Clinical Review and Evaluation

PMR Final Study Report

Application Type	sNDA: Efficacy and Labeling Supplements
Application Number(s)	NDA 207589 S-005, S-006 and S-007
Priority or Standard	Priority
Submit Date(s)	January 28, 2019
Received Date(s)	January 28, 2019
PDUFA Goal Date	July 28, 2019
Division/Office	Division of Dermatology and Dental Products (DDDP)
Review Completion Date	July 26, 2019
Established Name	Calcipotriene and betamethasone dipropionate
(Proposed) Trade Name	Enstilar Foam
Pharmacologic Class	Vitamin D analog and corticosteroid
Code name	LEO 90100
Applicant	LEO Pharmaceutical Products Ltd. A/S
Formulation(s)	Foam
Dosing Regimen	Once daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of plaque psoriasis of the body and scalp in patients 12 years and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	For the topical treatment of plaque psoriasis of the body and scalp in patients 12 years and older

Consultant Reviews

Labeling Reviews

- Division of Medical Policy Programs (DMPP): Sharon R. Mills, BSN, RN, CCRP reviewed Patient Package Insert (PPI) and Instructions for Use (IFU). (Review dated July 23, 2019)
- Division of Medication Error Prevention and Analysis (DMEPA) Madhuri R. Patel, PharmD reviewed Prescribing Information (PI), PPI and IFU (Review dated July 2, 2019)
- Division of Pediatric and Maternal Health (DPMH): reviewed PI
  - Pediatric Team Consult Response: Amy Taylor, M.D. (Review dated July 23, 2019)
  - Maternal Health Team Consult Response: Jane Liedtka, M.D. (Review dated June 17, 2019)

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1. Executive Summary

Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/ 0.064% is a fixed-dose combination product containing a vitamin D analog (calcipotriene 0.005%)[1] and a potent topical corticosteroid (betamethasone dipropionate 0.064%). The Applicant, LEO Pharmaceutical Products (LEO Pharma), Ltd submitted a Supplemental NDA (sNDA) to support revisions to product labeling to incorporate data regarding the use of Enstilar Foam in patients age 12 to 16 years with plaque psoriasis of the body and scalp. The Applicant conducted Trial LP0053-1108 to address the post marketing requirement (PMR) 2958-1 under the Pediatric Research Equity Act (PREA) to evaluate the effects of Enstilar Foam on calcium metabolism, hypothalamic-pituitary-adrenal axis (HPA Axis) and safety in the pediatric population age 12 years to 16 years. In addition, the Applicant proposed to revise labeling to comply with the Pregnancy and Lactation Labeling Final Rule (PLLR) and to include data from Trial LP0053-1276 (PMC 2958-2) in Section 12.2 Pharmacodynamics.

Trial LP0053-1108 was an open-label, pharmacokinetic (PK) and safety trial enrolling 106 pediatric subjects age 12 to 16 years with plaque psoriasis. Enrolled subjects had plaque psoriasis on the body and scalp of at least mild severity, defined as an Investigator Global (IGA) scores of 2 or 3 and at least 10% of the surface area of the scalp affected and at least 2% total BSA affected. All subjects applied Enstilar Foam once daily for up to 4 weeks.

There were no unexpected adverse events (AEs) or safety signals. There were no deaths, serious adverse events, discontinuations due to adverse events or AEs categorized as “severe.” A total of 22 (20.8%) subjects reported 32 AEs. Among these AEs, there were 4 AEs which were classified as lesional/perilesional (acne, erythema, skin reaction, and application site pain) in 4 subjects (3.8%). The only preferred terms (PTs) reported by more than one subject were upper respiratory infection (8 subjects, 7.5%), nasopharyngitis (4 subjects, 3.8%) and acne (2 subjects,1.9%). A total of 5 (4.7%) subjects reported 6 adverse reactions (ARs.) Investigators assessed 5 ARs as possibly or probably related and myopia as “unknown” relationship.

[1] Calcipotriene is identical to calcipotriol. Calcipotriol is the International Non-proprietary Name and calcipotriene is the US Adopted Name (USAN).

A subset of 33 subjects, referred to as the HPA axis cohort, received Enstilar Foam under maximal use conditions and performed HPA axis testing, evaluation of calcium metabolism using 24-hour urine samples, and PK assessments. These subjects had at least moderate disease severity according to the Physician Global Assessment (PGA) scale on the body and scalp, at least 10% BSA affected, and at least 20% of the scalp area affected. All analyzed pharmacokinetic (PK) samples were below the limit of quantitation for calcipotriene and its metabolite MC1080 at Week 4. However, levels of betamethasone dipropionate (BDP) were quantifiable in 12 subjects (36%) and levels of its metabolite betamethasone 17-propionate (B17P) were quantifiable (LLOQ 30.0 pg/mL) in 6 subjects (18%). Of the 33 subjects who participated in the assessment of HPA axis suppression, 3 subjects (9%) had serum cortisol concentrations less than 18 mcg/dl after ACTH challenge at Week 4. There were no clinically relevant changes in urinary calcium or albumin-corrected serum calcium.

The Applicant provided sufficient data to confirm that the risk benefit conclusions in this pediatric population are similar to the adult population. In addition, the Applicant proposed labeling which was compliant with PLLR. This reviewer recommends an approval action for this application, NDA 207589 Supplement-005/006/007, to revise the current indication to the topical treatment of plaque psoriasis in patients 12 years and older. As the labeling review is still in progress, this recommendation is contingent upon the successful completion of labeling negotiations with the Applicant.

1.1. Benefit-Risk Assessment

The Review team based the analysis of the risks and benefits for Enstilar Foam for the topical treatment of plaque psoriasis in patients 18 years and older from data from adequate, well-controlled, 4 -week, clinical trials (LP0053-1001, LEO 90100-7, LEO 90100-35) and a maximal use trial (LEO 90100-30). (See Clinical Review by Patricia Brown, MD dated 9/16/2015.)

LEO Pharma Ltd markets other calcipotriene and betamethasone dipropionate combination products, Taclonex (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/0.064% and Taclonex (calcipotriene and betamethasone dipropionate) Ointment, 0.005%/0.064%. The Applicant investigated the use of these products in the pediatric population age 12 to 16 years in several trials. All trials evaluated the effects of the combination products on safety including HPA axis and calcium metabolism and secondarily on treatment effect. The Applicant conducted 2 open-label, 8- week trials (MBL 0801 and MBL 0412 INT) evaluating Taclonex Topical Suspension in a total of 109 pediatric subjects with moderate to severe psoriasis of the scalp involving at least 10% of the scalp area. (See Clinical Review dated July 7, 2014). In addition, the Applicant conducted an open-label, 4-week trial evaluating Taclonex Ointment in 33 pediatric subjects with plaque psoriasis on the body involving 5-30% body surface area (BSA).

Findings from these trials indicated no changes in albumin-corrected serum calcium and adrenal suppression in 1/30 (3.3%) subjects receiving Taclonex Topical Suspension and none

receiving Taclonex Ointment. Furthermore, the Applicant evaluated the safety and bioavailability of Taclonex Topical Suspension for the treatment of subjects age 12 years to 16 years with plaque psoriasis of the body and scalp. Currently, this submitted data is under review.

In this supplement, the Applicant submitted results from Trial LP0053-1108 to provide safety and bioavailability data for Enstilar Foam for the treatment of subjects age 12 years to 16 years with plaque psoriasis of the body and scalp. The trial enrolled a total of 106 subjects with plaque psoriasis of at least mild severity defined as a PGA scores of 2 or 3 with at least 2% total BSA affected and at least 10% of the surface area of the scalp affected. A subset of the subjects, referred to as the HPA axis cohort, received Enstilar Foam under maximal use conditions and participated in HPA axis testing, evaluation of calcium metabolism with 24-hour urine samples and pharmacokinetic (PK) assessments. All subjects applied Enstilar Foam once daily for up to 4 weeks. In the HPA axis cohort, enrolled subjects had psoriasis of at least moderate severity on the body and scalp according to PGA and involvement with psoriasis of at least 10% BSA, and at least 20% of the scalp area. There were no clinically meaningful changes in parameters related to calcium metabolism and adrenal suppression occurred in 9%. Adverse reactions included acne, erythema, skin reaction and application site pain. The team identified no new safety signals.

These open-label pediatric trials, including Trial LP0053-1108, provide addition support for the positive benefit risk assessment of these fixed combination products in patients 12 years and older. Analyses of adverse events, HPA axis testing, parameters of calcium metabolism, and PK findings, indicate low systemic exposure and a similar safety profile in the pediatric population as the adult population. The submitted PK, PD and safety data in the pediatric population indicate a favorable risk benefit conclusion and support approval of this sNDA which provides for the use of Enstilar Foam in the population 12 years and older with plaque psoriasis (S-005).

2. Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, immune-mediated skin disorder which may develop in genetically susceptible individuals.[2] Chronic plaque psoriasis is the most common form of psoriasis in children and adults.[3] Other forms of psoriasis include guttate, pustular, and erythrodermic psoriasis. The characteristic lesion is a sharply demarcated, erythematous plaque with micaceous scale; the plaques may be localized or widespread in distribution. Common sites of involvement are scalp, elbows, knees, and presacral region. However, psoriasis may occur on

[2] Mallbris L et al. J Invest Dermatol. 2005 Mar;124(3):499-504.
[3] Paller AS et al. Psoriasis in children: Epidemiology, clinical manifestations, and diagnosis. UpToDate. Accessed April 5, 2019.

any cutaneous site including the palms, soles, nails, and genitalia. [4]The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, producing proinflammatory cytokines which trigger and perpetuate the inflammatory cascade.

The prevalence of psoriasis varies by geographic region. The estimated prevalence worldwide ranges from 0 to 1.37 percent of children and 0.51 to 11.3 percent of adults. [5]Studies of the United States population found prevalence rates of up to 4.6%.[2] Among the estimated 7.5 million Americans affected with psoriasis, 80 percent have mild to moderate disease, while 20 percent have moderate to severe disease affecting more than 5 percent of the body surface area.

The onset of psoriasis may occur at any age, but often occurs in childhood. In approximately 35–50% of individuals, psoriasis develops before the age of 20 years; in approximately 75% of individuals, psoriasis develops before the age of 40 years. [2] Regardless of the age of onset, psoriasis is characterized by a chronic course with intermittent remissions.

The areas of involvement and presentation of psoriasis may vary with age. In infants, psoriasis often presents with symmetrical, well-demarcated, thin, erythematous plaques with minimal scale in the diaper area. In children, psoriasis commonly presents on the scalp and may involve the face. ,[67] In all age groups, psoriasis is associated with an increased risk of a number of comorbid conditions including obesity, cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, autoimmune disorders, psychiatric and behavioral disorders.[8]

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected individuals. At the Patient Focused Drug Development Meeting held with the FDA (March 17, 2016), patients discussed current challenges with variability in effectiveness, tolerability, access to treatments, and uncertainty regarding long-term effects of available treatments. Therefore, the development and approval of additional safe and effective therapies for children and adults with plaque psoriasis continues to be an important goal.

[4] Shah KN. Diagnosis and treatment of pediatric psoriasis: current and future. Am J Clin Dermatol. 2013;14(3):195
[5] Michalek IM et al. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017;31(2):205.
[6] Morris A et al. Childhood psoriasis: a clinical review of 1262 cases. Pediatr Dermatol. 2001;18(3):188.
[7] Mercy K et al. Clinical manifestations of pediatric psoriasis: results of a multicenter study in the United States. Pediatr Dermatol. 2013 Jul;30(4):424-8. Epub 2013 Jan 30.
[8] Elmets et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol 2019; 80:1073-113

2.2. Analysis of Current Treatment Options

The effectiveness of drugs targeting immune signaling (etanercept),[9] inhibition of pro-inflammatory cytokines and chemokines (topical corticosteroids) and epidermal hyperproliferation and differentiation (vitamin D analogs) has been demonstrated in both children and adults. The response to both systemic and localized immunosuppression appears to be similar in all age groups.[10] For a discussion of the topical treatment options for chronic plaque psoriasis see the Clinical Reviews of NDA 22563 dated 09/17/2010 and 09/03/2012.

2.3. Patient Experience Data

Among the assessments of treatment effect, the Applicant included instruments to measure disease severity, maximal pruritus and sleep loss as perceived by the subject. Investigators conducted all patient reported outcome (PRO) assessments at Screening, Baseline, Week 2, 4, 6 and 8 using the following instruments:

- Subject's global assessment of disease severity on the body and scalp: a 5- point scale ranging from "clear" to "severe"
- Subject´s Assessment of Itch and Subject´s Assessment of Itch-related Sleep Loss: evaluated on visual analog scales (VAS) with anchors from "none" to "worst possible" to rate maximal itching or sleep loss during the last 24 hours
- Children's Dermatology Life Quality Index (CDLQI): a validated scale including 10 questions with 4 response choices (except Question 7 impact on school with 5 choices)
- The Family Dermatology Life Quality Index (FDLQI): a scale to be completed by family members of the subject including 10 questions with 4 response choices

The Applicant solicited no comments regarding the development of PROs to support labeling claims for this pediatric supplement. However, the FDA provided advice regarding the use of the VAS during a guidance meeting with the Applicant regarding a trial in adults (Meeting Minutes dated 9/9/2015). The FDA indicated that findings to support a PRO labeling claim must be statistically significant and clinically meaningful. The results of the PRO assessments will be discussed briefly in this review.

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 7.2.2

[9] Menter et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol 2019; 80:1029-72.
[10] Paller AS et al. Psoriasis in children: Management of chronic plaque psoriasis. UpToDate> Accessed April 5, 2019.

X	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 7.2.2
		☐	Performance outcome (PerfO)	
	☐		Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐		Patient-focused drug development or other stakeholder meeting summary reports	
	☐		Observational survey studies designed to capture patient experience data	
	☐		Natural history studies	
	☐		Patient preference studies (e.g., submitted studies or scientific publications)	
	☐		Other: (Please specify):	
X	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐		Input informed from participation in meetings with patient stakeholders	
	X		Patient-focused drug development or other stakeholder meeting summary reports	See discussion below
	☐		Observational survey studies designed to capture patient experience data	
	☐		Other: (Please specify):	
☐	**Patient experience data was not submitted as part of this application.**			

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development Meeting for psoriasis which was held by the FDA on March 17, 2016. Patients discussed current challenges with variability in effectiveness, tolerability, access to approved treatments, and uncertainty regarding long-term effects of available treatments. Therefore, the FDA considers that the development of additional safe and effective therapies for all patients including children to be an important goal.

3. Regulatory Background

The FDA approved Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% on October 16, 2015 for the topical treatment of plaque psoriasis in patients 18

years of age and older. The maximum approved dosage in the adult population was 60 g every 4 days

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The Agency waived the study requirement for pediatric subjects ages 0 to 11 years because there was evidence strongly suggesting that a combination product containing a potent corticosteroid would be unsafe in this pediatric group; the Agency deferred the submission of the pediatric assessments in subjects age 12 to 16 years because this product was ready for approval for use in adults and the pediatric study had not been completed (Agreed iPSP dated 12/3/2013). The Applicant was required to conduct the following deferred pediatric study under section 505B (a) of the FDCA:

> 2958-1 An open-label study to assess the effect of Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% on calcium metabolism in 100 evaluable pediatric subjects aged 12 years to 16 years and 11 months with plaque psoriasis of the body and scalp. Pharmacokinetics (PK) of Enstilar Foam and assessment of hypothalamic-pituitary axis (HPA) suppression will be conducted in a sub-set of 30 subjects with at least moderate plaque psoriasis under maximal use conditions.
>
> Final Protocol Submission: 03/2015
> Study Completion: 03/2017
> Final Report Submission: 06/2018

On March 27, 2015, the Applicant submitted Protocol LP0053-1108 (IND 114063 SD55). The FDA reviewed the protocol (Clinical Review dated 6/11/2019) and provided comments (Advice Letter dated 6/24/2019) regarding the safety monitoring (modify assessments to include body temperature, local tolerability and a physical examination at the end of treatment) and treatment withdrawal criteria (discontinue treatment of subjects in the non-HPA axis cohort who clear prior to the end of treatment.) The Applicant revised the protocol in response to FDA comments (submitted 7/15/2015.)

On February 10, 2017, the Applicant, LEO Pharma Inc, submitted a request for an extension of the timelines for completion of PMR 2958-1 for Enstilar Foam due to recruitment challenges. Based on feedback from investigators, the inclusion criteria of at least 10% of affected body surface area (BSA) and ≥20% of the scalp area with at least moderate severity, constituted a limited patient population. With the concurrence of PeRC (PeRC Meeting held 3/15/2017), the Division granted the request for an extension of the final report submission date to December 2018 (Letter dated 3/27/2017).

On December 6, 2018, the Applicant requested an extension of the milestone date for the final report submission for PMR 2958-1 to allow compilation of bioanalytical and method validation reports and datasets for Trial LP0053-1108. The Division agreed and granted an extension of the milestone date for the final report submission until January 31, 2019 (Letter dated 12/19/2019).

On January 28, 2019, the Applicant submitted the final study report for Trial LP0053-1108. For administrative purposes, the Division designated the other components of the submission as follows (Letter dated 3/22/2019):

- NDA 207589/S-005- Provides for response to the January 22, 2019 Pediatric Written Request (PWR)-Pediatric Exclusivity Board 7/3/2019
- NDA 207589/S-006- Provides for Pregnancy Lactation Labeling Rule (PLLR) Conversion
- NDA 207589/S-007- Provides for an update of Section *12.2 Pharmacodynamics* of labeling with data from Trial LP0053-11276, PMC 2958-2, vasoconstriction assay (VCA) trial
- NDA 207589 /S-008- Provides for results from an adult trial to support a comparative claim: Refuse to File Letter dated 3/28/2019 - no inclusion of ISE/ Summary of Clinical Efficacy or inclusion of efficacy in labeling

Pediatric Written Request
After clarifying that the Pediatric Written Request (PWR) issued in 2007 had expired, the FDA recommended that the Applicant submit a Proposed Pediatric Study Request (PPSR) delineating the planned studies utilizing calcipotriene and the fixed combination of calcipotriene and betamethasone dipropionate for the treatment of psoriasis. The FDA reminded the Applicant to address any other indications for which calcipotriene or calcipotriene/betamethasone dipropionate may have public health benefits in children (Advice Letter dated September 18, 2018).

On September 27, 2019, the Applicant submitted a Proposed Pediatric Study Request ("PPSR") for calcipotriene and betamethasone dipropionate. The PPSR included completed assessments required under PREA for Enstilar Foam (NDA 207589) and Taclonex Topical Suspension (NDA 022185). When the Applicant was informed that previously submitted data could not be used to support a PWR, the Applicant withdrew the PPSR for Taclonex Topical Suspension. On January 22, 2019, the FDA issued a Written Request for Pediatric Studies under the pediatric exclusivity program for calcipotriene 0.005% and betamethasone dipropionate 0.064% foam. The FDA determined that further studies in conditions such as vitiligo or morphea would not produce health benefits in children at this time.

PMC 2958-2
The Applicant conducted Trial LP0053-1276 to address the following post marketing commitment (PMC) 2958-2 which was issued under Section 506B with the approval of Enstilar Foam (October 16, 2015):

> Conduct a single point vasoconstriction assay (VCA) trial in healthy subjects with adequate bracketing using visual assessment to determine the topical corticosteroid potency classification for Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%.

On September 22, 2017, the FDA received the final study report for Trial LP0053-1276, a single point vasoconstriction (VCA) study for identification of the potency class. After reviewing the methodology and data, the Clinical Pharmacology reviewer, Luke Oh, Ph.D. concluded that "NDA 207589 post marketing commitment (PMC) 2958-2 study report is acceptable from a Clinical Pharmacology perspective and the PMC is considered fulfilled." (Clinical Pharmacology Review dated 7/27/2019).

The FDA informed the Applicant (Advice letter dated 9/21/2018) that the PMC was fulfilled and requested that the Applicant submit a prior approval labeling supplement to revise Section 12.2 Pharmacodynamics of the prescribing information. The draft labeling which was submitted with this supplement (S-007) included a subsection describing the results of the vasoconstriction assay (VCA) which characterized Enstilar Foam as a "potent vasoconstrictor."

Pregnancy and Lactation Labeling Final Rule (PLLR)
Among the proposed revisions to the prescribing information, the Applicant included language to address the Pregnancy and Lactation Labeling Final Rule (PLLR) (S-006). According to the approval date of October 16, 2015, the deadline for the submission of revised labeling for PLLR conversion was June 29, 2019. The proposed revisions to Section 8 were based on language for another dosage form of calcipotriene and betamethasone dipropionate [Taclonex (calcipotriene and betamethasone dipropionate Ointment, 0.005%/0.064%] which was recently converted to PLLR format. See review by Nancy Xu (NDA 021852/S-020 dated 12/20/2018; Approval Letter dated 12/21/2018.)

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. The Division did not request that the Office of Scientific Investigations (OSI) conduct clinical inspections of domestic or foreign sites.

4.2. Product Quality

The Applicant determined that the formulation of Enstilar Foam which was approved for use in adult population was acceptable for use in the target pediatric populations. Therefore, the Applicant submitted no new product quality data.

The CMC Reviewer, Steve Hathaway, Ph.D., analyzed the request for categorical exclusion from the requirement to conduct an Environmental Assessment (EA; SD 237 dated 5/20/2019) in accordance with 21 CFR 25.31(b). The Applicant stated that a categorical exclusion from the environmental assessment requirements of 21 CFR 25.40 was justified because:

1. "The estimated concentrations of the substances at the point of entry into the aquatic environment (EIC) will be below 1 part per billion, and

2. to the Applicant's knowledge, no extraordinary circumstances exist, as described in 21 CFR 25.21, that indicate that approval of the supplement to the NDA will significantly affect the quality of the human environment."

The Applicant provided the calculation of the Expected Introduction Concentration (EIC) of an active moiety into the aquatic environment (calcipotriene: (b) (4) ppb and betamethasone dipropionate (b) (4) ppb). The CMC reviewer concluded, "The quantities of drug substance expected to enter the environment as a result of the proposed action falls well below the 1 ppb threshold for action. The Applicant's request for categorical exclusion from the EA requirement is acceptable." See Review dated July 12, 2019.

The Applicant proposed no changes to the to the CMC-related sections of the Prescribing Information, Patient Information, or carton and container labeling. However, the CMC reviewer proposed minor editorial changes to harmonize the presentation of the information about the drug substances with other calcipotriene/betamethasone dipropionate product labeling.

5. Pharmacology Toxicology

The Applicant submitted no new nonclinical data in this efficacy supplement. The Pharmacology/Toxicology team conducted a comprehensive review of the nonclinical data which was submitted to support the original approval of Enstilar Foam. For an analysis and discussion of the nonclinical data, refer to the review by Norman See, Ph.D. dated July 7, 2015.

Regarding this submission, the Dr. See indicated "The Applicant completed all necessary nonclinical studies to support evaluation of Enstilar Foam in the pediatric population aged 12 to 17 years." The Pharmacology/Toxicology Reviewer provided comments regarding the relevant subsections of labeling, Sections 8 *Use in Specific Populations* and 13 *Nonclinical Toxicology* (Memorandum by Norman See, Ph.D. dated June 3, 2019.)

6. Clinical Pharmacology

In the current submission, the Applicant provided the final study report for LP0053-1108 to address PMR 2958-1 and proposed labeling to include the findings from LP0053-1276 to address PMC 2958-2. For LP0053-1108, the Clinical Pharmacology reviewer, Cindy (Liping) Pan, Ph.D. evaluated the pharmacokinetics (PK), effects on calcium metabolism and the potential for HPA axis suppression from once daily administration of Enstilar Foam for 4 weeks in the pediatric population. Dr. Pan indicated that the trial results support the systemic safety of the Enstilar Foam following once daily application to the body and scalp of subjects 12 to 16 years of age with at least mild psoriasis. Dr. Pan recommended "The Office of Clinical Pharmacology, Division of Clinical Pharmacology III has reviewed the final study report of the PMR (2958-1) and have concluded that the Applicant has fulfilled this PMR."

For a detailed analysis of the PK and PD data and recommended revisions to the proposed language in Section 12 of labeling, see the review by Cindy (Liping) Pan, Ph.D. dated 7/24/2019. A summary of the clinical pharmacology and biopharmaceutics findings from her review are presented below. Refer to the Clinical Pharmacology Review by Chinmay Shukla, Ph.D. (dated 8/24/2015) for a comprehensive review of the clinical pharmacology data submitted to support the approval of the original application for Enstilar Foam.

For a review of the data intended to address Post Marketing Commitment (PMC) 2958-2 to conduct a single point vasoconstriction (VCA) study, see the review by Luke Oh, Ph.D. dated 7/27/2018.

6.1. Pharmacokinetics

Dr. Pan analyzed the pharmacokinetic (PK) data in the pediatric population and compared the results to the PK data in the adult population from the original NDA submission (Review by Chinmay Shukla, Ph.D. dated 8/24/2015). Dr. Pan summarized the data as presented below.

Table 1: Comparison of PK Data Between Adults and Adolescents Following LEO90100 Application Under Maximal Use Conditions

	Adults (n=35) [a]				Adolescents (n=33) [a]		
Analyte	n	C_{max} (pg/mL)	AUC_{last} (h*pg/mL)		n	C_{max} (pg/mL)	AUC_{∞} [b] (h*pg/mL)
BDP	5	33.7 - 81.1	16.9 – 82.5		12	31.1 – 480	1250
B17P	27	30.2 - 1133	18.5 – 4254		6	30.8 – 91.7	501
Calcipotriol	1	N.C	N.C		0	N/A	N/A
MC1080	3	23.3 - 26.6	55.3 – 65.5		0	N/A	N/A

a: mean weekly dose 62 g (range 58 to 467 g/4wk) for adults, 115g (range 22 to 842 g/4wk) for adolescents
b: AUC data from 2 different subjects for BDP (n=1) and betamethasone 17-propionate (n=1)
B17P=betamethasone 17-propionate, BDP=betamethasone dipropionate, N.C=a parameter that could not be reliably estimated, N/A=not applicable
LLOQ: 30 pg/mL for BDP and B17P, 50 pg/mL for calcipotriol and 20 pg/mL for MC1080

Source: Clinical Pharmacology Review by Cindy (Liping) Pan, Ph.D. Table 3
Abbreviations: AUC_{∞} = area under the concentration-time curve from time zero to infinity; C_{max} = maximum drug concentration

6.2. Pharmacodynamics

Subjects participating in the ACTH challenge testing applied a mean weekly dose of 115 grams to a mean body surface area involvement of 16% and mean scalp involvement of 56%. Among the 33 subjects with evaluable data, 3 subjects (9%) had adrenal suppression 30 minutes after ACTH challenge testing at Week 4. Dr. Pan observed that none of the 3 subjects with HPA axis suppression had quantifiable PK analytes. Refer to Table 6 of the Clinical Pharmacology review for a summary of the serum cortisol concentrations for the 3 subjects with adrenal suppression following ACTH challenge testing.

The Applicant conducted an evaluation of the effects of Enstilar Foam on calcium metabolism in 106 pediatric subjects. Changes in albumin-corrected serum calcium concentration and 24-hour urinary calcium excretion in the maximal use subset (HPA set) were small. There were no clinically meaningful changes. The following tables from the Clinical Pharmacology review summarized the data:

Table 2: Albumin-Corrected Serum Calcium Concentrations

	Albumin-corrected serum calcium (mmol/L)	
	Baseline (n=104)	Week 4 (n=103)
Mean	2.237	2.222
SD	0.092	0.116
Median	2.240	2.250
Minimum	1.88	1.87
Maximum	2.49	2.41

Source: Clinical Pharmacology Review by Cindy (Liping) Pan, Ph.D., Table 5
Abbreviation: SD = standard deviation

Table 3: 24-Hour Urinary Calcium Excretion in HPA Set (n=34)

	Calcium excretion rate (mmol/24hr)	
	Baseline (n=24)	Week 4 (n=23)
Mean	2.866	2.538
SD	1.554	1.938
Median	2.570	1.770
Minimum	0.33	0.30
Maximum	6.10	7.08

Source: Clinical Pharmacology Review by Cindy (Liping) Pan, Ph.D., Table 6
Abbreviation: SD = standard deviation

7. Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The Applicant conducted a single, open-label Trial LP0053-1108 to address PMR 2958-1 and support the use of Enstilar Foam in patients 12 years and older with plaque psoriasis. Trial LP0053-1108 was entitled, “Safety and Effect of LEO 90100 aerosol foam on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to <17 Years) with Plaque Psoriasis.” Key elements of the trial are summarized below.

Table 4: Clinical Trial LP0053-1108

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects	Study Population	No. of Centers and Countries
Studies to Support Safety							
LP0053 -1108	Multi-center, open-label, repeat-dose safety trial with assessments of PK, HPA axis, calcium (CA) metabolism and treatment effects	Once daily up to 4 weeks topically to body and scalp	-AEs **-**At Wk 4: **-**Cortisol ≤18 mcg/ dl at 30 min ACTH Challenge **-**Albumin corrected serum CA **-**Calcium excretion from 24-hr urine -CA: Cr ratio from 24- hr urine	Screening: 4 weeks Treatment: 4 weeks Follow-up: 4 weeks	Treated: 106 Completed: 103	Age 12 -16 **-HPA axis cohort:** ≥Moderate psoriasis -≥10% BSA -≥20% scalp area. **-Non-HPA axis cohort:** -≥Mild disease -≥2% BSA -≥10% affected scalp area.	26 sites in 4 countries: -Nether-lands, -Poland -Romania -U.S.

Source: Reviewer's table
Abbreviations: ACTH = adrenocorticotrophic hormone, CA = calcium, Cr = creatinine, PK = pharmacokinetics, HPA = hypothalamic-pituitary-adrenal (axis), hr = hour; Wk = week

In addition, the Applicant proposed to include the results from the single-point VCA trial (LP0053-1276) in Section 12.2 *Pharmacodynamics* of the prescribing information. As the Clinical Pharmacology and Clinical teams previously reviewed the final study report for Trial LP0053-1276 (reviews dated 7/27/2018 and 8/6/2018 respectively), the primary data was not discussed in this review.

7.1.2. Review Strategy

The focus of this review was the evaluation of the local and systemic safety of Enstilar Foam when applied once daily for up to 4 weeks in the population age 12 to 16 years with plaque psoriasis. Systemic safety assessments included documentation of adverse events, vital signs, clinical laboratory parameters, testing for HPA axis suppression, effects on calcium metabolism and systemic exposure (PK).

The evaluation of efficacy was a secondary objective of Trial LP0053-1108. However, the design of the trial included no vehicle control to allow interpretation of study findings. Therefore, the efficacy data was considered supportive of previous conclusions from adequate and well controlled trials which were conducted in adults. As the pathophysiology of plaque psoriasis and response to treatment are similar in the adult and pediatric populations, efficacy in the population age 12 to 16 years was extrapolated from data in the adult population.

Data Sources
The sources of data used for the evaluation of the safety and treatment effects of Enstilar Foam in the pediatric population included a final study report submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)], bioanalytic reports and literature references.

This application was submitted in eCTD format and entirely electronic. The electronic submission is located in the following network path:

\\CDSESUB1\evsprod\NDA207589\207589.enx

Data and Analysis Quality
In general, the data submitted by the Applicant to support the safety of Enstilar Foam for the proposed indication appeared adequate.

7.2. Review of Relevant Trial

7.2.1. Study Design and Endpoints

Clinical Trial LP0053-1108

The primary objective of Trial LP0053-1108 was to evaluate the safety of once daily use of Enstilar Foam in pediatric subjects (aged 12 to 16 years) with psoriasis of the body and scalp; the secondary objective was to evaluate the treatment effect of Enstilar Foam in this pediatric population.

Study Population
The key entry criteria that defined the general study population and the subgroup of subjects who participated in the assessment of HPA Axis suppression are the following:

Table 5: Entry Criteria

	Subjects	
Key Inclusion Criteria	**Non-HPA Axis**	**HPA Axis**
Males and females age 12 to less than 17 years	X	X
Signs of plaque psoriasis on the body and scalp	X	X
Psoriasis on the body: at least 2% BSA	X	
Psoriasis on the scalp: at least 10% of the scalp area	X	
Psoriasis on the body: at least 10% BSA		X
Psoriasis on the scalp: at least 20% of the scalp area		X
Maximum total involvement with psoriasis: 30%	X	X
PGA on the body and scalp	≥mild	≥moderate

Key Inclusion Criteria	Subjects	
	Non-HPA Axis	HPA Axis
Serum albumin-corrected Ca below upper reference limit at SV2	X	X
Normal HPA Axis function at SV2		X

Key Exclusion Criteria	Subjects	
	Non-HPA Axis	HPA Axis
Known hypersensitivity to any components of the test product	X	X
Current diagnosis of other forms of psoriasis	X	X
Other confounding conditions or inflammatory skin diseases	X	X
Known or suspected disorders of calcium metabolism	X	X
History of serious allergy, asthma, cutaneous allergic reaction		X
Known or suspected hypersensitivity to Cortrosyn/ Synacthen		X
Clinical signs or symptoms of Cushing's disease or Addison's disease		X
Abnormal sleep pattern		X
Known or suspected severe renal or hepatic disease	X	X

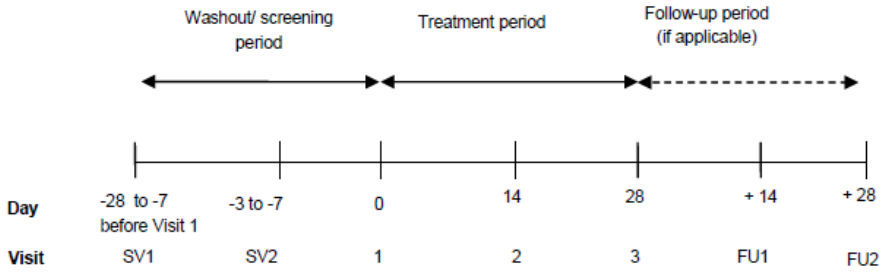
Source: Reviewer's Table-Modified from Module 2.7.3 Summary of Clinical Efficacy Addendum, Panel 2 and 3
Abbreviations: ACTH = adrenocorticotropic hormone, BSA = body surface area, HPA = hypothalamic-pituitary-adrenal, IGA = Investigator's Global Assessment Scale, SV2 = screening visit 2

Study Design

This was an international, multi-center, prospective, open-label, trial in subjects aged 12 to 16 years with plaque psoriasis on the body and scalp. All subjects received topical treatment with Enstilar Foam once daily for up to 4 weeks and participated in assessments of calcium metabolism. A subset of subjects with psoriasis of at least moderate severity performed PK and PD assessments under maximal use conditions.

The trial consisted of 3 periods: 7 to 28-day screening/washout period, a 28-day treatment period, and optional 28-day follow-up period. Investigators assessed safety and treatment effects during 5 visits with 2 additional visits for follow-up if needed. The overall design is illustrated below:

Figure 1: Trial Design – Days and Visits



Abbreviations: SV1 = screening visit 1, SV2 = screening visit 2, FU1 = follow-up 1, FU2 = follow-up 2

Subjects participating in HPA axis testing and PK assessments continued to apply Enstilar Foam regardless of whether lesions cleared with treatment; all other subjects discontinued treatment to lesions which were clear according to the investigational staff at Visit 2. Subjects could restart treatment if psoriasis recurred.

Investigators scheduled optional follow-up Visit 1 (14 days following the last treatment) for subjects with ongoing serious adverse events (SAEs) or related/ non-assessable ongoing non-serious AEs at the end of treatment. Investigators scheduled optional follow-up Visit 2 (28 days following the last treatment) for subjects with a serum cortisol concentration ≤18 mcg/dl at 30 minutes after HPA axis testing (ACTH challenge.)

Subjects performing assessments under maximal use conditions received sufficient study product to apply to all affected areas once daily without limitation. Subjects not performing assessments under maximal use conditions applied the study product per labeling and received a maximum of 120 g of Enstilar Foam per week or less depending on their age and BSA as tabulated below:

Table 6: Dosing Criteria for Subjects in the Non-HPA Axis Cohort in Trial

Age range (years)	BSA[a]	Maximum weekly dose LEO 90100	Number of cans dispensed[b]
12 to <15	≤1.3 m^2	60 g	2
12 to <15	>1.3 m^2	90 g	3
>15	≤1.7 m^2	90 g	3
>15	>1.7 m^2	120 g	4

a. BSA calculated using the Mosteller formula: BSA (m2) = ([height (cm) × weight (kg)]/3600)½ (Mosteller, 1987)
b. Number of cans distr buted at dispensing visits (baseline and Week 2).
Source: Module 2.7.3 Summary of Clinical Efficacy Addendum; Panel 4
Abbreviations: BSA = body surface area, HPA = hypothalamic-pituitary-adrenal

Assessments

At screening, investigators performed physical examinations, provided instructions regarding calcium consumption during the trial, obtained a 25-hydroxy vitamin D level and laboratory evaluation (hematology, chemistry and urinalysis). Safety monitoring included AEs, concomitant medications, vital signs, physical examinations, pregnancy testing, and clinical safety laboratory assessments, including parameters for the assessment of calcium metabolism (spot urine samples). Investigators instructed subjects to record the daily intake of dairy products and calcium-fortified products in the 4-day period prior to SV2 and Week 4.

The subset of the subjects, referred to as the HPA axis cohort, who received treatment under maximal use conditions performed HPA axis testing, evaluation of calcium metabolism using 24-hour urine samples, and PK assessments. Both investigators and subjects evaluated efficacy throughout the trial. The schedule of key safety and efficacy assessments are presented below:

Table 7: Schedule of Safety Assessments in Trial LP0053-1108

Assessment	Visit							
	SV1	SV2	Visit 1	Week 2	Week 4	FU1[a]	FU2[b,c]	EW
AEs		X	X	X	X	X	X	X
ACTH challenge test[c]		X			X		X	
Biochemistry, haematology, and urinalysis[d]		X			X	X		X
Vital signs		X	X	X	X			X
Physical examination	X				X			X
Local safety and tolerability			X	X	X			X
PK				X	X			

a) This visit was 14 days after the last on-treatment visit. The visit was only required for subjects who at the last on-treatment visit had an ongoing SAE, an ongoing non-serious AE classified as possibly or probably related to the IMP, or an albumin-corrected serum calcium value above reference range.
b) This visit was 28 days after the ACTH challenge test performed at Week 4; The visit was only required if the serum cortisol concentration was ≤18 mcg/dL 30 minutes after ACTH challenge.
c) Subjects in HPA axis cohort only.
d) 24-hour urine samples only collected in HPA axis cohort.
Source: Module 2.7.4 Summary of Clinical Safety Addendum, Panel 1
Abbreviations: ACTH = adrenocorticotropic hormone; SV1 = screening visit 1, SV2 = screening visit 2, FU1 = follow up 1, FU2 = follow up 2, AE = adverse events, PK = pharmacokinetics

Table 8: Schedule of Investigator and Subject Efficacy Assessments in Trial

Assessment	Visit				
	SV2	Visit 1	Week 2	Week 4	EW
PGA on body and scalp	X	X	X	X	X
Physician's assessment of the extent and severity of clinical signs of psoriasis vulgaris (PASI)	X	X	X	X	X
Physician's assessment of the extent of psoriasis vulgaris (total, body, scalp)	X	X		X	X
Subject's global assessment of disease severity (body and scalp)	X	X	X	X	X
Subject's assessment of itch		X	X	X	X
Subject's assessment of itch-related sleep loss		X	X	X	X
CDLQI		X	X	X	X
FDLQI		X		X	X

Abbreviations: CDLQI = Children's Dermatology Life Quality Index, EW = early withdrawal (if applicable), FDLQI = Family Dermatology Life Quality Index, PASI = Psoriasis Area and Severity Index, PGA = physician's global assessment of disease severity, SV = screening visit, ACTH = adrenocorticotrophic hormone, AE = adverse event, FU = follow-up visit; HPA = hypothalamic-pituitary axis, PK = pharmacokinetics, SAE = serious adverse event, SV = screening visit.

Primary Endpoints

- Adverse events
- Subjects with serum cortisol concentration of ≤18 mcg/dL at 30 minutes after ACTH challenge at Week 4
- Change in albumin-corrected serum calcium from baseline (SV2) to Week 4
- Change in calcium excretion from baseline (SV2) to Week 4 in 24-hour urine
- Change in calcium: creatinine ratio from baseline (SV2) to Week 4 in 24-hour urine

Secondary Endpoints

Safety

- Subjects with serum cortisol concentration of ≤18 mcg/dl at both 30 and 60 minutes after ACTH challenge at Week 4.
- Change in calcium: creatinine ratio from baseline (SV2) to Week 4 in spot urine.

Efficacy/treatment effect

- Subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the Physician´s global assessment of disease severity (PGA) on the body at Week 4.
- Subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the PGA on the scalp at Week 4.
- Percentage change in PASI from baseline (visit 1) to Week 4.
- Subjects with 'treatment success' (i.e., 'clear' or 'very mild') according to the subject's global assessment of disease severity on the body at Week 4. [A 2-grade improvement not required for treatment success according to the subject's assessment.]
- Change in itch as assessed by the visual analogue scale (VAS) from baseline (visit 1) to Week 4.

See Appendix 1 (Section 12.1) for the scales used to evaluate treatment effect.

Concomitant Medications

Concomitant medication was defined as any medication used by a subject during the clinical trial with the exception of the investigational product. Subjects were prohibited from using any topical or systemic therapy for the treatment of psoriasis except on the face and "sensitive areas." In the axillae, groin and skin folds, any topical treatment was allowed except for corticosteroids or vitamin D analogues. In addition, the protocol permitted stable doses of oral vitamin D supplementation ≤400 IU/day and unlimited use of emollients. Products specifically excluded for use by all subjects and their washout periods are tabulated below.

Table 9: Prohibited Products for All Subjects

Prohibited Medication including Non-Drug Therapies and Procedures	Location	Exclusion Period Restrictions
Systemic treatment with biological therapies (marketed or not marketed), with a possible effect on body or scalp psoriasis	Not applicable	Etanercept: 4 weeks prior to Visit 1 Adalimumab, Infliximab: 2 months prior to Visit 1 Ustekinumab: 4 months prior to Visit 1 or experimental products: 4 weeks/5 half-lives (whichever is longer) prior to Visit 1 and any time during the trial treatment phase
Systemic treatment with therapies other than biologicals, with a possible effect on body or scalp psoriasis (e.g., retinoids, immunosuppressants, PUVA)	Body and Scalp	Within 4 weeks prior to visit 1 and any time during the trial treatment phase
UVB therapy within 2 weeks prior to Visit 1	Body and Scalp	Within 2 weeks prior to visit 1 and any time during the trial treatment phase
Any topical treatment on the body or scalp including corticosteroids (except for emollients and non-steroid medicated shampoos) within 2 weeks prior to Visit 1	Body and Scalp	Within 2 weeks prior to visit 1 and any time during the trial treatment phase
Systemic calcium, vitamin D supplementation > 400 IU/day, antacids, diuretics, antiepileptics, diphosphonates or calcitonin Note: Stable doses of oral vitamin D supplementation ≤ 400 IU/day is permitted provided there are no dose adjustments during the study period)	Not applicable	Within 4 weeks prior to visit 1 and any time during the trial treatment phase
Initiation of, or changes to, concomitant medication that could affect body or scalp psoriasis (e.g. beta-blockers, lithium, anti-malaria drugs, ACE inhibitors).	Not applicable	Any time during the trial treatment phase
Excessive exposure of treated areas to either natural or artificial sunlight (including tanning booths, sunlamps, etc.).	Body and Scalp	Any time during the trial treatment phase
Note:	*The time between SV1 and Visit 1 cannot be longer than 4 weeks, and between SV1 and SV2 not longer than 3 weeks, therefore subjects receiving, or having recently received these treatments at SV1 cannot be enrolled.*	

Source: NDA 207589 Section 5.3.5.2 LP0053-1108 Consolidated Clinical Trial Protocol
Abbreviations: PUVA = psoralen-ultraviolet A, UVB = ultraviolet B, ACE = angiotensin-converting enzyme, SV = screening visit

Additional treatments requiring a washout period before Visit 1 and prohibited throughout the trial for subjects performing HPA axis and PK assessments are tabulated below.

Table 10: Prohibited Products for Subjects Performing HPA Axis/PK Assessments

Prohibited Medication including Non-Drug Therapies and Procedures	Location	Exclusion Period Restrictions
Systemic treatment with corticosteroids (including inhaled and nasal steroids)	Not applicable	Within 12 weeks prior to SV2 and any time during the trial treatment phase
Oestrogen therapy (including contraceptives) or any other medication known to affect cortisol levels or HPA axis integrity (4 weeks prior to SV2)	Not applicable	Within 4 weeks prior to SV2 and any time during the trial treatment phase
Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin), systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole, metronidazole), hypoglycaemic sulfonamides, antidepressive medications (4 weeks prior to SV2).	Body and Scalp	Within 4 weeks prior to SV2 and any time during the trial treatment phase
Topical ketoconazole	Body and Scalp	Within 2 weeks prior to SV2 and any time during the trial treatment phase

Source: NDA 207589 Section 5.3.5.2 LP0053-1108 Consolidated Clinical Trial Protocol
Abbreviations: HPA = hypothalamic-pituitary axis, SV = screening visit

Investigator(s)

There were 26 participating study sites in the United States, Poland, Netherlands and Romania. Poland had more study sites than any other country. Refer to the Appendix for the list of study sites and financial disclosures.

Data Analysis

As LP0053-1108 was an open-label trial, there was no hypothesis testing. The Applicant summarized the trial results using descriptive statistics. The Applicant performed no formal power calculations to determine the sample size. The FDA agreed with a sample size of 100 subjects. Definition of analysis sets:

- **Full analysis set**: all 106 subjects who were assigned to treatment with the study product.
- **Safety analysis set**: Full analysis set excluding subjects who either received no treatment with the study product or for whom no post-baseline safety evaluations were available (i.e. 106 subjects)
- **Per protocol analysis set**: subjects from the full analysis set who were in the HPA axis cohort, excluding subjects who:
  - Received no treatment with the IMP.
  - Provided no results for the ACTH challenge test at Week 4.
  - Did not fulfil the inclusion criterion concerning evidence of normal adrenal function at baseline. (i.e. 33 subjects)

- **PK analysis set:** subjects from the full analysis set who had PK assessments, and by excluding subjects who:
  - Received no treatment with the investigational product (IMP).
  - Provided no PK data at Week 4. (i.e. 33 subjects)
- **24-hour urine HPA set** was defined by including subjects from the safety analysis set who were in the HPA axis cohort. (i.e. 34 subjects)
- **Spot urine non-HPA set** was defined by including subjects from the safety analysis set who were in the non-HPA axis cohort.

Protocol Amendments
The Applicant submitted 5 versions of LP0053-1108. The key changes resulted from comments from regulatory agencies or clarifications. The key amendments are summarized below:

Version 2 (08-Jul-2015) Response to FDA Advice Letter dated June 24, 2015

a) Added safety and tolerability assessments by scoring of the clinical signs and symptoms from the application site on a 4-point scale (from absent to severe.)
b) Clarified that Subjects taking part in the HPA axis testing and PK Assessments should continue with treatment regardless of whether their lesions cleared at Visit 2. The remaining 70 subjects, whose psoriasis clears on individual lesions at Visit 2 according to the (sub)investigator, may discontinue treatment but will stay in the trial.
c) Modified the clear or almost clear categories of Physician´s global assessment of disease severity (PGA) scale.
d) Excluded subjects with clinically significant abnormality following review of screening laboratory tests, physical examination or blood pressure/heart rate measurement
e) Added vital signs at baseline and Week 2 and evaluation of temperature by oral or ear temperature. A physical examination was added at Week 4.

Version 3 (18-Jan-2016)

Minor clarifications with regard to ACTH testing (i.e. cortisol was to be measured at SV2 and Week 4 and Synacthen® was used for testing in Poland and Romania.)

Version 4 (14-MAR-2016)

Clarified the minor error (e.g. dietary instructions to be provided to subjects in HPA axis cohort and capture of intake of calcium-rich nutrients with an eDiary 3 days prior to the spot urine collection and during the 24-hour urine collection).

Version 5 (29-Aug-2016)

a) Provided for a separate schedule of trial procedures for the Non-HPA Axis Cohort and the HPA Axis Cohort to clarify procedures for each group.
b) Clarified the storage conditions per United States (US) and European Union (EU) standards.

7.2.2. Results of Efficacy Assessment

As the pathophysiology of plaque psoriasis and response to treatment are the similar in the pediatric and adult populations, efficacy in the pediatric population was extrapolated from the adult population. Refer to the Agreed Initial Pediatric Study Plan for the rationale provided by the Applicant to support extrapolation (Agreed Initial Pediatric Study Plan Advice Letter dated 12/3/2013).

Protocol LP0053-1108 specified assessments of treatment effect to be conducted by both the investigator and the subject. In view of the limited utility of efficacy data from an open-label trial to inform labeling, the Applicant did not interact with the FDA to develop assessment tools for patient reported outcomes in the pediatric population.

The following are secondary "efficacy" endpoints:

- The proportion of subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the **Physician´s global assessment of disease severity (PGA)** on the body at Week 4.
- The proportion of subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the **PGA on the scalp** at Week 4.
- Percentage change in **PASI** from baseline (visit 1) to Week 4.
- Subjects with 'treatment success' (i.e., 'clear' or 'very mild') according to the **Subject's global assessment of disease severity** on the body at Week 4. [A 2-grade improvement not required for treatment success according to the subject's assessment.]
- **Change in itch** as assessed by the visual analogue scale (VAS) from baseline (visit 1) to Week 4.

The key measure of treatment effect was the proportion of subjects with 'treatment success' according to the PGA at Week 4. These results tabulated below by visit.

Table 11: Treatment Success on Physician Global Assessment at Week 2 and 4

Visit	Body		Scalp	
Treatment Success*	N	%	N	%
Visit 2 (Week 2)				
Yes	31	30	31	31
Total	103	100	103	103
Visit 3 (Week 4)				
Yes	74	72	78	76
Total	103	100	103	100

*Defined as Physician Global Assessment (PGA) score of 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline and 'clear' for subjects with 'mild' disease at baseline
Source: Adapted from Clinical Study Report Panel 47

The following are the results from the assessments of treatment effect at Week 4:

- A total of 74 of 103 (71.8%) subjects achieved treatment success according to the PGA on the body and 78 of 103 (75.7%) subjects achieved treatment success on the scalp.
- A total of 86 of 103 (83.5%) subjects achieved treatment success according to the **subject's global assessment** of disease severity on the body and 84 of 103 (81.6%) subjects achieved treatment success on the scalp.
- The mean **PASI** decreased from 8.61 at baseline to 1.40 at Week 4; a mean change of -82.1%.
- The **mean BSA** (excluding the scalp) affected by psoriasis decreased from 10.4% at baseline to 3.2%. The mean affected area on the scalp decreased from 50.6% at baseline to 11.7%.
- There was a trend toward improvement in the patient reported outcomes: itch intensity, itch-related sleep loss, Children's Dermatology Life Quality Index and Family Dermatology Life Quality Index.

7.3. Review of Safety

7.3.1. Safety Review Approach

The review of the safety of Enstilar Foam in the pediatric population age 12 to 16 years focused on data from a single trial, Trial LP0053-1108. The analyses included treatment emergent adverse events (TEAEs), serious AEs (SAEs), AEs leading to discontinuation, adverse reactions (ARs) and AEs associated with the product classes, vitamin D analogs and topical corticosteroids.

7.3.2. Review of the Safety Database

Exposure

Extent of Exposure

Investigational staff used direct questioning to evaluate compliance with dosing instructions and documented exposure to the study product using the weight of the containers when dispensed and returned. Overall, the mean duration of exposure was 28.4 days (range 5 to 40 days) and the total extent of exposure was 2,986 subject-treatment-days.

Table 12: Extent of Exposure: Average Weekly Amount of Investigational Product Used (g)

Weekly Amount of IP Used (g)/ Statistics	Safety Analysis Set N=106	HPA Axis/PK Subset N=33
Visit 1 to Visit 3 (4 weeks)		
N	85	31
Mean (SD)	97.4 (64.5)	114.7 (54.2)
Median	96.9	114.3
Minimum/maximum	0.9/255.5	5.0/210.5

Source: Modified from Clinical trial report Panel 26
Abbreviation: IP = investigational product, HPA = hypothalamic-pituitary axis, PK = pharmacokinetics, SD = standard deviation

The total amount of study product used during the trial is tabulated below. The mean total amount of study product used during the entire treatment period was higher for the HPA axis/ PK subset (468.3 g) than for the safety analysis set (398.2 g).

Table 13: Total Amount of Product Used (G): Safety Analysis Set Vs. HPA Axis/PK Subset

Amount of IP Used (g) / Statistics	Safety Analysis Set N=106	HPA Axis/PK Subset N=33
Visit 1 to Visit 3 (4 weeks)		
N	85	31
Mean (SD)	398.2	468.3
Median	387.8	493.1
Minimum/maximum	4.1/1022.1	21.5/842.1

Source: Modified from Clinical trial report Panel 27
Abbreviation: HPA = hypothalamic-pituitary axis, PK = pharmacokinetics, SD = standard deviation

The Applicant submitted revised exposure data which included a correction factor (0.41) to account for volatile propellants (LP0053-1108 Clinical Trial Report Erratum, Panel 26 and 27.) This data supported the same conclusions:

1) the average weekly amount used by subjects in the Safety Analysis Set (mean: 40 g, median: 40 g) was less than the average weekly amount used by subjects in the HPA/PK Subset (mean: 47 g, median: 47 g) over the total treatment period.
2) the total amount of product used by subjects in the Safety Analysis Set (mean: 163 g, median: 159 g) was less than the total amount of product used by subjects in the HPA/PK Subset (mean: 192 g, median: 202 g).

Table 14: Compliance With Treatments: Safety Analysis Set and HPA Axis / PK Subset

Missed Any Applications	Safety Analysis Set N=107	HPA Axis / PK Subset N=31
No	101 (95.3%)	33 (100.0%)
Yes: <=10% applications missed	3 (2.8%)	0 (0.0%)
Yes: >10% to <=20% applications missed	1(0.9%)	0 (0.0%)
Yes: >50% applications missed	1 (0.9%)	0 (0%)
Total	106 (100.0%)*	33 (100.0%)

Source: Modified from Clinical trial report Panel 28
Abbreviation: HPA = hypothalamic-pituitary axis, PK = pharmacokinetics

Most subjects enrolled in the trial were compliant with the dosing instructions and missed less than 10% of the protocol specified doses.

Characteristics of the Safety Population

Demographic and Baseline Characteristics

Most of the 106 subjects enrolled in Trial LP0053-1108 were female (61/106, 57.4%) with psoriasis of moderate severity on the body (81/106, 76.4%) and scalp (77/106, 72.6%) and a mean age of 14.2 years. The mean total extent of psoriasis on the body and scalp was 13.2% of BSA. Below is a summary of the characteristics of the study population at Baseline.

Table 15: Demographic and Baseline Characteristics

Characteristics / Statistics	Subjects N (%) Total Population N=106	HPA Axis/PK Subgroup (Max Use) N=33
Sex [n (%)]		
F	61 (57.5%)	17 (51.5%)
M	45 (42.5%)	16 (48.5%)
Age [n (%)]		
≥12 years and ≤14	59 (55.7%)	
≥15 years and ≤17	47 (44.3%)	
Age (years)		
Mean (SD)	14.2 (1.4)	14.2 (1.4)
Median	14.0	14.0
Minimum/Maximum	12/16	12/16
Race [n (%)]		
White	102 (96.2%)	33(100.0%)
Native Hawaiian / other PI	1(0.9%)	0 (0.0%)
Other	3 (2.8%)	0 (0.0%)
Ethnicity [n (%)]		
Hispanic/Latino	3 (2.8%)	1 (3.0%)
Not Hispanic/Latino	103 (97.2%)	32 (97.0%)
Extent of BSA (body)		
Mean (SD)	10.4 (7.1)	16.3 (3.4)
Median	10.0	17.0
Minimum/Maximum	2/28	10/21
Extent of BSA (Scalp)		
Mean (SD)	50.6 (25.0)	55.5 (18.8)
Median	50.0	50.0
Minimum/Maximum	10/100	25/90
Total BSA		
Mean (SD)	13.2 (7.5)	18.5 (3.4)
Median	12.0	19.0
Minimum/Maximum	3/30	11/23
Baseline PASI		
Mean (SD)	8.61 (3.98)	10.54 (2.49)
Median	8.45	10.80
Minimum/Maximum	2.0/ 20.7	4.2/14.0
Height (cm)		
Mean (SD)	165.79 (9.77)	168.00 (9.33)
Median	165.0	167.0
Minimum/Maximum	138.0/ 190.0	147.0/190.0
Weight (kg)		
Mean (SD)	60.0 (14.41)	58.51 (12.83)
Median	58.0	56.80
Minimum/Maximum	36.0/ 123.0	40.0/88.0
BMI (kg/m^2)		
Mean (SD)	21.69 (4.25)	20.56 (3.28)
Median	20.95	20.7
Minimum/Maximum	15.5/40.6	16.1/30.3
Duration of psoriasis (years)		
Mean (SD)	4.3 (2.9)	3.5 (2.4)
Median	3.0	3.0
Minimum/Maximum	1/12	1/8

Characteristics / Statistics	Subjects N (%) Total Population N=106	HPA Axis/PK Subgroup (Max Use) N=33
Skin classification		
Type I	5 (4.7%)	1 (3.0%)
Type II	44 (41.5%)	12 (36.4%)
Type III	46 (43.4%)	16 (48.5%)
Type IV	10 (9.4%)	4 (12.1%)
Type V	1 (0.9%)	0 (0.0%)
Type VI	0 (0.0%)	1 (3.2%)
PGA Scalp		
Mild (2)	15 (14.2%)	0 (0.0%)
Moderate (3)	77 (72.6%)	33 (100.0%)
Severe (4)	14 (13.2)	0 (0.0%)
PGA Body		
Mild (2)	23 (21.7%)	0 (0.0%)
Moderate (3)	81 (76.4%)	33 (100.0%)
Severe (4)	2 (1.9%)	0 (0.0%)

Source: Reviewer's Table
Abbreviations: PGA = Physician's global assessment, HPA = hypothalamic-pituitary axis, PK = pharmacokinetics; SD = standard deviation; BSA = body surface area; BMI = body mass index

Justification of the Demographic Distribution of the Study Population

The majority of subjects enrolled in Trial LP0053-1108 were White (102/106, 96.2%), not Hispanic/Latino (103/106, 97%) and from Poland (36/106, 34%). The Applicant pursued aggressive strategies to recruit subjects for the study including children of ethnic and racial minorities. The Applicant stated that recruitment challenges prevented enrollment of additional subjects from the United States.

Table 16: Distribution of Subjects by Country

Country	Number of subjects
Poland	63
Romania	32
The Netherlands	9
United States	2
Total	**106**

Source: Response to Filing Communication dated 4/12/2019 (SD 227)

The Applicant noted that the action of the product is local and does not depend on metabolic pathways that may differ between races and ethnic groups. Therefore, the safety and efficacy results obtained in adolescents who are White and non-Hispanic are expected to be similar to the results in adolescents of other races and ethnicities. In addition, Applicant indicated that the study population was sufficiently representative of the target population because the prevalence of psoriasis among Black/African Americans or Hispanics is lower than the prevalence of psoriasis among Whites in the United States. (SD 227 dated 4/12/2109) The

following summary of the racial distribution of psoriasis in the United States is from a cross-sectional study of 6,216 adults (age 20 to 59 years) [Rachakonda et al., 2014].

Table 17: Prevalence of Psoriasis of Adults in the United States by Race

Race	Prevalence rate	95% confidence interval
Caucasian/white	3.6%	(2.7%-4.4%)
Black/African American	1.9%	(1.0%-2.8%)
Hispanic	1.6%	(0.5%-2.8%)
Other 'non-white'	1.4%	(0.3%-2.6%)

Source: SD 227 dated 4/12/2109.

Pooled data from 564 adult subjects which was submitted to support the initial approval of Enstilar Foam included 25% Hispanic subjects, 7% African American/Black subjects and 2% a Asian subjects. Although the numbers of non-White subjects were low, analysis of AEs demonstrated a similar incidence of AEs by race and ethnicity (See Clinical Review of NDA 207589 by Patricia Brown, MD dated 2/16/2015). Further, a study in adults using another dosage form of the fixed combination of calcipotriene and betamethasone (Taclonex Topical Suspension) identified a similar safety and efficacy profile in African American/Black and Hispanic/Latino adult subjects with body and scalp psoriasis compared with the predominantly White study population (See Review of NDA 22185 by Brenda Carr, MD dated 4/23/2008). Although, there is limited data regarding the prevalence or demographic characteristics of psoriasis in the pediatric population in the United States, it is expected that the results obtained in trial LP0053-1108 can be extrapolated to the US population.

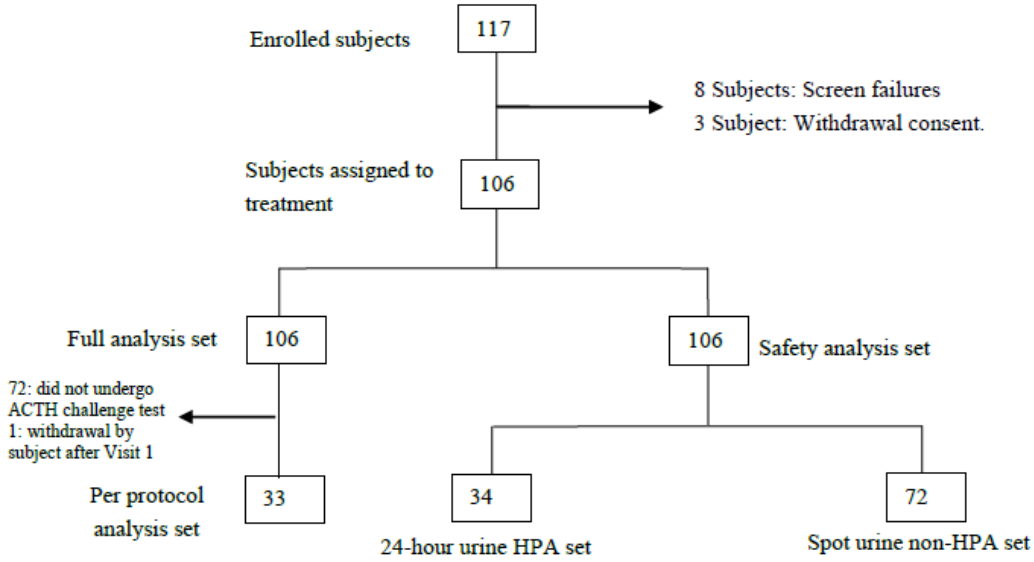
Concomitant Medications at Baseline

The Applicant coded the concomitant medications at baseline according to the organ system using the Anatomical Therapeutic Chemical (ATC) Classification System of active ingredients. The most common concomitant medications were "dermatologicals" used for dermatitis (excluding corticosteroids) reported by 8 of 106 subjects (7.5%). Other agents which included antihistamines, anti-depressants and estrogens were used by no more than 2 subjects (1.9%) each. Subjects in the HPA axis/PK subset reported no concomitant medications.

Disposition and Analysis Sets

Among 117 enrolled subjects, 8 subjects were screening failures and 3 withdrew consent. A total of 106 subjects attended Visit 1 (Week 0) and 3 subjects withdrew consent before Visit 2 (Week 2.) A total of 103 subjects completed the trial and none withdrew due to an adverse event.

Figure 2: Analysis Sets, Trial LP0053-1108



Abbreviation: HPA = hypothalamic-pituitary axis, ACTH = adrenocorticotropic hormone
Source: Statistical Methods Section 16 1.9 Figure 2

Investigators assigned 106 subjects to treatment but could not confirm that one subject, who withdrew, received treatment. However, the Applicant determined that since absence of treatment could not be confirmed, both the full analysis set (used for efficacy analyses) and safety analysis set included 106 subjects. Among 34 subjects who agreed to participate in the ACTH challenge testing one subject withdrew. Therefore, the HPA axis/PK subset included 33 subjects.

Protocol Deviations

None of the protocol deviations led to exclusion from any analysis set. The key protocol deviations involved the eligibility criteria and procedures. Regarding eligibility, the most common deviations were failure to confirm eligibility because laboratory test results were not available prior to enrollment. Among the procedural deviations were failure to complete the eDiary per protocol, visits outside of the allowed window, failure to conduct pregnancy testing at both timepoints (2 subjects) and failure to repeat ACTH-challenge testing when serum cortisol levels were ≤18 mcg/dL 30 minutes at Week 4 (2 subjects). Of the 2 subjects who did not have repeat ACTH-challenge testing at follow-up, 1 subject had normal cortisol values 60 minutes after ACTH challenge at Week 4 and the other subject did not have a normal response to the ACTH challenge test at screening. These protocol deviations did not have an impact on data integrity or subject safety.

Adequacy of the Safety Database

The size of the safety database was sufficient for the evaluation of Enstilar Foam applied once daily for up to 4 weeks in the pediatric population. The Applicant provided an acceptable rationale for limited numbers of non-White subjects in the study population. Therefore, the

safety database presented by the Applicant is sufficient to characterize the pharmacokinetics, pharmacodynamics and safety profile of Enstilar Foam for the treatment of plaque psoriasis in the pediatric population age 12 to 16 years.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
Overall, the quality of the data submitted is adequate to characterize the safety of Enstilar Foam applied once daily for up to 4 weeks. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events
Per ICH Harmonized Tripartite Guideline for Good Clinical Practice, E6 (R1), the Applicant defined an adverse event (AE) as "An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product."

Per protocol, AEs were elicited with "non-leading questions" form the signing of the informed consent until Day 28. The Applicant included significant abnormal laboratory values, and intercurrent diseases as AEs. The Applicant coded adverse events (AEs) using the Medical Dictionary for Regulatory Activities (MedDRA, version 15.1) and categorized AEs by system-organ class (SOC) and preferred term (PT). Adverse drug reactions (ARs) were those adverse events where the investigator had not excluded a causal relationship to IP (i.e. not described the relationship as 'not related'). In this review, an AE or AR refers to a treatment emergent adverse event (TEAE) or a treatment emergent adverse reaction (AR).

Investigators described the nature of the AEs and graded AEs by seriousness, intensity (mild, moderate, or severe), causal relationship to the product (probable, possible, not related or not assessable), duration and outcome. Cutaneous events were classified by location and as lesional/perilesional or distant from the treated lesions. A lesional/perilesional AE was defined as an AE located less than or equal to 2 cm from the lesional border of areas treated with the investigational product (IP); a distant AE was defined as an AE located greater than 2 cm from the lesional border.

Routine Clinical Tests
Subjects provided blood and urine samples for routine clinical laboratory testing at screening and Week 4. Laboratory tests included hematology (hemoglobin/hematocrit, white blood cell count and differential count, platelets), biochemistry (including calcium, phosphate, alkaline phosphatase, albumin, and parathyroid hormone), urine pregnancy testing, urinalysis (glucose and ketones), spot urine collection (non- HPA Axis Cohort) and 24- hour urine collection

(calcium, phosphate, creatinine and volume; HPA Axis Cohort). See the schedule of assessments above.

7.3.4. Safety Results

Deaths, Serious Adverse Events (SAEs), and Discontinuations Due to Adverse Events (AEs)
There were no deaths, serious adverse events, discontinuations due to adverse events (AEs) or AEs categorized as "severe."

Adverse Events
A total of 22 (20.8%) subjects reported 32 AEs. Among these AEs, there were 4 AEs which were classified as lesional/perilesional (acne, erythema, skin reaction, and application site pain) in 4 subjects (3.8%). Among the treatment emergent adverse events (TEAEs), the only preferred terms (PTs) reported by more than 1 subject were upper respiratory infection (8 subjects, 7.5%), nasopharyngitis (4 subjects, 3.8%) and acne (2 subjects,1.9%).

Table 18: Treatment Emergent Adverse Events by SOC and PT (if PT Reported by More Than 1 Subject)

System Organ Class (SOC) / Preferred Term (PT)	No. Subjects N=106	No. TEAEs
Overall	22 (20.8%)	32
Infections and infestations	18 (17.0%)	18
URI	8 (7.5%)	8
Nasopharyngitis	4 (3.8%)	4
Skin and subcutaneous tissue disorders	5 (4.7%)	6
Acne	2 (1.9%)	2
General disorders & administration site conditions	2 (1.9%)	2
Musculoskeletal & connective tissue disorders	2 (1.9%)	2
Eye disorders	1 (0.9%)	1
Injury, poisoning & procedural complications	1 (0.9%)	1
Neoplasms benign, malignant& unspecified	1 (0.9%)	1
Surgical & medical procedures	1 (0.9%)	1

Source: Clinical trial report, LP0053-1108, Panel 31
Abbreviations: URI = upper respiratory infection

Adverse Reactions (ARs)
A total of 5 (4.7%) subjects reported 6 AEs which were assessed as related or unknown. The protocol defined adverse reactions as events in which the causality was possibly or probably related or not assessable. Investigators assessed 5 AEs as possibly or probably related and myopia as "unknown" relationship. Among these ARs, 2 were assessed as moderate (erythema and myopia) and 4 were assessed as mild. The ARs are tabulated below.

Table 19: Drug-Related Treatment Emergent Adverse Events (Adverse Reactions)

System Organ Class (SOC) / Preferred term (PT)	No. Subjects N=106	No. TEAEs
Overall	5 (4.7%)	6
Skin and subcutaneous tissue disorders	2 (1.9%)	2
Acne	1 (0.9%)	1
Erythema	1 (0.9%)	1
Skin reaction	1 (0.9%)	1
General disorders & administration site conditions	2 (1.9%)	2
Application site pain	1 (0.9%)	1
Product physical consistency issue	1 (0.9%)	1
Eye disorders	1 (0.9%)	1
Myopia	1 (0.9%)	1

Source: Clinical trial report, LP0053-1108, Panel 32

Section 6 of labeling will include the following ARs: acne, erythema, skin reaction and application site pain. As there is no data or biologic plausibility to support a relationship between Enstilar Foam and of myopia, this PT will not be included in labeling.

Laboratory Findings

Some laboratory parameters showed variability. However, the shifts in the biochemistry parameters were not considered clinically meaningful. See 7.5.3 Analysis of Submission-Specific Safety Issues for the discussion of the laboratory findings.

Vital Signs and Physical Examinations

In Trial LP0053-1108, investigators evaluated vital signs which included systolic and diastolic blood pressure, heart rate, and oral or ear temperature at screening, and Weeks 1 through 4. Investigators performed physical examination which included general appearance, regional lymph nodes, and a dermatologic examination of the skin at screening and Week 4. There were no clinically significant abnormalities in vital signs and no clinically significant findings following the physical examinations.

Electrocardiograms (ECGs) and QT

The Applicant did not conduct ECG monitoring during Trial LP0053-1108 or during the development program for Enstilar Foam in the adult population. The pro-arrhythmic potential of the components of this fixed combination product, calcipotriene and betamethasone, are well characterized. The systemic exposure to calcipotriene is limited. Per the Pharmacology/Toxicology reviewer, there were no effects on cardiac parameters from either calcipotriene and betamethasone in dogs or minipigs. (See Pharmacology/ Toxicology Reviews by Norman See dated February 20, 2008 and June 18, 2012).

In the development program for another dosage form of calcipotriene and betamethasone, Taclonex Topical Suspension, investigators performed cardiovascular monitoring in Trial MBL 0404 FR which was conducted under maximal use conditions. There were no clinically significant changes in PR or QRS intervals. See reviews by Dr. Brenda Carr dated April 23, 2008 and Dr. Patricia Brown dated September 10, 2012.

Immunogenicity
As the product is not a therapeutic protein, the Applicant did not assess the potential for immunogenicity.

7.3.5. Analysis of Submission-Specific Safety Issues

Rebound
Rebound is a well -described risk with the use of systemic and topical corticosteroids.[11] The Applicant defined rebound as a severe deterioration of psoriasis that is significantly worse than prior to the initiation of treatment or a change in the character of the psoriasis, e.g., from plaque to pustular form, or both.[12] The Applicant reported that 2 subjects experience rebound after completing the trial. Brief narratives are provided below.

A 14-year-old male subject (b) (6) with psoriasis of moderate disease severity on the body and severe disease severity on the scalp according to the PGA applied Enstilar Foam once daily for 28 days. At the end of treatment, the subject had psoriasis of mild severity on both the body and scalp. Approximately 42 days after the last application of Enstilar Foam , the subject reported the development of exudative plaques of psoriasis involving his entire scalp despite treatment. The subject experienced no rebound of psoriasis on the body. There was no report of the outcome or treatment.

A 14-year- old female subject (b) (6) with psoriasis of moderate disease severity on the body and scalp according to the PGA applied Enstilar Foam once daily for 28 days. At the end of treatment, the subject was assessed as “clear” on the body and “almost clear” on the scalp. Approximately 43 days after the last application of Enstilar Foam , the subject reported the development of extensive, severe plaques of psoriasis involving her entire scalp. The subject received treatment with local narrowband UVB therapy and 5% salicylic acid solution. Later she received betamethasone and salicylic acid topical solution and her scalp cleared. The subject experienced no rebound of psoriasis on the body.

Local Tolerability
The Applicant evaluated local safety at all visits by documenting the development of application site or perilesional erythema, edema, dryness, and erosion on 4-point scale. “Perilesional” was defined as the area with 2 cm of the border of the psoriatic plaque. Investigators recorded the worst score across all treatment areas.

[11] Sheary B. Steroid Withdrawal Effects Following Long-term Topical Corticosteroid Use. Dermatitis.2018: 29 (4);213-8
[12] Committee for Medicinal Products for Human Use, 2004

The Applicant conducted tolerability assessments using the following scale:

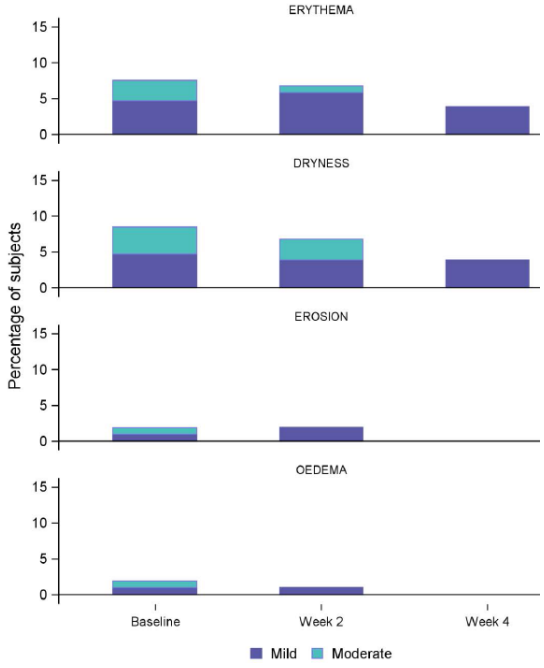
Table 20: Physician's Assessment of Local Safety and Tolerability

	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: Clinical trial report LP0053-1108 Panel 11

There were fewer local reactions at Week 4 than Week 2. At Week 2, a total of 7 of 103 subjects (6.8%) reported erythema and dryness, the most frequent local reactions; at Week 4, a total of 4 of 103 subjects (3.9%) reported erythema and dryness. By Week 4, no subjects reported reactions of moderate severity, and fewer subjects experienced mild reactions compared to baseline. These trends were similar to findings in the adult population (LP0053-1001, Trial LEO 90100-30). The local safety findings from Trial LP0053-1108 are presented below.

Figure 3: Local Safety and Tolerability by Visit: Safety Analysis Set



Source: Clinical trial report LP0053-1108 Panel 45

Effects on Calcium Metabolism

The Applicant evaluated all subjects for the effect of Enstilar Foam on calcium metabolism by calculating total calcium excretion, total phosphate excretion, total creatinine excretion, calcium: creatinine ratio and phosphate: creatinine ratio. Subjects participating in the HPA axis testing and PK sampling provided a 24-hour urine collection while all other subjects provided a spot urine sample.

The Applicant analyzed the laboratory parameters related to calcium metabolism using reference ranges based on age and sex. The mean and median values for albumin-corrected serum calcium and 24-hour urinary calcium excretion in LP0053-1108 did not exceed the reference range at baseline or Week 4. Review of shift tables for albumin- corrected calcium levels and 24-hour urinary calcium excretion showed no shifts from normal or low to high through the end of treatment. A total of 6 subjects shifted from low to normal albumin-corrected calcium levels while 9 subjects shifted from normal to low. A total of 3 subjects shifted from low to normal 24-hour urinary calcium excretion while 9 subjects shifted from normal to low. No subjects developed elevated albumin-corrected calcium levels or elevated 24-hour urinary calcium excretion. These changes are not clinically meaningful.

Pharmacokinetics

Investigators measured plasma levels of calcipotriene and betamethasone dipropionate and their major metabolites after 4 weeks of once daily application of Enstilar Foam to 10-30% of the total body surface area (body and scalp) in 33 subjects. Calcipotriene and its major metabolite, MC1080, were below the lower limit of quantification in all plasma samples. Betamethasone dipropionate was quantifiable in 12 of 33 (36%) subjects. The metabolite of betamethasone dipropionate (B17P) was quantifiable in 6 of 33 (18%) subjects.

HPA Axis Suppression

Adrenal suppression as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL occurred in 3 of 33 (9.1%) subjects after ACTH challenge at Week 4. Two of the 3 subjects had a normal serum cortisol concentration at 60 minutes; the third subject had a borderline abnormal cortisol level at baseline (18 mcg/dL). Per Applicant, none of the subjects had “clinical manifestations” of adrenal suppression.

For a comprehensive discussion of the PK and PD findings, see the Clinical Pharmacology Review by Cindy (Liping) Pan, Ph.D. dated July 24, 2019.

7.3.6. Safety Analyses by Demographic Subgroups

The review team examined adverse events by age, sex and race. However, given the small sample size, the results should be interpreted with caution. Analysis of adverse events by age group, showed that the percentage of subjects experiencing at least 1 AE was similar in subjects aged 12 to 14 years (12 /59 subjects; 20.3%) and in subjects aged 15 to 16 years (10/47 subjects; 21.3%). There were 3 preferred terms which were reported by more than 1 subject in

any age group. Among these 3 AEs, upper respiratory tract infection and nasopharyngitis were experienced more frequently in the 15 to 16-year- old age group [4/47 (8.5%) and 2/47 (4.3%) respectively] compared with the 12 to 14-year-old age group [4/59 (6.8%) and 2/59 (3.4%), respectively.] Acne was experienced more frequently in the 12 to 14-year-old age group [2/59, 3.4%] than the 15 to 16-year-old age group (0%).

Table 21: Treatment-Emergent Adverse Events by Age Group

	Safety Analysis Set (n=106)			
	12 to 14 (n=59)		15 to 16 (n=47)	
System Organ Class (SOC)	# Subj (%)	# TEAEs	# Subj (%)	# TEAEs
Total number	12 (20.3%)	18	10 (21.3%)	14
Infections and infestations	10 (16.9%)	10	8 (17.0%)	8
Skin and subcutaneous tissue disorders	3 (5.1%)	4	2 (4.3%)	2
General disorders & administration site conditions	2 (3.4%)	2	0 (0.0%)	0
Musculoskeletal & connective tissue disorders	0 (0.0%)	0	2 (4.3%)	2
Eye disorders	0 (0.0%)	0	1 (2.1%)	1
Injury, poisoning & procedural complications	1 (1.7%)	1	0 (0.0%)	0
Neoplasms benign, malignant& unspecified	1 (1.7%)	1	0 (0.0%)	0
Surgical & medical procedures	0 (0.0%)	0	1 (2.1%)	1

Source: Adapted from Final Study Report LP0053-1108 Table 3–58
Abbreviations: subj = subjects; TEAE = treatment-emergent adverse event

Overall, male subjects (12/45; 26.7%) experienced a greater percentage of adverse events than female subjects (10/61; 16.4%.) Among the 3 preferred terms which were reported by more than 1 subject, females reported upper respiratory tract infection more frequently [6/61 subjects (9.8%)] than males [2 /45 subjects (4.4%)]. In contrast, males reported nasopharyngitis more frequently [2 /45 subjects (4.4%)] than females [2 /61 subjects (3.3%)] and males reported both cases of acne [2 /45 subjects (4.4%)].

Table 22: Treatment Emergent Adverse Events by Sex

	Safety Analysis Set (n=106)			
	Males (n=45)		Females (n=61)	
System Organ Class (SOC)	# Subj (%)	# TEAEs	# Subj (%)	# TEAEs
Total number	12 (26.7%)	15	10 (16.4%)	17
Infections and infestations	9 (20.0%)	9	9 (14.8%)	9
Skin and subcutaneous tissue disorders	3 (6.7%)	4	2 (3.3%)	2
General disorders & administration site conditions	0 (0.0%)	0	2 (3.3%)	2
Musculoskeletal & connective tissue disorders	0 (0.0%)	0	2 (3.3%)	2
Eye disorders	0 (0.0%)	0	1 (1.6%)	1
Injury, poisoning & procedural complications	1 (2.2%)	1	0 (0.0%)	0
Neoplasms benign, malignant& unspecified	0 (0.0%)	0	1 (1.6%)	1
Surgical & medical procedures	1 (2.2%)	1	0 (0.0%)	0

Source: Adapted from Final Study Report LP0053-1108 Table 3–59
Abbreviations: subj = subjects; TEAE=treatment-emergent adverse event

In Trial LP0053-1108, only 1 non-white subject reported 2 adverse events. As 102 of 106 subjects (96.2%) in this trial were White, there is limited utility in the analysis of AEs by race.

7.3.7. Supportive Safety Data From Other Clinical Trials

120-Day Safety Update
During the reporting period (June 22, 2018 to January 28, 2019) for the 120-day safety update report (SUR), the Applicant indicated that there were no ongoing clinical trials in the pediatric population or post marketing data to indicate a difference in the safety profile in the adolescent population compared to the adult population. There was no new safety information to inform labeling. (SD 243 dated May 28, 2019.)

7.3.8. Safety in the Postmarket Setting

Expectations on Safety in the Postmarket Setting
Analysis of safety data from Trial LP0053-1108 identified no additional safety signals in the population age 12 to 16 years with exposure to the Enstilar Foam .

7.4. Summary and Conclusions

7.4.1. Statistical Issues

Trial LP0053-1108 was not designed to establish efficacy. There were no statistical issues affecting the overall conclusions.

7.4.2. Conclusions and Recommendations

Enstilar Foam , a reformulation of Taclonex Ointment (NDA 021852), is one of 3 approved dosage forms of calcipotriene and betamethasone dipropionate. The Applicant conducted Trial LP0053-1108 to establish the safety of Enstilar Foam in the pediatric population age 12 to 16 years per PMR 2958-1 and to fulfill the Pediatric Written Request. Trial LP0053-1108 was an open-label, pharmacokinetic (PK) and safety trial enrolling 106 pediatric subjects age 12 to 16 years with plaque psoriasis. Enrolled subjects had plaque psoriasis on the body and scalp of at least mild severity, defined as an Investigator Global (IGA) scores of 2 or 3 and at least 10% of the surface area of the scalp affected and at least 2% total BSA affected. All subjects applied Enstilar Foam once daily for up to 4 weeks. A subset of 33 subjects, referred to as the HPA axis cohort, received Enstilar Foam under maximal use conditions and performed HPA axis testing, evaluation of calcium metabolism using 24-hour urine samples, and PK assessments. These subjects had at least moderate disease severity according to the Physician Global Assessment

(PGA) scale on the body and scalp, at least 10% BSA affected, and at least 20% of the scalp area affected.

The data indicated no new safety signals. All analyzable samples for calcipotriene and its major metabolite were below the limit of quantification; there were no clinically meaningful changes from Baseline in measures of calcium metabolism, the primary safety issue. There were no deaths, serious adverse events, discontinuations due to AEs or AEs categorized as "severe." A total of 5 (4.7%) subjects reported 6 treatment emergent ARs which included acne, erythema, skin reaction, application site pain, myopia and "product physical consistency issue." Two subjects experienced rebound psoriasis on the scalp after discontinuing treatment, a well-described phenomenon with the use of topical corticosteroids. Signs of local tolerability improved during the trial.

A total of 3 of 33 (9%) subjects experienced HPA axis suppression following ACTH challenge as indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL at Week 4. In the adult trial with Enstilar Foam, no subjects experienced adrenal suppression following ACTH challenge. However, HPA axis suppression was documented with other dosage forms of calcipotriene and betamethasone dipropionate. Among 32 adults who applied Taclonex Topical Suspension on the scalp and Taclonex Ointment on the body for up to 8 weeks under maximal use conditions, the rate of HPA axis suppression was 16% (5/32) at Week 4 and 18% (2/11) at Week 8 (Section 12.2 Pharmacodynamics of Taclonex Topical Suspension and Taclonex Ointment labeling).

Per agreement with the FDA, the size of the safety database and the safety evaluations were sufficient to identify local and systemic treatment-emergent adverse reactions. The submitted PK, PD and safety data support approval of this sNDA (S-005) which provides for the use of Enstilar Foam for the topical treatment of plaque psoriasis in patients 12 years and older.

In addition, revisions to labeling incorporated data regarding the relative potency of the corticosteroid component of the drug product from PMC 2958-2 and revised fertility and lactation information to conform to the PLLR format. The Applicant provided adequate information to support the revised labeling. This reviewer recommends approval of these supplements (S-006 and S-007).

8. Advisory Committee Meeting and Other External Consultations

The Agency conducted no Advisory Committee Meeting regarding this application because the safety profile of the moiety is well characterized.

9. Pediatrics

The Applicant submitted the clinical study report for Trial LP0053-1108 in response to a Written Request (WR) for Pediatric Studies under the pediatric exclusivity program for calcipotriene 0.005% and betamethasone dipropionate 0.064% foam (issued January 22, 2019). The Pediatric Exclusivity (PE) Board met on July 3, 2019 to determine whether the terms of the Written Request were met. The Division concluded that the Applicant had "fairly responded" to the terms of the WR although the study population lacked the ethnic diversity representative of the target population. The Division agreed that the Applicant initiated appropriate efforts to try to ensure enrollment of children of ethnic and racial minorities. The PE Board voted to grant pediatric exclusivity to this combination product (General Advice Letter dated 7/23/2019). The Pediatric Review Committee (PeRC) agreed with the Division that PREA PMR 2958-1 was fulfilled and the data was sufficient to support amended labeling (PeRC Meeting held July 17, 2019).

Amy M. Taylor, MD, MHS, the Division of Pediatric and Maternal Health (DPMH), Pediatric Team, agreed with expanding the age group for which Enstilar Foam is indicated and provided recommendations for labeling (Sections 1, 5, 6, 8, 12). A description of the trial and relevant results will be included in Sections 5.2 Effects on Endocrine System, 6.1 Clinical Trials Experience, 8.4 Pediatric Use and 12 Clinical Pharmacology of labeling to convey to the prescriber that the safety and effectiveness of Enstilar Foam have been established in pediatric patients 12 to 16 years. Dr. Taylor recommended that 8.4 Pediatric Use section of labeling convey a limited amount of information and refer to other sections of labeling for the data. To optimize access to the necessary prescribing information, the clinical team recommended that all the key findings be included in the Pediatric Use section. Refer to the Review by Dr. Amy Taylor dated July 23, 2019.

At this time, no additional postmarketing requirements or commitments for deferred pediatric studies are needed under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)).

10. Labeling Recommendations

10.1. Prescribing Information

The Applicant submitted proposed Prescribing Information (PI), Patient Information (PPI), Instructions for Use (IFU) and carton labeling for Enstilar Foam. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed PI, PPI, IFU and carton labeling for Enstilar Foam and did not identify areas of vulnerability that may lead to medication errors (Review dated 7/2/2019).

The members of the review team who provided recommendations regarding PI are tabulated below. Comments from the team will be reflected in the final labeling which will be appended to the approval letter.

Table 23: Reviewers Providing Labeling Comments and Location in the Document

Section	Reviewers Providing Comments & Location in This Review
1. Indications and usage	Clinical: Section 7.4.1
6. Adverse reactions	Clinical: Section 7.3.4
8. Use in specific populations	DPMH: Amy Taylor (Pediatrics): Section 9, 10.1 Jane Liedtka (Maternal Health) Section: 10.1 Pharmacology/Toxicology: Norman See/Barbara Hill: Section 5 Clinical Pharmacology Reviewer: Liping Pan/Chinmay Shukla: Section 6 Clinical: Section 7.3.5
12. Clinical pharmacology	Clinical Pharmacology: Liping Pan /Chinmay Shukla: Section 6 Clinical team: Section 6; 7.3.5
13. Nonclinical toxicology	Pharmacology/Toxicology: Carmen Booker/Barbara Hill: Section 5
17. Patient counseling information	Clinical, Clinical Pharmacology, DPMH, ADL

Source: Reviewer's Table

Associate Director for Labeling (ADL), Nancy Xu, MD, provided comments throughout the PI to address current labeling policy. The team incorporated those recommendations which contributed to greater accessibility to information and clarity of findings for prescribers. The review team inserted headings and revised the content of Section 17 Patient Counseling Information to reflect the revisions in other sections of the PI.

Section 5 Warnings and Precautions was updated to convey (b) (4) The increased risk of cataracts and glaucoma with topical corticosteroids will be conveyed to prescribers in labeling (b) (4) Labeling must be based whenever possible on data derived from human experience [21 CFR 201.56(a)(3)}; (b) (4)

Pregnancy and Lactation Labeling Rule (PLLR) Conversion

In this submission, the Applicant revised Section 8 *Use in Specific Populations* of Enstilar Foam labeling to comply with the Pregnancy and Lactation Labeling (PLLR) format. The proposed language was based on the text approved for Section 8 for another marketed dosage form of calcipotriene and betamethasone dipropionate, Taclonex Ointment (revised December 2018). In addition, discussions regarding labeling for Taclonex (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/ 0.064% informed labeling decisions for Enstilar Foam. Jane Liedtka M.D., from DPMH, Maternal Health Team, provided recommendations for

Section 8.1 and 8.2 of labeling to reflect current best practices. (Review by Dr. Jane Liedtka dated June 17, 2019).

Limited data is available with the use of Enstilar Foam or the calcipotriene component of this combination product in pregnant or lactating women. Class labeling for high potency corticosteroids was included to inform the risk to female patients during pregnancy and lactation. DPMH recommended replacing statements regarding the presence of topically administered calcipotriene and betamethasone dipropionate in human milk and their effects on the breastfed infant. Recommended language indicates that the concentrations of calcipotriene are likely to be low; however, large topical doses of betamethasone dipropionate could produce detectable levels in human milk (See Appendix).

10.2. Patient Labeling

The Applicant submitted a proposed patient package insert (PPI) and Instructions for Use (IFU). The Division of Medical Policy Programs (DMPP) reviewed and provided comments on the PPI and IFU. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Sharon R. Mills, BSN, RN, CCRP (Review dated July 23, 2019.)

11. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided a summary of the Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in the covered clinical trial for Enstilar Foam. Prior to trial initiation, all investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv). Per Applicant, none of the investigators had a financial interest or arrangement to disclose.

Table 24: Covered Clinical Trial LP0053-1108

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 26 sites (investigators tabulated below)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:		

Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements: NA	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: NA	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: NA	Yes ☐	No ☐ (Request explanation from Applicant) NA

Source: Module 1.3.4 Financial certification and disclosure
Abbreviation: NA = not applicable

Table 25: List of Investigators by Country

Center No.	No. Enrolled/ Treated	Investigator	Address
Netherlands			
NL-01	6/6	Marieke Seyger	Radboud University Nijmegen Medical Centre, P.O.Box 9101, Nijmegen, 6500 HB, Netherlands
NL-02	1/1	Milan Tjioe	Bravis Ziekenhuis, Boerhaveplein 1, Bergen Op Zoom 4614 VT, Netherlands
NL-03	2/2	Wilhelmus de Kort	Amphia Ziekenhuis, Molengracht 21, Breda 4818 DK, Netherlands
Total	9/9		
Poland			
PL-01	11/11	Edyta Gebska	Multiklinika Salute Sp z o.o., Czerwinskiego 19, Katowice 40-123, Poland
PL-02	2/2	Irena Maria Walecka-Herniczek	CSK Mswia, Oddzial Dermatologii, Woloska 137, Warszawa 02-507, Poland
PL-03	1/1	Dorota Bystrzanowska	High-med. Przychodnia Specjalistycza, Kasprowicza 27/2, Warszawa 01-817, Poland
PL-04	1/1	Dorota Wielowieyska Szybinska	Krakowskie centrum medyczne Sp z o.o., Kopernika 32, Krakow 31-501, Poland
PL-05	2/2	Lidia Rajzer	Malopolskie centrum medyczne S.C., Rejtana 2, Krakow 30-510, Poland
PL-08	11/9	Agata Kusiba-Stazynska	NZOZ Przychodnia Specjalistyczna, A-DERMSerwis, Waszyngtona 42/3, Czestochowa 42-200, Poland

Center No.	No. Enrolled/ Treated	Investigator	Address
PL-09	6/4	Dorota Krasowska	Samodzielny Publiczny Szpital Kliniczny nr 1, Radziwillowska 13, Lublin 20-080, Poland
PL-10	1/1	Melania Piasecka	Poradnia Dermatologiczno-wenerologiczna “MediDerm”, Krasinskiego 4/4a, Torun 87-100, Poland
PL-11	4/3	Wieslawa Kusiak	Lubelskie Centrum Diagnostyczne, Aleja Lotnikow 82 Polskich, Swidnik 21-040, Poland
PL-12	5/4	Joanna Narbutt	Dermoklinika Centrum Medyczne, Kosciuszki 93, Lodz 90-436, Poland
PL-13	1/1	Jacek Szepietowski	Samodzielny Publiczny Szpital Kliniczny Nr 1, Ul. Chalubinskiego 1, Wroclaw 50-368, Poland
PL-14	3/3	Maria Czubek	Copernicus Sp z o.o Podmiot Leczniczy, Oddzial Dermatologii, Powstancow Warszawskich 1/2, Gdansk 80-152, Poland
PL-15	13/11	Roman Nowicki	Klinika Dermatologii, wenerologii i arelgologii, Ul. Debinki 7, Gdansk 80-952, Poland
PL-16	10/10	Jacek Zdybski	Prywatna Praktyka Lekarska, Sienkiewicza 65/14, Ostrowiec Sw. 27-400, Poland
Total	71/63		
Romania			
RO-01	1/1	Simona Roxana Georgescu	Spitalul Clinic de Boli Infectioase si Tropicale Dermoto-venerology Clinical Department, 281-283, Mihai Bravu Av., Bucharest 30303, Romania
RO-02	5/5	Virgil Patrascu	Spitalul Clinic Judetean de Urgenta Craiova Dermato-venerology Clinical Department, 1 Tabaci Str., Craiova 200642, Romania
RO-03	1/1	Simona Fratila	Cabinet Medical Dr. Fratila S.R.L. 45 Piata Independentei, Bldg.A4, Flat 7, Oradea, Bihor 410067, Romania
RO-04	2/2	Rozalia Olsavszky	S.C. Dermestet S.R.L. Dermato-Venerology Clinical Department, 8 Capitan Gherorghe Preiotescu Intr, Flat 1, 040176, Bucharest 040176, Romania
RO-05	5/3	Silviu Morariu	Spitalul Clinic Judetean Mures, 12 Gheorghe Doja Str., Targu-Mures 800373, Romania
RO-07	20/20	Dorin Mihalache	Iasiprest SRL, Dermato-Venerology Clinical Department, 15 Ignat Str., Iasi, 700381 Romania"

Center No.	No. Enrolled/ Treated	Investigator	Address
Total	34/32		
USA			
US-04	1/1	Theodore Daly	Garden city dermatology, 901 Stewart Ave, Suite 201, Garden City, New York 11530-4883, United States
US-05	1/0	Jeffrey Sugarman	Redwood Family Dermatology, 2725 Mendocino Ave, Santa Rosa, California 95403, United States
US-07	1/1	Dr Robert Buka	Greenwich Village Dermatology, 214 Sullivan Street, New York, New York 10012, United States
Total	3/2		

Source: Module 5.3.5.2 Appendix 1.4 of the Clinical Trial Report for LP0053-1108

Melinda McCord, M.D.
Medical Officer/Dermatology

12. Appendices

12.1. Efficacy Assessment Scales

Table 26: Physician´s Global Assessment of Disease Severity (PGA) – Psoriasis of the Body and Scalp

Score	Disease severity	Description
0	Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present)
1	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
2	Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions Erythema = light red colouration
3	Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red colouration
4	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 colouration; extreme red colouration; or deep red colouration

Note: For subjects in the non-HPA axis cohort, disease severity on the body and scalp had to be graded as at least 'mild' at SV1, SV2 and visit 1. For subjects in the HPA axis cohort, disease severity on the body and scalp had to be at least 'moderate' at SV1, SV2 and visit 1.
Source: Clinical Trial Report P0053-1108 Panel 12

Table 27: Extent of Psoriasis (PASI)

Score	Extent of plaque psoriasis
0	No involvement
1	<10% involvement
2	10-29% involvement
3	30-49% involvement
4	50-69% involvement
5	70-89% involvement
6	90-100% involvement

Source: Clinical Trial Report P0053-1108 Panel 13

Table 28: Severity Scores for Redness, Thickness, and Scaliness (PASI)

Clinical sign	Score	Severity	Description
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: Clinical Trial Report P0053-1108 Panel 14

Table 29: Subject's Global Assessment of Disease Severity

Clear	No psoriasis symptoms at all
Very mild	Very slight psoriasis symptoms, does not interfere with daily life
Mild	Slight psoriasis symptoms, interferes with daily life only occasionally
Moderate	Definite psoriasis symptoms, interferes with daily life frequently
Severe	Intense psoriasis symptoms, interferes or restricts daily life very frequently

Source: Clinical Trial Report P0053-1108 Panel 15

Investigational staff administered a visual analogue scale (VAS) to assess the maximal intensity of itch which was anchored by ('no itch at all') and 10 ('worst itch you can imagine'). The VAS used to assess itch-related sleep loss was anchored at 0 ('no sleep loss at all') and 10 ('worst possible sleep loss'). The Children's Dermatology Life Quality Index and Family Dermatology Life Quality Index questionnaires are included in Appendix 7 and 8 of Protocol LP0053-1108.

12.2. Labeling Comments

Labeling Comments Section 8.2
Associate Director of Labeling (ADL) Nancy Xu, MD commented in reference to another dosage form of calcipotriene and betamethasone [Taclonex (calcipotriene and betamethasone dipropionate) topical suspension, 0.005%/0.064%]:

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELINDA L MCCORD
07/26/2019 12:37:59 PM

GORDANA DIGLISIC
07/26/2019 01:14:14 PM