, 0.5, 1, 2, 3, and 4) 30 minutes after removal of each semi-occlusive patch.

0 No response
0.5 Questionable or faint, indistinct erythema
1 Well-defined erythema
2 Erythema with slight to moderate oedema
3 Vesicles (small blisters) or papules (small circumscribed elevations)
4 Bullous (large blisters), spreading or other severe reaction

Cumulative Irritancy Index (CII) = sum of clinical scores across readings (Day 22)/number of readings

The Mean Cumulative Irritancy Index (MCII) = average of individual CIIs across subjects.

Rest Phase (Days 22 to 35)
This was a 2 week period during which no test product was applied.

Challenge Phase (Days 36 to Day 40/Day 41 if applicable):
Each investigational product was applied to a treatment-naive skin test site on the subject's upper back under semi-occlusive conditions for 48 hours. The dermal response was scored using a 6-point standardized visual assessment scale 30 minutes, 24, and 48 hours (potentially at 72 hours at the investigator's discretion) after removal of each semi-occlusive patch. During the challenge phase dermal responses were scored According to the following scale:

- No reaction
?+ Doubtful reaction (faint erythema only)
+ Weak positive reaction (erythema, infiltration, possibly papules)
++ Strong positive reaction (erythema, infiltration, papules, vesicles)
+++ Extreme positive reaction (intense erythema and infiltration and coalescing vesicles or bullae)
IR Irritant reaction
NT Not tested

At the last dermal response score, 48 hours after removal of the patch (Day 40), the the (sub)investigator (certified dermatologist) gave her/his opinion concerning a possible sensitization reaction of each test site taking into account all skin assessments performed during the challenge phase, using the following scale:

0: Negative
1: Equivocal
2: Positive

The investigator was to provide a narrative description of each positive sensitization reaction. If a sensitization reaction evaluation was equivocal, aa additional assessment could be performed at the investigator's discretion at 72 hours after patch removal (Day 41).

Rechallenge Phase (approximately Days 55 to 59):
Any subject with a sensitization reaction assessed as equivocal was to be re-challenged once after approximately 2-week rest period using a new naive test site, under the same conditions as for Day 36 in the challenge phase.

Results:
A total of 224 subjects were enrolled into the trial of which 218 were randomized (3 screening failures and 2 withdrawals of consent). A total of 214 subjects completed the trial; 4 subjects withdrew – one due to an SAE (rectal hemorrhage) on Day 3, one had a protocol violation (requiring treatment with anti-inflammatory) on Day 16, one withdrew voluntarily on Day 16, and one subject was lost to follow up after Day 1.

Table 54: Maximal Dermal Response Category during Induction Phase

	Enstilar Foam	Foam Vehicle	White petrolatum
	N = 213	N = 213	N = 213
Maximal dermal response/scale category	n (%)	n (%)	n (%)
No response (0)	76 (35.7)	148 (69.5)	161 (75.6)
Questionable or faint, indistinct erythema (0.5)	92 (43.2)	61 (28.6)	48 (22.5)
Well-defined erythema (1)	42 (19.7)	4 (1.9)	4 (1.9)
Erythema with slight to moderate edema (2)	3 (1.4)	0 (0.)	0 (0.)
Total	213 (100)	213 (100)	213 (100)

Source: Applicant's NDA from Module 5.3.5.4, Clinical Study Report Trial LP0053-66, Table 10, p 64.

The majority of subjects had a maximum dermal response score of 0 ('no response') or 0.5 ('questionable or faint, indistinct erythema'), reported for 168 (78.9%) subjects after application of Enstilar foam and 209 (98.1%) subjects after application of the aerosol foam vehicle and, again, 209 (98.1%) subjects after application the negative control.

The highest reported dermal response score was 2 ('erythema with slight to moderate edema'), found in 3 (1.4%) subjects after application of Enstilar® Foam.

The mean CII (MCII) during the induction phase was 0.102 for Enstilar foam, 0.019 for the foam vehicle, and 0.018 for the negative control (white petrolatum). These results, according to the applicant, are consistent with a low skin irritation potential for Enstilar® Foam and no irritation potential for the foam vehicle and the negative control. The applicant speculates that the slightly higher score for Enstilar® Foam is due to the presence of calcipotriol which is known to cause local irritation in some subjects.

Reportedly, the results in the present trial are in line with findings from previously conducted trials of similar designs that investigated the skin irritation potential and skin sensitization potential of Daivobet® (Taclonex) ointment versus ointment vehicle

At the end of the challenge phase (Day 40), the (sub) investigator evaluated each test site for possible sensitization reactions using a 3-point scale as described above. In the opinion of the investigator there were no signs/symptoms that were suggestive of an equivocal/positive sensitization reaction. Therefore, all subjects were concluded to have a 'negative' response. Since, in the opinion of the investigator, were no equivocal reactions, none of the subjects was re-challenged. There was no evidence of a sensitization reaction for any subject for Enstilar foam, foam vehicle, or white petrolatum.

Conclusion: Under the conditions of the study, Enstilar® Foam showed no potential for sensitization and repeated applications revealed limited potential for irritancy.

Adverse Events:
There were no deaths in the trial. One SAE was reported Rectal hemorrhage) and led to withdrawal from the trial. The SAE was assessed as having no relation to investigational product. No other AEs led to discontinuation from treatment or trial. The vast majority of the AEs were mild or moderate in severity. A total 3 AEs were rated as severe, folliculitis, headache, and rectal hemorrhage (also an SAE).

A total of 86 (39.6%) subjects reported 116 AEs. The most frequently reported AEs were nasopharyngitis and folliculitis, both reported by 20 (9.2%) subjects and headache, reported by 27 subjects (12.4%).

AEs on the application areas were those AEs judged by the investigator as located within 2 cm from the border of test site treated with investigational product. In this clinical trial, all AEs localized on the application areas were evaluated by the investigator as having a possible or probable relation to treatment, and all ADRs were localized on the application areas. Therefore, ADRs and AEs localized on the application areas were identical.

A total of 31 AEs were localized to the application areas and consisted of 20 events of folliculitis (12 mild, 7 moderate, 1 severe), 8 events of pruritus (5 mild, 3 moderate), 2 events of urticaria (I mild, 1moderate), and 1 event of skin irritation (mild). The majority of events (29 of 31) were reported after application of Enstilar foam. The 2 other events (urticaria (moderate) and skin irritation (mild)) were reported after application of the foam vehicle. The vast majority of AEs on the application areas were mild (19 events) or moderate (11 events) in intensity. One AE was evaluated as severe and concerned folliculitis reported after application of Enstilar foam. The reported outcome was 'recovered' after 23 days. The applicant speculates that the 20 events of folliculitis were due to the use of Enstilar® Foam under semi-occlusive conditions. In the Phase 2 and 3

trials, only one case of folliculitis was reported out of 564 subjects treated with Enstilar® Foam.

2) LEO 90100-30: "Effect of LEO 90100 on the HPA axis and Calcium Metabolism in Subjects with Extensive Psoriasis Vulgaris"

The trial was conducted at 8 sites located in Canada

Please also see Clinical Pharmacology Review (dated 8/24/2015) by Chinmay Shukla, PhD, DCP-3

Study Objectives:
Primary:
- To evaluate the effect of once daily use of Enstilar® Foam (LEO 90100) on the hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism in subjects with extensive psoriasis vulgaris

Secondary:
- To evaluate other safety aspects of Enstilar® Foam used once daily in subjects with extensive psoriasis vulgaris.
- To assess the pharmacokinetic (PK) profile of the active components and major metabolites of Enstilar® Foam following topical application under maximal use conditions.
- To evaluate the efficacy of Enstilar® Foam used once daily in extensive psoriasis vulgaris.

Subject Population:
Subjects of either sex, aged 18 years or above with psoriasis vulgaris involving trunk and/or limbs and scalp amenable to topical treatment with a maximum of 120 g of study medication per week, with a total extent on scalp and trunk/limbs of 15- 30% of body surface area (BSA) excluding face, genitals and skin folds, and including at least 30% scalp involvement. Disease severity on the trunk/limbs graded as at least moderate according to the IGA. Normal HPA axis function at baseline and albumin corrected serum calcium below the upper limit of the reference range.

Number of Subjects:
A total of 37 subjects were enrolled and started treatment with Enstilar® Foam; 35 subjects completed the trial as per protocol.

Duration of Treatment: 4 weeks

Study Design/Methodology:

This was a multi-center, prospective, non-controlled, open, single-group, 4-week study in subjects with extensive psoriasis vulgaris. Subjects received once daily topical treatment with Enstilar® Foam on all lesions on the trunk, limbs and scalp (excluding skin folds, face, and genitals) for up to 4 weeks.

The study consisted of a screening period (up to 56 days) followed by a 28 day treatment phase, and a 28 day follow-up phase. Screening visits were performed at Day-56 to -7 (SV1), and between Day -7 and Day-3 (SV2). Treatment start was Day 0 (Visit 1). On-treatment visits were Days 14 and 28 (Visits 2 and 3).

Subjects classified as 'Clear' (according to IGA at Day 14 (Visit 2)) were allowed to stop treatment at the investigator's discretion. Subjects remained in the study and were to attend Day 28 (Visit 3). If their psoriasis reappeared subjects were advised to reinitiate the treatment without consulting the investigator.

Adverse events were recorded at all visits except Day -56 to -7 (SV1). Psoriasis on the body was assessed by the investigator's global assessment of disease severity (IGA) at Day -7 to -3 (SV2) and Day 28 (Visit 3).

Pharmacokinetic Assessments:
Plasma levels of calcipotriol and betamethasone dipropionate and their main metabolites (MC1080 and betamethasone 17-propionate, respectively) were determined. Plasma samples were collected for PK at baseline (SV2) prior to the ACTH challenge test. Pre-dose trough samples were collected on Day 14 (Visit 2) and Day 28 (Visit 3) and then serial samples were obtained up to 7 hours post-application of study treatment on Day 28 (Visit 3).

Pharmacodynamic Assessments:
HPA axis testing by means of the rapid standard-dose cosyntropin test was conducted at baseline (SV2) and at Day 28 (Visit 3). Serum cortisol levels were evaluated before stimulation and 30 and 60 minutes after stimulation.

Effect on calcium metabolism was evaluated by measurements of albumin corrected serum calcium, serum phosphate and ALP, plasma PTH, 24 hour urinary excretion of calcium, phosphate, creatinine, as well as urinary calcium:creatinine and phosphate:creatinine ratios at baseline (SV2) and Day 28 (Visit 3).

Results:
Study Population:
Of the 57 screened subjects, 37 were found to be eligible and started treatment with Enstilar® Foam at Visit 1. Two subjects were withdrawn from treatment after 14 days (at/after Visit 2); one due to failure to meet the eligibility criterion for serum cortisol following the ACTH challenge at baseline (Subject 1023), and one due to prohibited concomitant medication (Subject 1028). The remaining 35 subjects completed 28 (±2)

days of treatment as per protocol. Two subjects had a follow-up visit; Subject 1023 who was withdrawn due to an exclusionary serum cortisol level was re-tested 28 days after end of treatment (FU2), and Subject 1074 had a follow up on an AE (erythema) 14 days after end of treatment (FU1).

Full Analysis Set/Safety Analysis Set:
The full analysis set was comprised of all subjects that received trial medication and included 37 subjects. All subjects who received treatment (full analysis set) provided safety data and therefore the safety analysis set consisted of 37 subjects and was identical to the full analysis set.

Demographics:
The trial included 20 (54.1%) men and 17 (45.9%) women, with the mean age of 48 years (median 49 years; range: 21 to 76 years). Most subjects were White (81.1%), and all but one subject (97.3%) self-reported Non-Hispanic or Latino ethnicity. The mean weight of subjects in the safety analysis set was 89.7 kg (range 52 to 125 kg) and the mean BMI was 31.1 kg/m^2 (range 21 to 57 kg/m^2).

Baseline Disease-Related Data:
All subjects included in the trial had a diagnosis of psoriasis vulgaris, with average disease duration of 16 years (range 1 to 41 years). At baseline, approximately three quarters of subjects had 'moderate' disease and the remaining one quarter had 'severe' disease according to the IGA of the trunk, limbs and scalp. The mean extent of the psoriasis on the trunk and limbs was 17.5% (range 12 to 28%) and the mean extent of psoriasis on the scalp was 50.2% of the scalp area (range 30 to 100%). (The mean baseline total extent of psoriasis was 20.9% BSA with a minimum of 16% to a maximum 30%, which was in compliance with the protocol.)
Comment from Clinical Pharmacology Reviewer:
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.

Table 55: IGA at Baseline

	Safety Analysis Set n= 37
Baseline IGA	**subjects (%)**

Moderate	28 (75.7)
Severe	9 (24.3)
Total	37 (100)

Source: Applicant's NDA, Module 5.3.4.2, Clinical Study Report LEO 90100-30, Table 14, p 71.

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

The mean duration of treatment with Enstilar® Foam was 28 days (range 14 to 35 days). Based on data from the 32 subjects who returned the trial medication and for whom the weigh data were available, the mean amount of Enstilar® Foam used per week over the total treatment period was calculated to 62 g. The mean total amount of trial medication used during the entire treatment period was 256 g (range 58.0 to 467 g).

[For NDA 22-85/S-10 maximal use study LEO 80185-G24 (Taclonex® topical suspension), it is noted that the mean weekly amount of study drug used was 49.63 g (range 6.08 to 90.45 g) during the first 4 weeks and 51.36 g (range 6.98 to 89.03 g) in the second 4 weeks. The mean weekly amount used in the total treatment period was 52.27 g (range 7.64 to 92.95 g). In the original application for NDA 22-185 (maximal use HPA Axis study MBL 0404 FR), the mean weekly amount of Taclonex topical scalp product used was 23.7 grams; the mean amount of Taclonex ointment used was 40.2 grams.]

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.

Since LEO 90100-30 was an open label study, this efficacy data will have minimal utility for labeling.

Pharmacokinetics:
The results indicated that plasma concentrations were below lower limit of quantification (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 1 below. For calcipotriol only 1 subject had quantifiable plasma levels and no PK parameters could be reliably determined.

The plasma concentrations of metabolite betamethasone 17-propionate were quantifiable in 27 out of 35 subjects (See table below):

Table 56: Summary of PK Parameters (Subjects with Quantifiable Plasma Concentrations)

Analyte	Number of subjects	C_{max} (pg/ml) Range (-)	AUC_{last}(h*pg/ml) Range (-)
betamethasone dipropionate (BDP)	5	52.2 (33.7 -81.1)	36.5 (16.9 -82.5)
betamethasone 17-propionate	27	148 (30.2-1133)	68.4 (18.5-4254)
calcipotriol	1	N.C	N.C
MC1080	3	24.4 (23.3-26.6)	59.3 (55.3-65.5)

N.C. = A parameter that could not be reliably estimated.
Source: Applicant's NDA, Module 5.3.4.2, Clinical Study Report LEO 90100-30, Table 45, p 99.

Pharmacodynamics:
HPA axis suppression results: 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 at Day 28 (Visit 3). 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.

Effect on calcium metabolism:
There was no significant mean change from baseline to Day 28 in albumin-corrected serum calcium, 24-hour urinary calcium excretion or the urinary calcium:creatinine ratio. No subjects developed elevated serum or urinary calcium levels above the normal range following treatment with Enstilar foam.

There was no clinically relevant mean change in the other serum and urinary parameters assessed in the study for the evaluation of calcium metabolism including serum phosphate, serum ALP, plasma PTH, 24-hour urinary phosphate excretion and urinary phosphate:creatinine ratio. Likewise there were no individual changes of concern in any of these parameters.

Adverse Events:
No deaths, SAEs, discontinuation of investigational product due to AEs or other significant AEs were reported in this trial. After study treatment had started, 4 (10.8%) subjects reported 6 AEs.

Table 57: Adverse Events – Incidence and Severity

	Enstilar® Foam	AE Intensity		
	N = 37	Mild	Moderate	Severe
Preferred Term	n (%)			
Fungal infection	1 (2.7)	X		
Arthralgia	1 (2.7)		X	
Headache	1 (2.7)		X	
Oropharyngeal pain	1 (2.7)	X		
Upper-airway cough syndrome	1 (2.7)	X		
Erythema	1 (2.7)			X

Source: Applicant's NDA, Module 5.3.4.2, Clinical Study Report LEO 90100-30, adapted from Table 49, p 105 and Table 3-5, p. 172.

Of the adverse events one (erythema) was considered by the Investigator to be probably related to study medication. This AE was also classified as lesional/perilesional. The remaining 5 adverse events were not considered to be related to study medication and were also not classified as perlesional.

Other Safety Observations:
Vital signs: Vital signs (blood pressure, heart rate) were assessed and the physical examination done at screening (SV2) and then at Day 28 (Visit 3). No clinically significant abnormalities in vital signs were noted during the trial.

Hematology: The hematology parameters assessed in this trial included hemoglobin, hematocrit, red blood cell (RBC) count, mean corpuscular volume (MCV), white blood cell (WBC) count, including differential count and platelets. Mean changes in the hematology parameters from baseline (SV2) to Visit 3 (Day 28) were small and not clinically significant. Individual clinically significant abnormalities were not seen.

Clinical Biochemistry: The clinical biochemistry parameters assessed in this trial included urea, creatinine, sodium, potassium, and chloride in serum, in addition to serum and urine markers of calcium metabolism. Mean changes in the biochemistry parameters from baseline (SV2) to Visit 3 (Day 28) were small and not considered to be clinically significant. Individual clinically significant abnormalities were not seen.

Urinalysis: Urine glucose and urine ketones were evaluated in spot urine samples (dip stick). Qualitative results for urine glucose and urine ketones (dip stick) were reported as negative for majority of subjects both at baseline and after treatment. Two subjects had traces of glucose (baseline1155, 1055 baseline and Day 28) and 2 subjects had traces of ketones (1156 & 1121 both baseline and Day 28). One subject (No. 1028, withdrawn at Day 14 due to use of prohibited concomitant medication) had 3+ glucose in urine at the end of treatment.

7.4.6 Immunogenicity

This is not applicable since the drug is not a therapeutic protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In each of the pooled controlled trials, subjects were provided with a maximum of 90 g of trial medication per week. Based on the average weekly amount of trial medication used, all adverse events were grouped into two categories: adverse events reported for subjects using <40 g/week and for subjects using ≥40 g/week.

Table 58: Adverse Events Occurring in ≥ 0.5% of Subjects (Enstilar® Foam Group) Investigational Product Use < 40 g/week in Controlled Trials

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
< 40 g/week						
Infections & Infestations						
Nasopharyngitis	6 (1.6)	1 (1.6)	1 (1.9)	0 (0)	2 (2.9)	0 (0)
Hordeolum	2 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders						
Diarrhea	2 (0.5)	0 (0)	0 (0)	1 (1.1)	1 (1.3)	0 (0)
Nausea	2 (0.5)	0 (0)	1 (1.9)	0 (0)	0 (0)	0 (0)
General disorders & administration site conditions						
Application site pain	3 (0.8)	0 (0)	1 (1.9)	2 (2.1)	1 (1.3)	0 (0)
Investigations						
Blood pressure increased	2 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
< 40 g/week						
Injury, poisoning & procedural complications						
Contusion	2 (0.5)	1 (1.6)	0 (0)	0 (0)	1 (1.3)	0 (0)
Excoriation	2 (0.5)	0 (0)	0 (0)	0 (0)	1 (1.3)	0 (0)
Total number of AEs[2]	71	14	8	13	20	1
(This table does not show all AEs)						
Total number of subjects	56 (15.3)	9 (14.5)	5 (9.4)	9 (9.5)	13 (16.9)	1 (2.8)

[1] Classification according to MedDRA version 15.1

[2] Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 48, pp 50-62.

Clinically significant differences between adverse event rates in those receiving < 40g versus > 40 g per week are not seen. For subjects using <40 g/week, the only common AE (occurring in ≥1% of subjects in the Enstilar® Foam group was nasopharyngitis, reported in 6 (1.6%) subjects. For subjects using ≥40 g/week, the only common event in the Enstilar® Foam group was flank pain, reported for 2 (1.3%) subjects.

Table 59: Adverse Events Occurring in ≥ 0.7% of Subjects (Enstilar® Foam Group) Investigational Product Use ≥ 40 g/week

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 40 g/week						
Infections & Infestations						
Folliculitis	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fungal skin infection	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Impetigo	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Viral pharyngitis	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Immune system disorders						
Hypersensitivity	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders						
Headache	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vascular disorders						

System Organ Class (SOC)	Enstilar® Foam	BDP foam	Calcipotriol foam	Foam Vehicle	Taclonex Ointment	Ointment vehicle
	N = 564	N = 99	N = 99	N = 152	N = 134	N = 51
Preferred Term[1]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 40 g/week						
Hypertension	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic & mediastinal disorders						
Oropharyngeal pain	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders						
Nausea	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)
Skin & subcutaneous tissue disorders						
Dermatitis contact	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Psoriasis	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal & connective tissue disorders						
Flank pain	2 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Muscle spasms	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Reproductive and Breast disorders						
Irregular menstruation	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
General disorders & administration site conditions						
Application site discoloration	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Application site irritation	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Influenza like illness	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Investigations						
Blood pressure increased	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total number of AEs[2]	19	5	3	4	0	1
(This table does not show all AEs)						
Total number of subjects	17 (11.4)	4 (14.3)	3 (8.6)	4 (8.2)	0 (0)	1 (7.7)

[1] Classification according to MedDRA version 15.1

[2] Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted from Table 48, pp 50-62.

For the pooled vehicle controlled trials, clinically significant differences between adverse event rates in those receiving < 40g versus ≥ 40 g Enstilar® Foam per week are not seen. For those using less than 40 g per week, nasopharyngitis was reported by 6 (2.0%) subjects, and application site pain was reported for 3 (1.0%) subjects.

Hordeolum, diarrhea, nausea, increased blood pressure, and excoriation were reported by 2 (0.7%) subjects each. For those using more than or equal to 40 g per week, one adverse event, flank pain, was reported for more than 1 subject, it was experienced by 2 (1.7%) subjects. Folliculitis, fungal skin infection, impetigo, viral pharyngitis, headache, hypertension, oropharyngeal pain, nausea, contact dermatitis, psoriasis, muscle spasms, application site discoloration, application site irritation, influenza like illness, and blood pressure increased were reported for 1 (0.9%) subject each.

7.5.2 Time Dependency for Adverse Events

Most subjects experienced adverse events at the time of or shortly (days to weeks) after product application. The pooled safety studies in this submission were not designed to evaluate the time dependency of adverse events.

7.5.3 Drug-Demographic Interactions

Adverse Events by Age:
For Enstilar® Foam, although the proportion of subjects experiencing at least one AE increased mildly with age this trend does not appear to be clinically significant. Similar findings were noted for calcipotriol foam, Enstilar® Foam vehicle, and ointment vehicle. Local (lesional/perilesional) AEs did not show a relationship between age and incidence.

Table 60: Adverse Events by Age Group (Controlled Trials)

Drug	< = 35 years	36 to 50 years	51 to 64 years	> = 65 years
Enstilar® Foam N = 564				
Total AEs[2]	13	26	38	18
Total subjects	10 (10.6%)	23 (13.9%)	29 (13.9%)	16 (16.5%)
Total **local** AEs	2	4	6	2
Total subjects	2 (2.1%)	4 (2.4%)	6 (2.9%)	2 (2.1%)
BDP foam N = 99				
Total AEs	8	2	9	0
Total subjects	4 (21.1%)	2 (6.7%)	7 (18.9%)	0 (0%)
Total **local** AEs	3	0	3	0
Total subjects	2 (10.5%)	0 (0%)	3 (8.1%)	0 (0%)
Calcipotriol foam N = 99				

Drug	< = 35 years	36 to 50 years	51 to 64 years	> = 65 years
Total AEs	0	5	10	1
Total subjects	0 (0)	4 (13.3%)	5 (15.2%)	1 (5.0%)
Total **local** AEs	0	0	6	1
Total subjects	0 (0%)	0 (0%)	3 (9.1%)	1 (5.0%)
Foam Vehicle N = 152				
Total AEs	2	6	6	3
Total subjects	2 (5.6%)	3 (4.8%)	5 (12.5%)	3 (23.1%)
Total **local** AEs	0	4	1	1
Total subjects	0 (0%)	1 (1.6%)	1 (2.5%)	1 (7.7%)
Taclonex ointment N = 134				
Total AEs	4	7	8	3
Total subjects	2 (10.5)	4 (9.1)	5 (9.3)	3 (17.6)
Total **local** AEs	2	2	2	1
Total subjects	1 (5.3)	2 (4.5%)	1 (1.9%)	1 (5.9)
Ointment vehicle N = 51				
Total AEs	0	0	1	1
Total subjects	0 (0)	0 (0)	1 (4.0)	1 (16.7)
Total local AEs	0	0	0	0
Total subjects	0 (0)	0 (0)	0 (0)	0 (0)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted by reviewer from Tables 85 & 86, pp 3-18, and pp 19-24.

Table 61: Adverse events by Age Group (Vehicle-Controlled Trials)

Drug	< = 35 years	36 to 50 years	51 to 64 years	> = 65 years
Enstilar® Foam N = 464				
Total AEs[2]	13	22	33	15
Total subjects	10 (14.7%)	19 (13.7%)	25 (14.5%)	13 (15.3%)
Total **local** AEs	2	3	6	1
Total subjects	2 (2.9%)	3 (2.2%)	6 (3.5%)	1 (1.2%)

Drug	< = 35 years	36 to 50 years	51 to 64 years	> = 65 years
Foam Vehicle N = 152				
Total AEs	2	6	6	3
Total subjects	2 (5.6%)	3 (4.8%)	5 (12.5%)	3 (23.1%)
Total **local** AEs	0	4	1	1
Total subjects	0 (0%)	1 (1.6%)	1 (2.5%)	1 (7.7%)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted by reviewer from Tables 159 & 160, pp 4-8, and pp 9-10.

In the vehicle controlled trials, in the foam vehicle group, a trend towards increasing total AEs and local AEs with age was noted. Small numbers of subjects however impede a definitive conclusion.

Adverse Events by Sex

In the Enstilar group the proportion of women (10.8%) experiencing at least one AE was mildly higher than in men (18.6). In general, the profile and incidence of AEs in the Enstilar group was generally similar between men and women. Regarding local (lesional/perlesional AEs) the proportion of subjects experiencing at least one AE was low and comparable in men and women.

Table 62: Adverse Events by Sex (Controlled Trials)

Drug	male	female
Enstilar® Foam		
Total AEs[2]	42	53
Total subjects	37 (10.8%)	41 (18.6%)
Total **local** AEs	8	6
Total subjects	8 (2.3%)	6 (2.7%)
BDP foam		
Total AEs	11	8
Total subjects	8 (14.5%)	5 (11.4%)
Total **local** AEs	1	5
Total subjects	1 (1.8%)	4 (9.1%)
Calcipotriol foam		
Total AEs	8	8
Total subjects	4 (6.7%)	6 (15.4%)

Total **local** AEs	5	2
Total subjects	2 (3.3%)	2 (5.1%)
Foam Vehicle		
Total AEs	6	11
Total subjects	3 (3.8%)	10 (13.7%)
Total **local** AEs	4	2
Total subjects	1 (1.3%)	2 (2.7%)
Taclonex ointment		
Total AEs	17	5
Total subjects	10 (11.5%)	4 (8.5%)
Total **local** AEs	4	3
Total subjects	3 (3.4%)	2 (4.3%)
Ointment vehicle		
Total AEs	2	0
Total subjects	2 (6.7%)	0 (0)
Total **local** AEs	0	0
Total subjects	0 (0)	0 (0)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted by reviewer from Tables 87 & 88, pp 24-37, and pp 38-41.

Similar to the controlled trials, a higher proportion of women than men experienced at least one AE. For local (perilesional/lesional) AEs the proportion of subjects experiencing at least one AE was similar between men and women.

Table 63: Adverse Events by Sex (Vehicle-Controlled Trials)

Drug	male	female
Enstilar® Foam, N = 464		
Total AEs[2]	35	48
Total subjects	31 (10.7%)	36 (20.8%)
Total **local** AEs	7	5
Total subjects	7 (2.4%)	5 (2.9%)
Foam Vehicle, N = 152		
Total AEs	6	11
Total subjects	3 (3.8%)	10 (13.7%)

Total **local** AEs	4	2
Total subjects	1 (1.3%)	2 (2.7%)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted by reviewer from Tables 163 & 164, pp 15-18, and p 19.

Adverse Events by Race:

The majority of subjects in all the pooled treatment groups in the controlled trials were white. There was no evidence of an increased incidence of adverse events or of local adverse events in any of the race subgroups. Small numbers however preclude definitive conclusions.

Table 64: Adverse Events by Race (Controlled Trials)

Drug	White	Black or African American	Asian	American Indian or Alaska Native	Other
Enstilar® Foam N = 564					
Total AEs[2]	79	9	3	1	3
Total subjects	64 (13.0%)	8 (19.0%)	2 (15.4%)	1 (20.0%)	3 (27.3%)
Total **local** AEs	10	3	0	0	1
Total subjects	10 (2.0%)	3 (7.1%)	0 (0)	0 (0)	1 (9.1%)
BDP foam N = 99					
Total AEs	17	1	0	0	1
Total subjects	11 (13.6%)	1 (12.5%)	0 (0)	0 (0)	1 (50.0%)
Total **local** AEs	4	1	0	0	1
Total subjects	3 (3.7%)	1 (12.5%)	0 (0)	0 (0)	1 (50.0%)
Calcipotriol foam, N = 99					
Total AEs	12	0	4	0	0
Total subjects	9 (9.9%)	0 (0)	1 (33.3%)	0 (0)	0 (0)
Total **local** AEs	3	0	1	0	0
Total subjects	3 (3.3%)	0 (0)	1 (33.3%)	0 (0)	0 (0)
Foam Vehicle N = 152					

Total AEs	15	1	1	0	0
Total subjects	11 (8.1%)	1 (11.1%)	1 (33.3%)	0 (0)	0 (0)
Total **local** AEs	5	1	0	0	0
Total subjects	2 (1.5%)	1 (11.1 %)	0 (0)	0 (0)	0 (0)
Taclonex oint., N = 134					
Total AEs	22	0	0	0	0
Total subjects	14 (12.0%)	0 (0)	0 (0)	0 (0)	0 (0)
Total local AEs	7	0	0	0	0
Total subjects	5 (4.3%)	0 (0)	0 (0)	0 (0)	0 (0)
Oint. Vehicle N = 51					
Total AEs	2	0	0	0	0
Total subjects	2 (4.5%)	0 (0)	0 (0)	0 (0)	0 (0)
Total local AEs	0	0	0	0	0
Total subjects	0 (0)	0 (0)	0 (0)	0 (0)_	0 (0)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted by reviewer from Tables 89 & 90, pp 42-55, and pp 56- 61.

Vehicle-Controlled Trials:
Similar to the controlled trials, the majority of subjects were white and other subgroups by race generally consisted of low numbers of subjects. There was no evidence of an increased incidence of adverse events or of local adverse events in any of the race subgroups. Small numbers however preclude definitive conclusions.

Table 65: Adverse Events by Race (Vehicle-Controlled Trials)

Drug	White	Black or African American	Asian	American Indian or Alaska Native	Other
Enstilar® Foam N = 464					
Total AEs[2]	68	8	3	1	3
Total subjects	54 (13.6%)	7 (19.4%)	2 (16.7%)	1 (20.0%)	3 (27.3%)
Total **local** AEs	9	2	0	0	1
Total subjects	9 (2.3%)	2 (5.6%)	0 (0)	0 (0)	1 (9.1%)

Foam Vehicle N = 152					
Total AEs	15	1	1	0	0
Total subjects	11 (8.1%)	1 (11.1%)	1 (33.3%)	0 (0)	0 (0)
Total **local** AEs	5	1	0	0	0
Total subjects	2 (1.5%)	1 (11.1 %)	0 (0)	0 (0)	0 (0)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted by reviewer from Tables 165 & 166, pp 20-23, and p 24.

Adverse Events by Ethnicity:
Controlled Trials:

There was no evidence of an increased incidence of adverse events or of local adverse events between ethnic subgroups. Variability was high between treatment groups due to small numbers of subjects.

Table 66: Adverse Events by Ethnicity (Controlled Trials)

Drug	Not Hispanic or Latino	Hispanic or Latino
Enstilar® Foam N = 564		
Total AEs[2]	76	19
Total subjects	64 (15.1%)	14 (10.1%)
Total **local** AEs	14	0
Total subjects	14 (3.3%)	0 (0)
BDP foam, N = 99		
Total AEs	16	3
Total subjects	12 (15.2%)	1 (5.0%)
Total **local** AEs	4	2
Total subjects	4 (5.1%)	1 (5.0%)
Calcipotriol foam, N = 99		
Total AEs	14	2
Total subjects	8 (10.3%)	2 (9.5%)
Total **local** AEs	7	0
Total subjects	4 (5.1%)	0 (0)
Foam Vehicle, N = 152		
Total AEs	16	1

Total subjects	12 (9.8%)	1 (3.3%)
Total **local** AEs	6	0
Total subjects	3 (2.5%)	0 (0)
Taclonex ointment, N = 134		
Total AEs	22	0
Total subjects	14 (13.2%)	0 (0)
Total **local** AEs	7	0
Total subjects	5 (4.7%)	0 (0)
Ointment vehicle, N = 51		
Total AEs	2	0
Total subjects	2 (4.3%)	0 (0)
Total **local** AEs	0	0
Total subjects	0 (0)	0 (0)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted by reviewer from Tables 91 & 92, pp 62-73, and pp 74- 77.

Vehicle-Controlled Trials:

There was no evidence of a clinically significant difference in incidence of adverse events or of local adverse events between ethnic subgroups. Variability was high between treatment groups due to small numbers of subjects.

Table 67: Adverse Events by Ethnicity (Vehicle-Controlled Trials)

Drug	Not Hispanic or Latino	Hispanic or Latino
Enstilar® Foam N = 464		
Total AEs[2]	66	17
Total subjects	5 (15.8%)	12 (10.3%)
Total **local** AEs	12	0
Total subjects	12 (3.4%)	0 (0)
Foam Vehicle, N = 152		
Total AEs	16	1
Total subjects	12 (9.8%)	1 (3.3%)
Total **local** AEs	6	0
Total subjects	3 (2.5%)	0 (0)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety, adapted by reviewer from Tables 167 & 168, pp 25-28, and p 29.

7.5.4 Drug-Disease Interactions

Controlled Trials:

For the controlled trials, the majority of subjects (from 72.4 to 79.8%) in all pooled treatment groups had "moderate" disease at baseline; the numbers of subjects with "mild" and "severe" disease at baseline in all pooled treatment groups were low (ranging from 2 to 24 subjects) except for the Enstilar® Foam group, having 81 and 50 subjects with mild and severe disease, respectively.

Table 68: Adverse Events (Total and Local) by Baseline Disease Severity (IGA) Controlled Trials

Drug	Mild	Moderate	Severe
Enstilar® Foam N = 564			
Total AEs[2]	10	81	4
Total subjects	8 (9.9%)	66 (15.2%)	4 (8.0%)
Total **local** AEs	1	10	3
Total subjects	1 (1.2%)	10 (2.3%)	3 (6.0%)
BDP foam, N = 99			
Total AEs	2	13	4
Total subjects	2 (20.0%)	9 (11.4%)	2 (20.0%)
Total **local** AEs	1	5	0
Total subjects	1 (10.0%)	4 (5.1%)	0 (0%)
Calcipotriol foam, N = 99			
Total AEs	1	13	2
Total subjects	1 (8.3%)	7 (9.5%)	2 (15.4%)
Total **local** AEs	1	6	0
Total subjects	1 (8.3%)	3 (4.1%)	0 (0)
Foam Vehicle, N = 152			
Total AEs	3	11	3
Total subjects	2 (8.3%)	8 (7.3%)	3 (16.7%)

Total **local** AEs	0	5	1
Total subjects	0 (0)	2 (1.8%)	1 (5.6%)
Taclonex ointment, N = 134			
Total AEs	0	22	0
Total subjects	0 (0)	14 (13.3)	0 (0)
Total **local** AEs	0	7	0
Total subjects	0 (0)	5 (4.8%)	0 (0)
Ointment vehicle, N = 51			
Total AEs	0	2	0
Total subjects	0 (0)	2 (5.1)	0 (0)
Total **local** AEs	0	0	0
Total subjects	0 (0)	0 (0)	0 (0)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety – Adverse Events, Part 2, adapted by reviewer from Tables 93 & 94, pp 78-91, and pp 92-96.

For the controlled trials, for all adverse events and for local (lesional/perilesional) adverse events there was no evidence of a clinically significant trend for increasing adverse event incidence with baseline disease severity.

Vehicle-Controlled Trials:
The majority of subjects in both pooled treatment groups had "moderate" disease at baseline [76.7% (356 subjects) in the Enstilar® Foam group and 72.4% 9110 subjects) in the foam vehicle group].

Table 69: Adverse Events (Total and Local) by Baseline Disease Severity (IGA) Vehicle-Controlled Trials

Drug	Mild	Moderate	Severe
Enstilar foam N = 464			
Total AEs[2]	9	73	1
Total subjects	7 (9.7%)	59 (16.6%)	1 (2.8%)
Total **local** AEs	1	10	1
Total subjects	1 (1.4%)	10 (2.8%)	1 (2.8%)
Foam Vehicle, N =			

152			
Total AEs	3	11	3
Total subjects	2 (8.3%)	8 (7.3%)	3 (16.7%)
Total **local** AEs	0	5	1
Total subjects	0 (0)	2 (1.8%)	1 (5.6%)

Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Source: Applicant's NDA from Module 5.3.5.3, Statistical Tables for Integrated Analysis of Safety – Adverse Events, Part 2, adapted by reviewer from Tables 169 & 170, pp 30-33, and pp 34-35.

For the vehicle-controlled trials, for all adverse events and for local (lesional/perilesional) adverse events there was no evidence of a clinically significant trend for increasing adverse event incidence with baseline disease severity.

7.5.5 Drug-Drug Interactions

No formal analyses were performed for drug-drug interactions with this topical drug product.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity was not assessed as part of the clinical development program. Controlled clinical trials were too short to allow for evaluation of carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancy was reported during the clinical trials conducted with Enstilar foam.

7.6.3 Pediatrics and Assessment of Effects on Growth

The applicant submitted an initial Pediatric Study Plan on June 26, 2013. Agreement to the initial Agreed iPSP was achieved on December 3, 2013.

The applicant has requested a waiver for pediatric patients aged 0 to 11years (b) (4) The reason stated for waiving pediatric studies is that the product would be unsafe in this age group.

The primary safety concern is the potential for adverse effects associated with betamethasone dipropionate, a potent corticosteroid. Hypothalamic-pituitary-adrenal (HPA) axis suppression can occur with corticosteroid use. The risk is generally proportional to potency. In addition, children have a higher BSA to body mass ratio than adolescents and adults which increases the potential for systemic effects due to absorption into the systemic circulation of topically applied compounds.

A decreased response to adrenocorticotropic hormone (ACTH) stimulation was not seen in the adult MUSE trial with Enstilar® Foam. However, with other Taclonex products a decreased response has been seen.

Ointment Labeling (NDA 21852: Section 12.2 Pharmacodynamics):

(b) (4) HPA axis suppression was evaluated in adult subjects (N=32) with extensive plaque psoriasis involving at least 30% of the scalp and, in total, 15-30% of the body surface area. Treatment consisted of once daily application of Taclonex Scalp® Topical Suspension on the scalp in combination with Taclonex® Ointment on the body. Adrenal suppression as indicated by a 30-minutes post-stimulation cortisol level < 18 mcg/dL was observed in 5 of 32 subjects (15.6%) after 4 weeks of treatment as per the recommended duration of use.

(b) (4) HPA axis suppression was evaluated in subjects 12 to 17 years (N=32) with plaque psoriasis of the body involving 5-30% of the body surface area. Treatment consisted of once daily application of Taclonex® Ointment to the affected areas for up to 4 weeks. Mean weekly dose was 29.6 g with a range of 8.1-55.8 g/week. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL was observed in none of 32 evaluable subjects after 4 weeks of treatment.

Taclonex Topical Suspension Labeling (NDA 22185: Section 12.2 Pharmacodynamics):

(b) (4) HPA axis suppression was evaluated in adult subjects (N=32) with extensive psoriasis involving at least 30% of the scalp and, in total, 15-30% of the body surface area. Treatment consisted of once daily application of Taclonex® Topical Suspension on the scalp in combination with Taclonex® Ointment on the body for 4 to 8 weeks. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL was observed in 5 of 32 subjects (15.6%) after 4 weeks of treatment and in 2 of 11 subjects (18.2%) who continued treatment for 8 weeks.

(b) (4) HPA axis suppression was evaluated in adult subjects (N=43) with extensive psoriasis involving 15-30% of the body surface area (including the scalp). Treatment consisted of once daily application of Taclonex® Topical Suspension to the body (including the scalp in 36 out of 43 subjects) for 4 to 8 weeks. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL was observed in 3 out of 43 subjects (7.0%) after 4 weeks of treatment and in none of the 36 subjects who continued treatment for 8 weeks.

(b) (4) HPA axis suppression was evaluated in subjects 12 to 17 years (N=30) with plaque psoriasis of the scalp involving at least 20% of the scalp area. Treatment consisted of once daily application of Taclonex® Topical Suspension to the affected area on the scalp for up to 8 weeks. Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL was observed in 1 of 30 evaluable subjects (3.3%) after 4 weeks of treatment and in no subjects who continued treatment for 8 weeks.

It is noted that the FDA has previously granted a partial waiver for the age group 0 to 11 years for Taclonex® Ointment (NDA 21852), January 9, 2006, Taclonex Scalp® Topical Suspension (NDA 22185), May 9, 2008, and for Taclonex® Topical Suspension (NDA 22185/S-10), October 17, 2012.

Deferral:
The applicant requests a deferral for patients aged 12 to (b) (4) years. The reason is adult studies are completed and ready for approval.

A proposal for a PMR, based upon the Agreed iPSP is as follows:

> Conduct an open-label trial to assess the effect on calcium metabolism of Enstilar® Foam in 100 evaluable pediatric subjects aged 12 years to 16 years and 11 months with plaque psoriasis of the scalp and body. Pharmacokinetics (PK) of Enstilar Foam and assessment of hypothalamic-pituitary axis (HPA) suppression will be conducted in a subset of at least 30 subjects with at least moderate psoriasis under maximal use conditions

This application was presented to the Pediatric Review Committee (PeRC) on September 2, 2015. The PeRC agreed with the planned partial waiver and deferral for patients aged 12 to (b) (4) years.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose:
Overdose was not reported as an adverse event in the clinical development program.

Drug Abuse:
No instances of drug abuse were reported in the clinical development program.

Withdrawal and Rebound:
The occurrence of rebound and relapse of disease after discontinuation of treatment with Enstilar foam was not examined in the trials submitted for this application.

7.7 Additional Submissions / Safety Issues

- **120 Day Safety Update:**

The applicant submitted a 120 day safety update on April 17, 2015 (supporting document # 3). The update includes information from two clinical trials that were ongoing as of March 31, 2015:

- Trial LP0053-1003 to compare the efficacy and safety of LEO 90100 (Enstilar® Foam) to that of Taclonex® Topical Suspension in adult subjects with plaque psoriasis
- Trial LP0053-1030 to gather insight on patient reported factors that influence preference following once daily topical treatment with LEO 90100 (Enstilar® Foam) and Taclonex® Topical Suspension in adult subjects with plaque psoriasis

Regarding trial LP0053-1030, this is an international (Canada and Germany), multi-center, prospective, open-label, randomized, 2-arm, cross-over study with 14-days once daily treatment in subjects with plaque psoriasis. The objective of this trial is to gather insight on how product attributes affect usability by investigating the factors that are thought to influence patient preference with regard to topical anti-psoriatic treatments.

The enrollment of subjects to this trial started in February 2015. As March 31, 2015, 41 (out of 200 planned) subjects had been recruited and started treatment with trial medication. At the time of the 120 day safety update, the applicant states no serious adverse events (SAEs) were reported, and no subject discontinued due to an AE.

Regarding trial LP0053-1003, this is an international (USA, France, and United Kingdom - approximately 15 sites each) phase 3, multi-center, prospective, randomized, active- and vehicle controlled, investigator blinded, 4-arm, parallel group, 12-week trial in subjects with plaque psoriasis. Subjects were required to have plaque psoriasis on the body of at least 'mild' disease severity by the Physician's Global Assessment (PGA), a modified Psoriasis Area and Severity Index (m-PASI) score of at least 2, and lesions involving a body surface area (BSA) of 2% to 30%. A total of 460 subjects were to be randomized in a 4:4:1:1 ratio, to the two active groups and to the vehicle groups.

The primary objective of the trial was to compare the efficacy of treatment with LEO 90100 (Enstilar® Foam) at Week 4 to that of calcipotriene plus BDP topical suspension (Taclonex® Topical Suspension) at Week 8 in subjects with plaque psoriasis. The secondary objective was to compare the safety and efficacy of LEO 90100 (Enstilar® Foam) to that of calcipotriene plus BDP topical suspension (Taclonex® Topical Suspension) for up to 12 weeks.

Trial LP0053-1003 began in June 2014 and had the last subject visit in March of 2015. At the time of the 120 safety report, a thorough analysis of unblinded safety data had not taken place. The applicant states, however, all safety data from this trial were reviewed during the trial under blinded conditions to monitor for serious safety or

tolerability events. The applicant provides a summary of safety data available at the time of the 120 day safety report.

A total of 504 subjects were enrolled in trial LP0053-1003. Of these, 463 subjects were randomized and received trial medication; 185 subjects to LEO 90100 (Enstilar® Foam), 188 to calcipotriene plus BDP topical suspension (Taclonex® Topical Suspension), 47 to foam vehicle and 43 to topical suspension vehicle.

The overall frequency of AEs was similar across treatment groups and the incidence of SAEs, AEs leading to discontinuation of treatment with trial medication and severe AEs was low and comparable across treatment groups.

Table 70: Overview of Adverse Events Trial LP0053-1003

	LEO 90100 (Enstilar® Foam) N = 185		Calcipotriene BDP Topical Susp. N = 188		Foam Vehicle N = 47		Topical Suspension vehicle N = 43	
	No. # of AEs*	No. # of subjects (%)	No. # of AEs*	No. # of subjects(%)	No. # of AEs*	No. # of subjects(%)	No. # of AEs*	No. # of subjects(%)
All AEs	142	77 (41.6)	152	85 (45.2)	25	18 (38.3)	29	19 (44.2)
SAEs	4	4 (2.2)	3	3 (1.6)	-	-	1	1 (2.3)
AEs leading to D/C**	4	4 (2.2)	5	4 (2.1)	2	2 (4.3)	-	-
Severe AEs	8	6 (3.2)	5	5 (2.7)	1	1 (2.1)	-	-
Related AEs	19	14(7.6)	8	7(3.7)	6	4 (8.5)	4	2 (4.7)

*Different AEs with the same preferred term and system organ class, involving the same subject, have been counted as one.
**Includes AEs leading to permanent discontinuation of treatment with trial medication, whether or not also leading to withdrawal from the trial.
Source: Applicant's 120 Day Safety Update, April 17, 2015, Table 1, p. 9.

According to the applicant, at the time of the 120 Safety Update Report, a thorough analysis of unblinded safety data had not taken place. However, summaries are available (in the 120 Day Safety Update) of unblinded adverse events and related adverse events over 12 weeks. The applicant states that the adverse event profile for LEO 90100 (Enstilar® Foam) appears similar to that of calcipotriene plus BDP topical suspension (Taclonex® Topical Suspension). This reviewer agrees with this assessment.

Of adverse events assessed as causally related to treatment, pruritus was the most common in the LEO 90100 group (Enstilar® Foam) [5 (2.7%) subjects versus 1 (0.5%) subject in the calcipotriene plus BDP topical suspension group (Taclonex® Topical

Suspension) and 1 (2.1%) in the foam vehicle group]. None of the remaining related adverse events in the LEO 90100 (Enstilar® Foam) group (psoriasis, erythema, blister, skin swelling, application site pruritus, nasopharyngitis, skin infection, salivary gland calculus, burns first degree, hyperglycemia, insulin resistance, conjunctivitis, urine calcium/creatinine ratio decreased and pregnancy) occurred in more than one subject (0.5%).

Serious Adverse Events (SAEs) reported in trail LP0053-1003 included the following:

- LEO 90100 (Enstilar® Foam): 4 events - worsening of psoriasis, prostate cancer, worsening of gastroesophageal reflux and congestive cardiac failure
- Calcipotriene plus BDP topical suspension (Taclonex® Topical Suspension): 3 events - post procedural hemorrhage, type 2 diabetes mellitus and ischemic stroke
- Topical suspension vehicle: 1 event – cholecystitis

Only 1 SAE, exacerbation of psoriasis after 69 days of treatment with LEO 90100 (Enstilar® Foam), was considered by the investigator to be possibly related. This subject showed poor response to therapy with LEO 90100; the baseline PGA score of "moderate" remained unchanged at all subsequent visits prior to worsening on Day 69 when it was upgraded to "severe.. The subject had been previously treated with various topical agents, including calcipotriene plus BDP ointment.

A total of 47 subjects discontinued the trial prematurely, before Week 12. When data were unblinded it was noted that withdrawal rates were comparable between the LEO 90100 (Enstilar® Foam) and calcipotriene plus BDP topical suspension groups (Taclonex® Topical Suspension). More subjects withdrew due to lack of efficacy in the vehicle arms. Adverse events led to withdrawal of 3 (1.6%) subjects in the active treatment arms.

The adverse events that led to withdrawal of subjects from the trial were as follows:

- LEO 90100 (Enstilar® Foam): worsening of psoriasis (2 subjects), application site pruritus (1 subject), pregnancy (1 subject)
- Calcipotriene plus BDP topical suspension (Taclonex® Topical Suspension): worsening of psoriasis (2 subjects, in one case accompanied by joint swelling), erythema (1 subject) and ischemic stroke (1 subject)
- Foam vehicle: worsening of psoriasis (1 subject), erythema (1 subject)

Clinical laboratory evaluations of calcium metabolism were performed in trial LP0053-1003; the assessments included albumin-corrected serum calcium and urinary calcium:creatinine ratio in spot urine samples at baseline and after 4, 8 and 12 weeks of treatment.

According to the applicant, review of the calcium corrected serum albumin data identified no subjects with treatment emergent values outside the protocol predefined

levels for a clinically significant albumin corrected serum calcium value, i.e., <2.0 mmol/l (low threshold) or >2.9 mmol/l (high threshold).

The applicant sates that tabulation of data for urinary calcium:creatinine ratio in spot urine samples were not available at the time of the 120 Day Safety Report.

Conclusion:
The applicant states that there is no change in the risk/benefit assessment of LEO 90100 (Enstilar® Foam), and no changes to the draft labeling are proposed at this time. This reviewer agrees with this assessment.

- **Long Term Safety:**

The applicant plans not to conduct any additional long-term trial specifically with Enstilar® Foam. To meet the requirement to document safety as described in ICH E1A the applicant proposes to establish a bridge from Enstilar® Foam to the two approved products, Taclonex® Ointment (Daivobet® Ointment) and Taclonex® Topical Suspension (Daivobet® gel). At the Pre-NDA meeting of March 26, 2014, the applicant proposed that the bridge be based upon the following:

- Direct comparison of safety data for LEO 90100 and Taclonex ® ointment from Phase 2 trial LEO 90100-35
- Comparative vasoconstriction data (LP0053-69)
- Systemic exposure data from the Maximum Use Systemic Exposure trial (LEO 90100-30) compared with historical data from similar trials with Taclonex® Ointment (MCB 0201 FR and MBL 0404 FR) and Taclonex® Topical Suspension (LEO 80185-G24).
- Adverse event data from short term trials with LEO 90100 (LP0053-1001, LEO 90100-7, and LEO 90100-35), Taclonex® Ointment (MCB 0003 INT, MCB 0002 INT, MCB 0001 INT, MCB 0201 FR, and MCB 9905 INT) and Taclonex® Topical Suspension (LEO 80185-G23, MBL 0202 INT, and LEO 80185-G21)
- Comparative safety data from long-term clinical trials with Taclonex® Ointment (MCB 0102 INT) and Taclonex® Topical Suspension (MBL 0502 US and MBL 0407 INT)

At the Pre-NDA meeting of March 26, 2014, the Agency stated that the applicant's approach to establishing this bridge appeared reasonable. However, the Agency noted that the applicant had conducted a multi-point vasoconstriction assessment. The Agency stated that such an approach will not be acceptable for providing any comparison between different dosage forms.

Comparison of Safety Data from trial LEO 90100-35:

LEO 90100-35 was a phase 2, multi-center, prospective, randomized, investigator-blinded, 4-arm, active- and vehicle controlled, parallel-group, 4 week trial conducted in the US in subjects with psoriasis vulgaris of the body (2 to 30% BSA) classified as at least 'mild' by the Investigator's Global Assessment of Disease Severity (IGA). Eligible subjects were randomized in a 3:1:3:1 ratio to receive Enstilar® Foam, the foam vehicle, Taclonex® ointment, or the ointment vehicle, respectively. The trial medication was to be applied once daily to psoriasis vulgaris lesions on the body (excluding genitals and skin folds) for up to 4 weeks.

For the primary endpoint, "treatment success" (IGA) at week 4, Enstilar® Foam was shown to be a statistically significantly more effective treatment than Taclonex® ointment (54.6% versus 43.0%; p=0.025).

Table 71: Adverse Events Trial LEO 90100-35

	LEO 90100 (n=141)	Daivobet® ointment (n=134)	Foam vehicle (n=49)	Ointment vehicle (n=51)
Total number of AEs	20	23	2	2
Total number (%) of subjects reporting:				
AE	16 (11.3%)	14 (10.4%)	1 (2.0%)	2 (3.9%)
SAE	0 (0.0%)	2 (1.5%)	0 (0.0%)	0 (0.0%)
ADR	1 (0.7%)	4 (3.0%)	0 (0.0%)	0 (0.0%)
Withdrawals due to AE	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)

Source: Applicant's NDA, Module 5.3.5.3, Bridging Report, Table 4, p. 15

Enstilar® Foam (LEO 90100) and Taclonex® (Daivobet) Ointment showed similar adverse event profiles.

Only one adverse drug reaction was reported in the Enstilar® Foam group, application site pruritus. The ADRs reported in the Taclonex® ointment group included application site dryness, application site pain, psoriasis and pruritus. There were no clinically relevant mean changes from baseline in albumin-corrected serum calcium or urinary calcium:creatinine ratio (spot urine) in any of the treatment groups. The mean amount of trial medication used per week over the total treatment period was similar across the treatment groups, with a mean of 31.6 g in the Enstilar® Foam group (range 2.2 to 87.9 g) and 30.6 g in the Taclonex® Ointment group (range 1.3 to 87.7 g).

For trial LEO 90100-35, the applicant concluded that no new safety concerns were identified for Enstilar® Foam compared to Taclonex® Ointment. This reviewer believes this is a reasonable assessment.

Comparison in Terms of Corticosteroid Potency (Vasoconstriction Trial LP0053-69):
On the basis of the vasoconstriction trial the applicant concluded that the (b) (4) However, the Division has concluded that the VCA trial conducted by the applicant is not acceptable and the potency classification of LEO90100 could not be determined.

Comparison Based on MUSE Trials:
This comparison is based on the use of systemic exposure data for Enstilar® Foam from the Maximum Use Systemic Exposure trial (LEO 90100-30) compared with historical data from similar trials with Taclonex® Ointment (MCB 0201 FR and MBL 0404 FR) and Taclonex® Topical Suspension (LEO 80185-G24).

Table 72: Description of MUSE Trials

LEO clinical trial code	Design of trial	Assessments	Duration of trial treatment	Treatment group	Dosing
LEO 90100-30 (n=37)	National (Canada), multicentre, open, non-controlled, single group trial	HPA axis Calcium metabolism PK	4 weeks	LEO 90100	Once daily application to lesions on the body and scalp
MBL 0404 FR (n=35)	National (France), single centre, open, non-controlled, single group trial	HPA axis Calcium metabolism PK	8 weeks	Daivobet® ointment (body) + Daivobet® gel (scalp)	Once daily application to lesions on the body and scalp
MCB 0201 FR (n=24)	National (France), single centre, randomised, double-blind, active-controlled, 2-arm parallel group trial	HPA axis	4 weeks	Daivobet® ointment (n=12) BDP ointment (Diprosone®) (n=12)	Once daily application to lesions on the body
LEO 80185-G24 (n=43)	National (Canada), multicentre, open, non-controlled, single group trial	HPA axis Calcium metabolism PK	8 weeks	Daivobet® gel	Once daily application to lesions on the body and scalp

Source: Applicant's NDA, Module 5.3.5.3, Bridging Report, Table 5, p. 17

All trials enrolled subjects with extensive psoriasis vulgaris on the trunk and/or limbs (from 15 to 30% of the BSA) with or without involvement of the scalp. In trials LEO 90100-30 and MBL 0404 FR, the involvement of the scalp (at least 30% of the scalp area) was required. In all trials, assessments were made at least at baseline and at Week 4. The mean age ranged from 41.3 years in trial MBL 0404 FR to 48.0 years in

trial LEO 90100-30. The percentage of subjects in the "severe" category (IGA) was similar between foam trial LEO 90100-30 and gel trial LEO 80185-G24 (24.3% and 30.2%, respectively), and higher in the ointment trial MBL 0404 FR (60.0%). The average weekly use of trial medication in the Enstilar® Foam trial LEO 90100-30 was similar to the use in the ointment trial MBL 0404 FR (with a mean of approximately 62 g vs. 65 g), and slightly higher than the amount used in the controlled ointment trial MCB 0201 FR and gel trial LEO 80185-G24 (approximately 50 g in both trials).

Pharmacokinetics:
In general, plasma/serum concentrations of calcipotriol, BDP and the primary metabolite of calcipotriol (MC1080) were below LLOQ in most subjects in all three trials and standard PK parameters could not be calculated. The primary BDP metabolite, betamethasone 17- propionate, was above LLOQ at one or several time points at Week 4 in at least 40% of subjects in all trials. Across three trials using different formulations (foam, ointment, gel) the systemic exposure following daily dosing for 4 weeks was similar. Individual variability was high and standard PK parameters were often not possible to calculate, but the median C_{max} for the four analytes (betamethasone dipropionate, betamethasone 17-propionate, calcipotriol, MC1080) across the three trials were similar.

Effect on HPA Axis:
HPA axis testing was conducted in all four trials (LEO 90100-30, MBL 0404 FR, MCB 0201 FR, and LEO 80185-G24) by means of a rapid standard dose (250 mg intravenously) Cortrosyn™ test (cosyntropin, synthetic ACTH). Testing was conducted at baseline and after 4 weeks of treatment in all trials. Serum cortisol levels were evaluated before stimulation and at 30 and 60 minutes after ACTH injection. The primary response criterion for evaluation of HPA axis function was the serum cortisol level 30 minutes after ACTH injection which was to be >18 mcg/dL to be considered a negative response indicating normal HPA axis function.

In trial LEO 90100-30, none of the 35 subjects who completed 4 weeks of treatment with Enstilar® Foam on the body and scalp showed adrenal suppression at Week 4. Likewise, in trial MCB 0201 FR, there was no evidence of adrenal suppression in the 11 subjects treated with Daivobet® (Taclonex®) ointment who underwent HPA axis testing at Week 4.

In trial MBL 0404 FR, cortisol levels ≤18 mcg/dL at 30 minutes post ACTH stimulation were observed in 5 of 32 (15.6%) subjects after 4 weeks of treatment with Daivobet® (Taclonex®) ointment on the body and Daivobet® gel (Taclonex® Topical Suspension) on the scalp

In the 43 subjects treated with Daivobet® gel (Taclonex® Topical Suspension) in trial LEO 80185-G24, a total of 3 (7.0%) subjects had serum cortisol levels ≤18 mcg/dL at 30 minutes post ACTH stimulation after 4 weeks of treatment.

Thus, the incidence of HPA axis suppression was generally low and comparable across multiple MUSE trials with similar exposure levels. The applicant concludes, based on HPA axis testing, there was no indication that systemic effects of BDP from the foam formulation would be higher compared with Daivobet® (Taclonex®) ointment and Daivobet® gel(Taclonex® Topical Suspension).

Effect on Calcium Metabolism:
The results of the evaluation of calcium metabolism in trial LEO 90100-30 are compared with the calcium metabolism results in trials MBL 0404 FR (NDA 022185) and LEO 80185-G24 (NDA 022185). Calcium metabolism was not assessed in the controlled ointment trial MCB 0201 FR. The primary evaluation of calcium metabolism included measurements of albumin-corrected serum calcium (serum calcium in trial MBL 0404 FR), 24-hour urinary calcium excretion and, in trials LEO 90100-30 and LEO 80185-G24, the urine calcium:creatinine ratio. Measurements were made at baseline, after 4 weeks, and after 8 weeks of treatment in the 8-week trials. The bioanalytical method used across trials, in which calcium metabolism was assessed, was the same.

Regarding changes in men values over time, there was no clinically significant mean change from baseline to Week 4 in any of the parameters assessed (albumin-corrected serum calcium, 24-hour urine calcium or the calcium:creatinine ratio) after treatment with Enstilar® Foam in trial LEO 90100-30 or after treatment with Daivobet® gel (Taclonex® Topical Suspension) in trial LEO 80185-G24 or Daivobet® (Taclonex®) ointment and Daivobet® gel (Taclonex® Topical Suspension) in trial MBL 0404 FR.

Regarding changes in individual subject values over time, elevated albumin corrected serum calcium levels outside the normal range were not observed in any of the subjects treated with Enstilar® Foam in trial LEO 90100-30. Also for trials MBL 0404 FR and LEO 80185-G24 (Taclonex® ointment and Taclonex® Topical suspension, respectively) no subjects experienced a serum calcium value above the upper reference limit at any time-point. For urine calcium parameters, none of the subjects treated with Enstilar® Foam developed 24- hour urinary calcium excretion or a calcium:creatinine ratio above normal range after 4 weeks of treatment. These results are consistent with those observed for Taclonex® ointment and Taclonex® Topical Suspension, where treatment-emergent increases in urine calcium parameters were observed at Week 4 in a limited number of subjects; for 24 hour urinary calcium excretion, one subject in trial LEO 80185-G24 (Topical Suspension); for calcium:creatinine ratio, 1 subject in trial LEO 80185-G24 (Topical Suspension).

Conclusion regarding MUSE Trials:
The applicant concludes that there was no indication that Enstilar® Foam is associated with more severe systemic effects than Taclonex® ointment or Taclonex® Topical Suspension, as assessed by measurements of HPA axis suppression and calcium metabolism.

Comparison Based on Data from Short-Term Trials with Enstilar Foam, Taclonex Ointment, and Taclonex Topical Suspension:
This comparison is based on adverse event data from short term trials with LEO 90100 (LP0053-1001, LEO 90100-7, and LEO 90100-35), Taclonex® Ointment (MCB 0003 INT, MCB 0002 INT, MCB 0001 INT, MCB 0201 FR, and MCB 9905 INT) and Taclonex® Topical Suspension (LEO 80185-G23, MBL 0202 INT, and LEO 80185-G21).

In all of these trials, the calcipotriol/BDP products were applied once daily except for trial MBC 9905 INT in which Taclonex® ointment was applied both once daily and twice daily. In the examination of adverse events and amount of trial medication used, only the arm with once daily dosing frequency for Taclonex® ointment is included. Treatment duration in the Enstilar® Foam and Taclonex® ointment trials was 4 weeks. For trial MCB 0002 INT (Taclonex® ointment) only the AEs reported during the first 4 weeks of the trial are included in the AE discussion (once daily treatment for up to 4 weeks in accordance with the US label). In the Taclonex® Topical Suspension trials, the duration of treatment was 8 weeks and the AEs reported during this treatment period were included in the AE discussion (once daily treatment for up to 8 weeks in accordance with the US label).

Psoriasis vulgaris on the body was evaluated using the Investigator's Global Assessment (IGA) and the extent and severity of clinical sings, from which the modified Psoriasis Area and Severity Index (m-PASI) was calculated. The body areas assessed were the trunk and limbs, and included the arms (including hands), trunk (including neck) and the legs (including buttocks and feet). The disease severity at baseline is described in terms of m-PASI because the IGA was not included in all Taclonex® ointment trials.

The safety populations included 564 subjects in the Enstilar® Group , 1539 subjects in the Taclonex® Ointment group, and 824 in the Taclonex® Topical Suspension group. The populations were comprised of adult subjects (18 years and above) with a clinical diagnosis of psoriasis vulgaris on the body (and on the scalp in trial LEO 90100-7). Overall, the distribution of age and sex was similar across the Enstilar® Foam group and the comparator groups. The mean m-PASI at baseline was slightly higher in the Taclonex® Ointment group (10.1) compared with the Enstilar® Foam group (7.5) and Taclonex® Topical Suspension group (8.1). The highest use of trial medication, mean of 30.83 g/week (average over 4 weeks), was reported for Enstilar® Foam, as compared with 28.53 g/week for Taclonex® Topical Suspension (average over 8 weeks) and 24.53 g/week for Taclonex® Ointment (average over first 4 weeks).

For the bridging analysis, all AEs reported in the individual trials were recoded to follow MedDRA version 15.1. Tabulations of AEs consist only of treatment emergent AEs.

The percentage of subjects reporting at least one AE was lower in the Enstilar® Foam (13.8%) compared with the Taclonex® Ointment group (24.4%) and the Taclonex® Topical Suspension group (32.0%). The incidence of the treatment related adverse

events (i.e., ADRs) and lesional/perilesional AEs was lowest in the Enstilar® Foam. ADRs were reported for 2.7% of subjects the Enstilar® Foam group, 7.5% in the Taclonex® ointment group, and 6.4% in the Taclonex® Topical Suspension group. Lesional/perilesional AEs were reported for 2.5% of subjects in the Enstilar® Foam group, 7.1% in the Taclonex® ointment group, and 5.1% in the Taclonex® Topical Suspension group.

No deaths occurred in any of the pooled groups. The incidence of SAEs was similar across the treatment groups; 0.5% of subjects in the LEO 90100 group, 0.6% in the Taclonex® ointment group and 0.2% in the Taclonex® Topical Suspension group. Of these, one SAE in the Enstilar® Foam group [hypersensitivity/urticaria in 1 (0.2%) subject] and one SAE in the Taclonex® Ointment group [subcutaneous abscess in 1 (0.1%) subject] were considered possibly related to the trial medication.

Table 73: Adverse Event Summary for Pooled Enstilar® Foam, Taclonex Ointment®, and Taclonex® Topical Suspension Trials

	LEO 90100 (n=564)	Daivobet® ointment (n=1539)	Daivobet® gel (n=824)
Total number of AEs	95	512	366
Total number (%) of subjects reporting:			
AE	78 (13.8%)	375 (24.4%)	264 (32.0%)
ADR	15 (2.7%)	115 (7.5%)	53 (6.4%)
Lesional/perilesional AE	14 (2.5%)	110 (7.1%)	42 (5.1%)
SAE	3 (0.5%)	9 (0.6%)	2 (0.2%)

Source: Applicant's NDA, Module 5.3.5.3, Bridging Report, Table 23, p. 40.

Regarding ADRs, the most common in the Enstilar® Foam group were application site pain reported in 3 (0.5%) subjects and application site pruritus reported in 2 (0.4%) subjects. Both of these ADRs were observed in the Taclonex® Ointment and the Taclonex® Topical Suspension groups at similar rates (ranging from .4 to .6 %).

Conclusion Regarding Short-Term Adverse Event Profiles:
The applicant concludes that there is no indication that Enstilar® Foam is associated with AEs, ADRs and lesional/perilesional AEs of either a higher frequency or severity than those seen with the two approved Taclonex® products. There were no AEs of concern unique to the Enstilar ® Foam group seen in the short-term trials.

Comparative Safety Data from Long-Term Clinical Trials with Taclonex® Ointment and Taclonex® Topical Suspension:
This section is based on exanimation of comparative safety data from long-term clinical trials with Taclonex® Ointment (MCB 0102 INT) and Taclonex® Topical Suspension (MBL 0502 US and MBL 0407 INT). The results of these trials have been previously submitted to the FDA as part of the NDA 021852 and NDA 022185.

Trial MCB 0102 INT (NDA 021852) was a randomized, double-blind, 3-arm trial comparing two treatment regimens involving the use of Taclonex® Ointment on the body over 52 weeks with 4 weeks of Taclonex® Ointment followed by 48 weeks of calcipotriol. In one arm, subjects received Taclonex® Ointment for 52 weeks. In the second arm subjects received Taclonex® ointment for 4 weeks followed by calcipotriol ointment for 4 weeks, and this sequence was then repeated for a total of 52 weeks. The third arm was a "control group" regimen which did not involve long-term topical corticosteroid treatment, where subjects received the Taclonex® ointment for 4 weeks followed by calcipotriol ointment for 48 weeks.

Trial MBL 0502 US (NDA 022185) was a randomized, double-blind, 2-arm, 8-week, vehicle-controlled trial followed by a 44-week open-label safety trial in scalp psoriasis in combination with an open-label, single-arm, 52-week safety trial in psoriasis vulgaris of the body (trunk and limbs). Subjects were randomized to 8 weeks of once daily treatment of scalp psoriasis with either Taclonex® Topical Suspension or the suspension vehicle. Following the 8- week double-blind phase, all subjects applied Taclonex® Topical Suspension to the scalp as needed for 44 weeks. Taclonex® Ointment was applied as needed to the trunk and/or limbs throughout the 52 week trial.

Trial MBL 0407 INT (NDA 022185) was a randomized, double-blind, 2-arm parallel-group, trial in subjects with scalp psoriasis. Subjects were treated with either Taclonex® Topical Suspension or calcipotriol in the suspension vehicle for up to 52 weeks as needed.

For all three trials, subjects with at least a moderate disease severity according to IGA were enrolled. Treatments in all three trials were applied once daily as required, up to 100 g/week, for up to 52 weeks.

Summary of Comparisons:
The pattern and the frequency of ADRs observed during the first 4 weeks (or 8 weeks for the scalp) of treatment in the long term trials was similar to that observed in the pooled short term trials with Taclonex® Ointment and Taclonex® Topical Suspension , with most common ADRs being those related to skin irritation. Most of the ADRs reported during these first weeks occurred also during the prolonged treatment (for 52 weeks when required) with similar incidence and intensity, and included pruritus, skin burning (preferred term: burning sensation and skin burning sensation) and worsening of psoriasis that were either related to calcipotriol or to the underlying disease. Apart from these events, ADRs that occurred during prolonged treatment in more than 1 subject were mostly skin infection and other skin events.

In all three long-term trials, an independent Adjudication Panel consisting of three dermatologists not otherwise involved in the trials identified corticosteroid related AEs where a causal relationship between the trial medication and such events was at least possible.

In trial MCB 0102 INT, the incidence of adjudicated corticosteroid related events was low and similar between the Taclonex® Ointment and the calcipotriol groups. The most common adjudicated corticosteroid reactions were skin atrophy and folliculitis. Other AEs of concern possibly related to long-term corticosteroid use reported in the two treatment groups using Taclonex® Ointment for up to 52 weeks (one arm just Taclonex® Ointment as needed the other Taclonex® Ointment alternating with calcipotriol ointment 4 weeks/4 weeks) included skin striae, furuncle, rash pustular, skin depigmentation, skin papilloma, ecchymosis and purpura. These occurred with a low incidence (in one or two subjects only) and the relationship to Taclonex® Ointment (in the opinion of the Adjudication Panel) was not clear in many cases. No systemic events were reported in the Taclonex® Ointment group.

In general, the findings regarding short term versus long term adverse events profile of Taclonex® Topical Suspension on the scalp were consistent with those for Taclonex® Ointment on the body. The incidence of adjudicated corticosteroid related events did not differ significantly between the Taclonex® Topical Suspension and calcipotriol groups. Skin atrophy was not observed and the most common corticosteroid–related events were folliculitis, rosacea, dermatitis and acne. There were no ADRs that increased in frequency or severity over time, and no serious ADRs associated with prolonged treatment.

Overall Conclusion for Long Term Safety:

Principal Observations:

1) On the basis of MUSE trails results, there was no indication that Enstilar® Foam is associated with more severe systemic effects than Taclonex® Ointment or Taclonex® Topical Suspension, as assessed by measurements of HPA axis suppression and calcium metabolism.

2) On the basis of data from short-term trials, there is no indication that Enstilar® Foam is associated with AEs, ADRs and lesional/perilesional AEs of either a higher frequency or severity than those seen with the two approved Taclonex® products. There were no AEs of concern unique to the Enstilar ® Foam group seen in the short-term trials.

3) On the basis of data from long-term clinical Trials with Taclonex® Ointment and Taclonex® Topical Suspension, the adverse reactions observed during long term treatment with the ointment and topical suspension products were predictable pharmacological class effects associated with calcipotriol and topical corticosteroids. There were no ADRs that increased in frequency or severity over time and there were no serious ADRs associated with prolonged treatment with Taclonex® Ointment or Taclonex® Topical Suspension as needed (up to 52 weeks).

The applicant states that a long term study with calcipotriol/BDP using the foam formulation is unlikely to yield new safety information. This appears to be a reasonable conclusion to this reviewer.

8 Postmarket Experience

Enstilar® Foam has not been marketed in any country.

9 Appendices

9.1 Literature Review/References

Literature references are cited in the body of the review.

9.2 Labeling Recommendations

The applicant submitted labeling that was reviewed and modified. The following sections of the revised draft labeling include significant changes from that proposed by the applicant:

2 DOSAGE AND ADMINISTRATION
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
12 CLINICAL PHARMACOLOGY
14 CLINICAL STUDIES

At the time of this review labeling discussions with the applicant were ongoing.

9.3 Advisory Committee Meeting

No advisory committee meeting was convened in response to this application.

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

/s/

PATRICIA C BROWN
09/16/2015

GORDANA DIGLISIC
09/16/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207589 **Applicant:** LEO Pharma A/S **Stamp Date:** 12/18/2014

Drug Name: Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%

NDA/BLA Type: 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	505(b)(1)			
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Dose selection reviewed in original NDA
EFFICACY					

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3698900

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? ●Pivotal Study #1: Phase 3 - LP0053-1001 (US) 426 subjects Arms: 1. (calcipotriene and betamethasone dipropionate) foam, 0.005%/0.064% 2. foam vehicle Indication: topical treatment of plaque psoriasis in adults (applied to body) ●Pivotal Study #2: Phase 2 – LEO 90100-7 (US) 302 subjects Arms: 1. (calcipotriene and betamethasone dipropionate) foam, 0.005%/0.064% 2. betamethasone dipropionate 3. calcipotriol Indication: topical treatment of plaque psoriasis (applied to body and scalp) ●Phase 2 Study: LEO 90100-35 376 subjects Arms: 1. (calcipotriene and betamethasone dipropionate) foam, 0.005%/0.064% 2. Daivobet® Ointment (Taclonex) 3. foam vehicle 4. Ointment vehicle Indication: topical treatment of plaque psoriasis (applied to body)	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Reviewed Phase 3 protocol. Agreed on primary endpoint.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess			X	Sponsor has submitted

Reference ID: 3698900

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?				(in NDA) waiver from conducting QT/QTc studies.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	This product has not been marketed.
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?				Long term safety addressed in trials MCB 102, MBL 502 and MBL 407
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		X		
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?		X		

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3698900

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		
37.	Are all datasets to support the critical safety analyses available and complete?		X		
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		X		
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter

None

Patricia C. Brown, M.D. — February 6, 2015
Reviewing Medical Officer — Date

Gordana Diglisic, MD — see sign-off date
Clinical Team Leader — Date

Reference ID: 3698900

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

/s/

PATRICIA C BROWN
02/06/2015

GORDANA DIGLISIC
02/06/2015