Clinical Review and Evaluation

PMR Final Study Report

Application Type	sNDA: Efficacy Supplement
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Priority or Standard	Standard
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Division/Office	Division of Dermatology and Dental Products (DDDP)
Review Completion Date	July 26, 2019
Established Name	Calcipotriene and betamethasone dipropionate
(Proposed) Trade Name	TACLONEX Topical Suspension
Pharmacologic Class	Vitamin D analog and corticosteroid
Code name	LEO 80185
Applicant	LEO Pharmaceutical Products Ltd. A/S
Formulation(s)	Topical Suspension
Dosing Regimen	Once daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of plaque psoriasis of the scalp and body 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 scalp and body in patients 12 years and older.

Consultant Reviews

Labeling Reviews

- Division of Medical Policy Programs (DMPP): Ruth Mayrosh, PharmD reviewed Patient Package Insert (PPI) and Instructions for Use (IFU). (Review dated June 20, 2019)
- Division of Medication Error Prevention and Analysis (DMEPA) Madhuri R. Patel, PharmD reviewed Prescribing Information (PI), PPI and IFU (Review dated July 18, 2019)
- Division of Pediatric and Maternal Health (DPMH): Reviewed PI
  - Pediatric División Consult Response: Amy Taylor, M.D. (Review dated June 17, 2019 ; comments provided for Sections 6, 8, 12 of labeling)
  - Maternal Health Consult Response, Pregnancy and lactation Labeling Rule (PLLR) Labeling Review: Jane Liedtka, M.D.(Review dated June 17, 2019; comments included in Section 8 of labeling)

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1. Executive Summary

TACLONEX® (calcipotriene and betamethasone dipropionate) Topical Suspension, 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 Pharma, Ltd submitted a Supplemental NDA (sNDA) to support revisions to product labeling which provided for the use of Taclonex Topical Suspension in patients with plaque psoriasis of the scalp and body 12 years and older. The Applicant conducted Trial LP0076-1017 to address the post marketing requirement (PMR) 1935-1 under the Pediatric Research Equity Act (PREA) to evaluate the effects of Taclonex Topical Suspension on calcium metabolism, hypothalamic-pituitary-adrenal axis (HPA Axis) and safety in the pediatric population age 12 years to less than 17 years. In addition, the Applicant submitted proposed labeling which is compliant with the Pregnancy and Lactation Labeling Rule (PLLR).

Trial LP0076-1017 was an open-label, pharmacokinetic (PK) and safety trial enrolling 107 pediatric subjects age 12 to <17 years with plaque psoriasis of the scalp and body. Enrolled subjects had plaque psoriasis on the scalp and body 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 3% total BSA affected. All subjects applied Taclonex Topical Suspension once daily for up to 8 weeks.

There were no deaths, unexpected adverse events or safety signals. One subject experienced a serious adverse event (suicide attempt) and one subject withdrew from the trial due to an adverse event (mild blood cortisol decreased which was assessed as possibly related.) Overall, a total of 38 (35.5%) subjects experienced 62 adverse events (AEs). All AEs were mild or moderate except one event of suicide attempt which was severe. Most adverse events (AEs) 61/62 (98%) were non-serious and reported by a single subject. The most common adverse events were nasopharyngitis and headache which were reported by 6 subjects each (5.6%). Investigators identified 8 adverse reactions (13%) which occurred in 7 subjects and included both local and systemic effects. Local safety findings included erythema and folliculitis, while systemic findings included decreased blood cortisol in 2 subjects in the maximal use cohort who participated in HPA axis testing.

A subset of subjects with psoriasis of at least moderate severity participated in pharmacokinetic (32 subjects) and hypothalamic pituitary adrenal (HPA) axis (31 subjects) assessments under maximal use conditions. All analyzed 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 4 subjects (13%) and levels of its metabolite

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

betamethasone 17-propionate (B17P) were quantifiable (LLOQ 30.0 pg/mL) in 5 subjects (16%).The highest observed value was 104 pg/mL for BDP.
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 22185 Supplement-027, to revise the current indication to the topical treatment of plaque psoriasis of the scalp and body 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 teams based the analysis of the risks and benefits for Taclonex Topical Suspension for the topical treatment of plaque psoriasis of the scalp and body in patients 18 years and older on data from adequate, well- controlled, 8-week, clinical trials (Trials MBL 0405 INT, MBL 0406 INT, LEO 80185-G21, LEO 80185-G23 and MBL 0202 INT) and a long-term safety Trial MBL 0407 INT. (See Clinical Reviews by Brenda Carr, MD dated 4/23/2008 and Patricia Brown, MD dated 9/10/2012.)

In addition, the Applicant investigated the use of their fixed combination products, Taclonex Topical Suspension and Taclonex Ointment, in the pediatric population age 12 to 17 years in several trials. 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). The Applicant also 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). All trials investigated the effects of the combination products on safety including HPA axis and calcium metabolism and secondarily on efficacy. Findings from these trials indicated no changes in albumin-corrected serum calcium and 1/30 (3.3%) receiving Taclonex Topical Suspension and none receiving Taclonex Ointment had adrenal suppression.

In this supplement, the Applicant submitted results from Trial LP0076-1017 evaluating Taclonex Topical Suspension in a total of 107 subjects with plaque psoriasis on the scalp and body of at least mild severity with at least 10% of the surface area of the scalp affected and at least 3% total BSA affected. All subjects applied Taclonex Topical Suspension once daily for up to 8 weeks and provided an assessment of calcium metabolism. In a subset of subjects with psoriasis on the scalp and body of at least moderate severity and 10-35% body surface area (BSA) affected, the Applicant evaluated the PK (32 subjects) and the potential for HPA axis suppression (31 subjects) under maximal use conditions.

The data indicated no new safety signals. There were no deaths; one subject experienced a serious adverse event (suicide attempt) and one subject withdrew from the trial due to an

adverse event (mild blood cortisol decreased which was assessed as possibly related.) Overall, a total of 38 (35.5%) subjects experienced 62 adverse events (AEs). All AEs were mild or moderate except one event of suicide attempt which was severe. The most common adverse events were nasopharyngitis and headache which were reported by 6 subjects each (5.6%). Investigators identified 8 adverse reactions (13%) which occurred in 7 subjects and included both local and systemic effects. Local safety findings included erythema and folliculitis, while systemic findings included decreased blood cortisol in 2 subjects in the maximal use cohort who participated in HPA axis testing.

All analyzable samples for calcipotriol and its metabolite were below the level of quantification; there were no clinically meaningful changes from Baseline in measures of calcium metabolism, the primary safety issue. Among the subjects participating in HPA axis assessments, 5 (16%) of 31 subjects experienced adrenal suppression. These pharmacodynamic findings in the pediatric population are similar to the labeled findings in adult population following treatment with calcipotriene and betamethasone dipropionate combination products. 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 less than 17 years was extrapolated from data in 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 Taclonex Topical Suspension in the population 12 years and older with plaque psoriasis of the scalp and body.

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 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.

[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.
[4] Shah KN. Diagnosis and treatment of pediatric psoriasis: current and future. Am J Clin Dermatol. 2013;14(3):195

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.,[6 7] 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.

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/retinoids) has been demonstrated in both children and adults. The response to both systemic and localized immunosuppression

[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
[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.

appears to be similar in all age groups.[10] For a discussion of the topical treatment options for chronic plaque psoriasis see the NDA 22185 S-010 Clinical Review by Patricia Brown dated 09/10/2012.

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:

- Patient's global assessment of disease severity on the scalp and body: a 5- point scale ranging from "clear" to "severe"
- Itch and Sleep Questionnaire: 3 visual analog scales (VAS) with anchors from "none" to "worst possible" to rate maximal itching on the scalp, maximal itching on the body and sleep loss during the last 24 hours.

Although patient reported outcomes may be important treatment effects to evaluate, the Applicant solicited no comments regarding the development of PROs to support labeling claims. 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
		□	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)		

[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
	□	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	
	□	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. See Section 2.1 *Analysis of Condition* above.

3. Regulatory Background

LEO Pharma A/S developed Taclonex Topical Suspension under IND 067835. The FDA approved Taclonex Topical Suspension[11] (NDA 022185) on May 9, 2008 for the topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults 18 years and older with data from 2 Phase 3 trials (MBL 0405 and MBL 0406 enrolling a total of 1922 subjects). The Applicant received a waiver of assessments in the pediatric population ages 0 months to <12 years because the product was not considered to be a safe treatment option in this age group due to the potent corticosteroid component. Assessments in the pediatric population age 12 years to less than 17 years were deferred because the product was ready for approval for use in adults and the pediatric studies were not completed. See Clinical Review by Brenda Carr, MD dated April 23, 2008. The results of the deferred assessments (MBL 0801 and MBL 0412 INT enrolling 109 subjects) supported the use of Taclonex Topical Suspension on the scalp in patients 12 years and older (NDA 022185/S-018 approved August 29, 2014).

[11] The original proprietary name was Taclonex® Scalp Topical Suspension. The Applicant requested a review of a new proprietary name "Taclonex® Topical Suspension" to reflect the use of the product on other sites of application beyond the scalp (i.e. body). (Letter dated April 7, 2011) On October 5, 2011, the Division of Medication Error Prevention and Analysis completed their review of the proposed proprietary name and concluded that it was conditionally acceptable pending approval of the safety and efficacy data supporting the use of this product on additional sites of application beyond the scalp.

The Applicant conducted 3 key trials (LEO 80185-G23, LEO 80185-G21 and MBL 0202 INT) to support the safety and efficacy of Taclonex Topical Suspension for the treatment of mild to moderate psoriasis on the body in the adult population. (See Clinical Review by Patricia Brown, MD dated 9/10/2012.) With approval of the additional indication for plaque psoriasis of the body (S-010, approved December 23, 2011), the FDA issued the following postmarketing requirement under PREA:

> 1935-1
> Conduct a trial in 100 evaluable pediatric patients with plaque psoriasis of the scalp and body ages 12 to 16 years, 11 months, to evaluate the safety and effect of Taclonex® (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/0.064% on calcium metabolism. Evaluate the hypothalamic-pituitary axis and pharmacokinetics of the two drug components, calcipotriene and betamethasone dipropionate, in a subset of at least 30 patients treated with Taclonex® Topical Suspension under maximal use conditions.
>
> Final Protocol Submission: 04/2013
> Trial Completion: 10/2015
> Final Report Submission: 10/2016

To address PREA PMR 1935-1, the Applicant submitted Protocol LP0076-l 017 (IND 067835 SD 113 received on April 29, 2013) which was entitled, "A Phase 2 Trial Evaluating the Safety and Efficacy of Once Daily use of LEO 80185 Gel Containing Calcipotriol 50 mcg/g plus Betamethasone 0.5 mg/g (as dipropionate) in Adolescent Subjects (aged 12 to 16 years, 11 months) with Scalp and Body Psoriasis".

The FDA provided comments regarding Protocol LP0076-1017 (Advice Letter dated October 7, 2013). The key comments concerned PK sampling timepoints, dosing to provide a sufficient amount to cover all affected areas and a recommendation for a Baseline 25-OH Vitamin D level. In response to FDA comments, the Applicant submitted an amended final protocol to the IND (SD 118 submitted to IND 067835 on November 21, 2013.) See Clinical Reviews dated 8/9/ 2013 and 5/1/2014. There were 5 versions of the protocol.

The Agency granted two Deferral Extension Requests (Letter dated 9/29/2015 with Final Report Submission extended to Dec 2017 and Letter dated 2/16/2017 with Final Report Submission extended to Sept 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. OSI recently inspected (4/16/2018-4/19/2018) the study site for the international coordinating investigator,[12] Dr. Lawrence Eichenfield. The resulting Compliance Classification was "No deviation from regulations (NAI)".

4.2. Product Quality

The Applicant determined that the formulation of Taclonex Topical Suspension 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. However, the Applicant provided qualitative and quantitative composition information and Certificates of Analyses to document that the investigational product used in Trial LP0076-1017 was identical to the United States approved product (SD 336 dated March 7, 2019). For the analysis of the Chemistry, Manufacturing, and Controls (CMC) information which supported the original approval and assured the identity, strength, purity and quality of the drug product, refer to the Review by Zhengfang Ge, Ph.D. dated February 7, 2008.

The CMC Reviewer, Steve Hathaway, Ph.D., analyzed the request for categorical exclusion from the requirement to conduct an Environmental Assessment (EA) 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." (SD 331 dated February 28, 2019)

The Applicant provided the calculation of the Expected Introduction Concentration (EIC) of an active moiety into the aquatic environment. The CMC reviewer concluded, "The EIC calculation was provided, confirming that the expected annual exposure to the aquatic environment is below 1ppb, and the categorical exclusion is granted." See Review dated March 29, 2019.

[12] Signatory investigator signed the protocol and served as an investigator

Except for formatting changes to conform to current practice, the Applicant proposed no changes to the to the CMC-related sections of the Prescribing Information, Patient Information, or carton and container labeling. Dr. Hathaway stated that "The labeling, with respect to the CMC-related sections, is acceptable as submitted" and concluded "This supplement is recommended for approval." See review by Joel Hathaway, Ph.D., dated March 29, 2019. The Associate Directors for Labeling (ADLs; Debra Beitzell MD and Eric Brodsky MD) provided additional recommendations for the CMC sections of labeling based on labeling policy. The CMC reviewer included those revisions which were appropriate for the product.

5. Pharmacology Toxicology

The Applicant submitted no new pharmacology/toxicology data in this pediatric efficacy supplement. The Pharmacology/Toxicology team conducted a comprehensive review of the nonclinical data which was submitted to support the original approval of Taclonex Topical Suspension. For an analysis and discussion of the nonclinical data, refer to the review by Norman See, Ph.D. dated February 20, 2008. Regarding this submission, the Dr. See indicated "The Applicant completed all necessary nonclinical studies to support evaluation of Taclonex Topical Suspension in the pediatric population aged 12 to 17 years." In addition, 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 6/11/2019.)

6. Clinical Pharmacology

The Clinical Pharmacology reviewer, Jihye Ahn, PharmD, evaluated the pharmacokinetics (PK) and effects on HPA axis suppression and calcium metabolism of once daily administration of Taclonex Topical Suspension (LEO 80185 gel). Dr. Ahn indicated that the trial results support the systemic safety of the Taclonex Topical Suspension following once daily application to the scalp and body of subjects 12 to < 17 years of age with psoriasis. After review of the results of Trial LP0076-1017, the Office of Clinical Pharmacology/Division of Clinical Pharmacology III "finds NDA 022185/S-27 acceptable pending agreement on recommended labeling changes." 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 Jihye Ahn, PharmD dated June 17, 2019. A summary of the clinical pharmacology and biopharmaceutics findings from her review are presented below.

Refer to the Clinical Pharmacology Review by An-Chi Lu, MS, Pharm.D. (dated 6/12/2014) for an analysis of the clinical pharmacology data submitted to support the approval of the treatment of plaque psoriasis on the scalp in subjects age 12 to 17 years.

6.1. Pharmacokinetics

The Applicant conducted PK and PD assessments in a subset of 31 subjects with moderate or severe psoriasis with a mean total BSA (including scalp) of 18.4% (range 10-29%). Subjects had a mean (SD) of 18% (4.7) of the body affected and a mean of 62.4% (26.4) of scalp affected with psoriasis. Subjects in this subset applied a mean of 157 g of Taclonex Topical Suspension during the first 4 weeks of the treatment period.

Per Dr. Ahn, the Applicant used an adequately validated bioanalytical assay to quantify human plasma PK samples from Trial LP0076-1017. Betamethasone dipropionate (BDP) was quantifiable in five PK samples from four subjects (13%) and betamethasone 17-propionate (B17P), a metabolite of BDP, was quantified in 12 PK samples from 5 subjects (16%). Neither calcipotriol nor its metabolite MC1080 were quantifiable in any of the PK samples. In Section 12.3 of labeling, the clinical pharmacology reviewer corrected the maximum percent body surface area of subjects applying Taclonex® Topical Suspension (b) (4) to 29%.

6.2. Pharmacodynamics

Using commercial analyzers, the Applicant examined human serum and urine samples for quantification of serum cortisol, serum calcium or urine calcium. The mean levels (SD) of albumin-corrected serum calcium levels were 2.25 (0.085) mmol/L at baseline. Following administration Taclonex Topical Suspension once daily, the mean changes from baseline for albumin corrected calcium levels were -0.012 (0.13) at Week 4, and -0.008 (0.13) at Week 8. The mean changes for 24-hour urine calcium excretion from baseline were -0.49 (1.67) at Week 4, and 0.04 (1.64) mmol/24hr at Week 8. The Clinical Pharmacology reviewer concluded that "overall, the albumin-corrected serum calcium levels and urine calcium excretion seemed to remain similar throughout the treatment period."

The Applicant assessed the effect on the HPA axis using an ACTH-challenge test at Screening, Visit 3 (Day 28), and Visit 5 (Day 56) in 31 subjects. The primary response endpoint was adrenal suppression as indicated by serum cortisol concentration ≤18 mcg/dL at 30 minutes after ACTH-challenge at Weeks 4 and 8. The Applicant also evaluated cortisol suppression 60 minutes after ACTH-challenge at Weeks 4 and 8 as the secondary/ exploratory response endpoint. The Applicant included five subjects who did not fulfill the inclusion criteria in the HPA analysis. When Dr. Ahn conducted an analysis of the HPA axis suppression rate without those subjects, the results were similar to those submitted by the Applicant. Per Applicant, HPA axis suppression was observed in a total of 5 subjects (16.1%); specifically, HPA axis suppression was observed in 4 subjects (12.9%) after 4 weeks of treatment and 2 subjects (6.5%) after 8 weeks. One subject had HPA axis suppression at both periods (Weeks 4 and 8).

For labeling of Section 12.2 Pharmacodynamics, Dr. Ahn revised the description of the trial to include the duration of treatment, corrected the maximum BSA of the tested subjects and

provided information regarding the criteria for HPA Axis suppression, "In all these trials, adrenal suppression is indicated by a 30-minute post-stimulation cortisol level ≤18 mcg/dL."

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 clinical Trial LP0076-1017, to address PMR 1935-1 and support the use of Taclonex Topical Suspension in patients 12 years and older with plaque psoriasis of the scalp and body. Trial LP0076-1017 was entitled, "Effect of calcipotriol plus betamethasone dipropionate gel on the HPA axis and calcium metabolism in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis." Key elements of the trial are summarized below.

Table 1: Clinical Trial LP0076-1017

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							
LP0076-1017 Conducted 03/07/2014 To 2/13/2018	Multicenter, open-label, repeat-dose safety trial with assessments of PK, HPA Axis, calcium metabolism and treatment effects	Once daily up to 8 weeks topically to the scalp and body	-Effects on calcium metabolism -PK -ARs -HPA Axis -VS -Local safety (lesional/ perilesional AEs)	8 weeks of treatment with 7- day follow-up period	107 enrolled 102 completed	Age 12 to 17 < years HPA: Moderate plaque psoriasis with ≥ 20% scalp and ≥ 10-35 % BSA affected Non-HPA: Mild plaque psoriasis with ≥ 10% scalp and ≥ >3 % BSA affected	30 sites in US, CA, DE, FR, UK, PL & RO

Abbreviations: HPA = hypothalamic-pituitary-adrenal axis; AR = adverse reactions; VS = vital signs; PK = pharmacokinetics; PD = pharmacodynamics, AEs = adverse events, BSA = body surface area
Source: Reviewer's Table

7.1.2. Review Strategy

The focus of this review was the local and systemic safety of Taclonex Topical Suspension which included PK and PD findings. Systemic safety assessments included documentation of adverse events, vital signs, laboratory parameters, testing for HPA axis suppression, effects on calcium metabolism and systemic exposure (PK.) Efficacy was a secondary objective of Trial LP0076-1017. However, the design of Trial LP0076-1017 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 less than 17 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 Taclonex Topical Suspension for the proposed indication 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 including the protocol, clinical study reports, Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format are located in the following network path:

\\cdsesub1\evsprod\nda022185\0184.enx

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

7.2. Review of Relevant Trial

7.2.1. Study Design and Endpoints

Clinical Trial LP0076-1017
Objectives
The primary objective of Trial LP0076-1017 was to evaluate the safety of once daily use of Taclonex Topical Suspension in pediatric subjects (aged 12 to less than 17 years) with psoriasis of the scalp and body; the secondary objective was to evaluate treatment effects of Taclonex Topical Suspension 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 2: Eligibility Criteria for Subjects Who Did and Did Not Participate in Testing for HPA Axis Suppression

	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 scalp and body	X	X
Psoriasis on the body: at least 3% BSA	X	
Psoriasis on the scalp: at least 10% of the scalp area	X	
Psoriasis on the body: 10-35% BSA		X
Psoriasis on the scalp: at least 20% of the scalp area		X
IGA on the scalp and body	≥mild	≥moderate
Serum albumin-corrected Ca within the normal range at SV2	X	X
Normal HPA Axis function at SV2		X

	Subjects	
Key Exclusion Criteria	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/suspected endocrine disorder that may impact results		X
Abnormal Sleep Pattern		X
Known or suspected hypersensitivity to Cortrosyn/ Synacthen		X
Known or suspected severe renal or hepatic disease	X	X

Abbreviations: BSA = body surface area, HPA = hypothalamic-pituitary-adrenal, SV2 = screening visit 2
Source: Reviewer's Table-Modified from Module 2.7.3 Summary of Clinical Efficacy, Panel 2

Concomitant Medications

Permitted concomitant medications included non-medicated shampoos, bath oil and moisturizing sops. The protocol permitted topical treatments, except corticosteroids, to be used on the face and intertriginous areas.

Prohibited Products/Products with Pre-Specified Washout Periods

- Initiation of, or changes to, concomitant medication that could affect scalp or body psoriasis (e.g. beta-blockers, lithium, anti-malaria drugs, ACE inhibitors).
- Excessive exposure of treated areas to either natural or artificial sunlight (including tanning booths, sunlamps, etc.).
- UVB therapy within 2 weeks prior to Visit 1
- Any topical treatment on the scalp or body including corticosteroids (except for emollients and non-steroid medicated shampoos) within 2 weeks prior to Visit 1

- Systemic calcium, vitamin D supplementation > 400 IU/day, antacids, diuretics, antiepileptics, diphosphonates or calcitonin within 4 weeks prior to SV2. (Stable doses of oral vitamin D supplementation ≤ 400 IU/day was permitted).
- Systemic biological therapies with a possible effect on psoriasis (etanercept within weeks prior to Visit 1; adalimumab and infliximab within 2 months prior to Visit 1, ustekinumab within 4 months prior to Visit 1 or experimental products (within 4 weeks/5 half-lives [whichever is longer] prior to Visit 1)
- Systemic therapies other than biologicals, with a possible effect on psoriasis (e.g., retinoids, immunosuppressants, PUVA within 4 weeks prior to Visit 1)

Prohibited Products for Participants in HPA Axis and PK Assessments

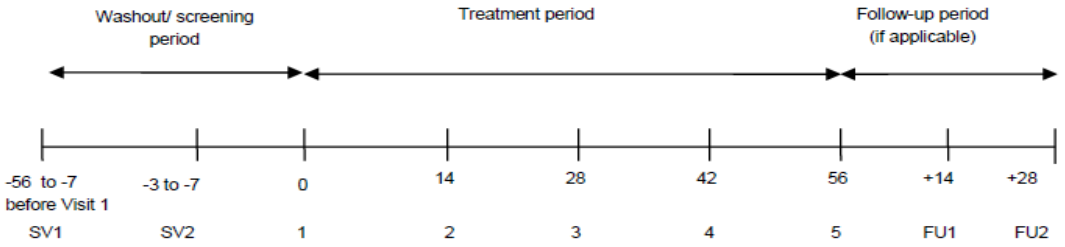
- Systemic treatment with corticosteroids (including inhaled and nasal steroids) (12 weeks prior to SV2)
- Estrogen therapy (including contraceptives) or any other medication known to affect cortisol levels or HPA axis integrity within 4 weeks prior to SV2
- Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin), systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole, metronidazole), hypoglycemic sulfonamides, antidepressants within 4 weeks prior to SV2). Topical ketoconazole within 2 weeks prior to SV2.

Study Design

This was an international, multicenter, prospective, open-label, trial in subjects aged 12 to less than 17 years with at least mild psoriasis on the scalp and body. Subjects received treatment with Taclonex Topical Suspension once daily for up to 8 weeks and provided assessments of calcium metabolism. A subset of subjects with psoriasis of at least moderate severity performed HPA axis and PK assessments under maximal use conditions.

The trial consisted of 3 periods: 7 to 56-day screening/washout period, a 56-day treatment period, and optional 28-day follow-up period. 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

Investigators instructed subjects to apply the study product once daily to all plaques of psoriasis for up to 56 days and to discontinue treatment to lesions which cleared during the trial. After 4 weeks, subjects who were clear of psoriasis, discontinued treatment and left the trial; subjects who had lesions of psoriasis at Week 4 continued to receive treatment for an additional 4 weeks.

Subjects performing HPA axis and PK assessments 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 the following number of bottles for dosing:

Table 3: Target Doses for Subjects Not Performing Pharmacodynamic Assessments

Age range (years)	BSA[a]	Maximum weekly dose LEO 80185	Number of bottles dispensed[b]
12 to <15	≤1.3 m^2	55 g	2
12 to <15	>1.3 m^2	75 g	3
>15	BSA ≤ 1.7 m^2	75 g	3
>15	BSA > 1.7 m^2	100 g	4

[a] BSA calculated using the Mosteller formula (BSA (m2) = ([Height (cm) × Weight (kg)] / 3600)½ (Mosteller RD, 1987)).
[b] Bottles including 60 g of LEO 80185 distributed at dispensing visits.
Abbreviations: BSA = body surface area, HPA = hypothalamic-pituitary-adrenal
Source: Module 2.7.3 Summary of Clinical Efficacy, Panel 3

Subjects or their primary caregivers recorded each application of the study product in a log to monitor compliance. Study personnel documented the weight of bottles of study product when dispensed and returned.

During the treatment period, subjects scheduled up to 5 visits: Visit 1 (Day 0), Visit 2 (Da 14), Visit 3 (Day 28), Visit 4 (Day 42) and Visit 5 (Day 56). The first optional follow-up visit occurred at 14 days after the last treatment for subjects with an ongoing adverse event that was assessed as possible/probable/not assessable relationship to the study product or abnormal albumin/corrected serum calcium that was above the reference range at the last onsite visit. The second optional follow-up visit occurred if the serum cortisol concentration was ≤18 mcg/dL at 30 minutes after ACTH-challenge at Visit 3 or Visit 5.

At the screening visits, 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 and concomitant medications at all visits during treatment and follow-up; vital signs (systolic and diastolic blood pressure (BP) and heart rate), laboratory evaluation, pregnancy testing and 24-hour urine collection at Week 4 and Week 8. Subjects in the maximal use cohort completed the PK evaluation at Week 4 and HPA Axis assessments at Baseline, Week 4 and Week 8 as

indicated. Investigators and subjects provided assessments of extent and severity of psoriasis, itch and sleep disturbance at all visits from screening to the end of treatment. See the Schedule of Assessments (Table 7).

The efficacy assessments are summarized in the following table:

Table 4: Schedule of Investigator and Subject Efficacy Assessments in Trial

Assessment	Visit						
	SV2	1	2	3	4	5	EW
Investigator's assessment of extent of total psoriasis (total, body, and scalp)	X	X		X		X	X
Investigator's global assessment of disease severity (scalp and body)	X	X	X	X	X	X	X
Investigator's assessment of the extent and severity of clinical signs of psoriasis vulgaris (for PASI)	X	X	X	X	X	X	X
Patient's global assessment of disease severity (scalp and body)	X	X	X	X	X	X	X
Patient's assessment of itching and sleep	X	X	X	X	X	X	X

Abbreviations: EW = early withdrawal (if applicable), PASI = Psoriasis Area Severity Index, SV = screening visit
Source: Module 2.7.3 Summary of Clinical Efficacy Panel 4

The protocol specified that both investigators and subjects evaluate the severity of the disease on the scalp and body separately using the 5-point scales below. The scalp was defined by the hair line. See Appendix 1

Other assessments of efficacy included:

Investigator Assessments

- Investigator's assessment of the extent of psoriasis (total, body, scalp) by "hand print" method, palm and fingers.
- Psoriasis Area Severity Index (PASI): using the Investigator's assessment of the extent (head, arms, trunk, legs on a 7-point scale) and severity of clinical signs of psoriasis (redness, thickness, scaliness on 5-point scales). See Section 5.4.3.1.5 of the Clinical trial report for the methodology of the calculation.

Subject Assessments

- Assessment of itching and sleep: using the Itch and Sleep Questionnaire which includes 3 questions to determine the maximal intensity of itching and sleep loss during the last 24 hours. Subjects rated the maximum intensity of their itch (separately on the body and scalp) and sleep loss from none to worst possible by marking a line on a visual analog scale (VAS).

Response Criteria

Primary Response Criteria

- Adverse drug reactions (ADRs)
- Subjects with serum cortisol concentration of ≤18 mcg/dL at 30 minutes after ACTH challenge at Week 4 and at Week 8
- Change in albumin-corrected serum calcium from baseline (SV2) to Week 4, Week 8, and end of treatment
- Change in 24-hour urinary calcium excretion from baseline (SV2) to Week 4, Week 8, and end of treatment

Secondary Response Criteria

Safety

- Adverse events (AEs)
- Subjects with serum cortisol concentration of ≤18 mcg/dL at both 30 and 60 minutes after ACTH-challenge at Week 4 and at Week 8
- Change in urinary calcium: creatinine ratio from baseline (SV2) to Week 4 and Week 8
- Change in serum alkaline phosphatase (ALP) from baseline (SV2) to Week 4 and Week 8
- The following pharmacokinetic parameters were to be calculated (when possible) at Week 4 for each assayed compound:
  - $AUC0_{-t}$, $AUC0_{-\infty}$
  - C_{max}
  - T_{max}, $T_{1/2}$

Efficacy

- Subjects with *controlled disease* (*clear* or *almost clear*" for subjects with at least *moderate* disease at baseline, *clear* for subjects with *mild* disease at baseline) according to the investigator's global assessment of disease severity on the body at end of treatment.
- Percentage change in Psoriasis Area Severity Index (PASI) from baseline to end of treatment.
- Subjects with *controlled disease* (*clear* or *very mild*) according to the patient's global assessment of disease severity on the body at end of treatment

Investigator(s)

There were 30 participating study sites in the United States, Canada, Germany, France, UK, Poland and Romania. The largest proportion of subjects enrolled from Romania. Refer to the Appendix for the list of study sites and enrollment.

Schedule of Assessments

The schedule of assessments is summarized in the following table.

Table 5: Schedule of Assessments

Visit	SV1 [1]	SV2 [1,2]	1	2	3[3]	4	5	EW[4]	FU1[5]	FU2[6]
Day	-56 to -7	-7 to -3	0	14 ± 2	28 ± 2	42 ± 2	56 ± 2	--	+ 14 ± 2	+ 28 ± 2
Informed consent	X									
Demographics	X									
Medical history	X									
Physical examination	X									
Height, weight and BSA[7]	X		X							
Inclusion/exclusion criteria	X	X	X							
Vital signs (blood pressure, heart rate)		X			X		X	X		
25-hydroxy Vitamin D		X								
Haematology/biochemistry/ urinalysis [8]		X			X		X	X	X [9]	
Pharmacokinetic sampling (assigned U.S., Romanian, and German sites only)[10]				X	X					
ACTH challenge test (assigned U.S., Romanian and German sites only) [11]		X			X		X			X
Instruction for 24-hour urine collection and dietary calcium intake diary	X			X		X				
Review of dietary calcium		X			X		X	X		
Collection of 24-hour urine [12]		X			X		X			
Urine pregnancy test [13, 14]		X			X		X	X		X
Adverse events		X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	
Investigator's assessment of extent of total psoriasis		X	X		X		X	X		
Investigator's assessment of extent of body psoriasis		X	X		X		X	X		

Visit	SV1 [1]	SV2 [1,2]	1	2	3[3]	4	5	EW[4]	FU1[5]	FU2[6]
Day	-56 to -7	-7 to -3	0	14 ± 2	28 ± 2	42 ± 2	56 ± 2	--	+ 14 ± 2	+ 28 ± 2
Investigator's assessment of extent of scalp psoriasis		X	X		X		X	X		
Investigator's global assessment of disease severity on the body		X	X	X	X	X	X	X		
Investigator's global assessment of disease severity on the scalp		X	X	X	X	X	X	X		
Patient's global assessment of disease severity on the body		X	X	X	X	X	X	X		
Patient's global assessment of disease severity on the scalp		X	X	X	X	X	X	X		
Investigator's assessment of the extent and severity of clinical signs of psoriasis vulgaris (for PASI)		X	X	X	X	X	X	X		
Patient's assessment of itching and sleep		X	X	X	X	X	X	X		
Dispensing of IMP			X	X	X	X				
Return of IMP				X	X	X	X	X		
IMP Compliance				X	X	X	X	X		

1. Per protocol, there were at least 4 days between SV1 and SV2 so dietary information (diary) could be collected.
2. On the day prior to the ACTH (adrenocorticotropic hormone) challenge, the following assessments were performed: vital signs, spot urine collection, pregnancy test, AEs (adverse events), concomitant medication, and assessments of psoriasis.
3. End of treatment: Subjects whose scalp and body psoriasis cleared after 4-week treatment at Visit 3 were to stop the IMP and leave the trial. Subjects who had signs of psoriasis after 4 weeks of treatment were to continue treatment for another 4-week period until Visit 5.
4. At any early withdrawal (EW) visit prior to Visit 5, testing scheduled for Visit 5 was performed except the ACTH-challenge test and the 24-hour urine collection.
5. Follow-up Visit 1 occurred only for subjects with an ongoing serious or non-serious adverse event(s) which was classified as possibly/probably related/not assessable relationship to the study product and for subjects with albumin-corrected serum calcium *above* reference range at the last on-treatment visit.
6. Applicable only to subjects in the U.S., Romania and Germany performing HPA axis assessments. Follow-up Visit 2 occurred only if serum cortisol is ≤18 mcg/dL at 30 min after the ACTH challenge test at Visit 3 or Visit 5.
7. Body surface area (BSA) was calculated using the Mosteller formula (Mosteller RD, 1987).
8. Staff performed blood and spot urine sampling at the end of treatment for subjects who were withdrawn prior to Visit 5.
9. If laboratory results suggested albumin-corrected serum calcium *above* reference range at the last on treatment visit, a follow-up test was performed.
10. Applicable only to subjects in the U.S., Romania and Germany performing PK assessments. At Visit 2, a pre-dose trough sample was taken. At Visit 3, the first PK sample (trough) was taken prior to the ACTH-challenge test. Then following the 30- and 60-minute blood samples for the ACTH-challenge test, the IMP was applied. Further PK analysis blood samples were taken at 1, 3 and 5 hours after application of trial medication.
11. Applicable only to subjects in the U.S., Romania and Germany performing HPA axis assessments. Per protocol, ACTH challenge tests were performed at 8.00 a.m. ±30 min after checking vital signs and collecting blood and urine samples.
12. It was acceptable that the 24-hour urine sample was collected up to three days prior to the trial visit.
13. For female subjects of childbearing potential (FCBP).
14. For subjects who withdrew early, pregnancy testing was conducted at their last treatment visit
Source: Clinical Trial Report for LP0076-1017, Panel 5 page 36

Data Analysis
The protocol specified the following 3 analysis sets:

- Full analysis set - all subjects who received the study product
- Safety analysis set - all subjects who applied study product and provided information on the presence or confirmed absence of adverse events.
- Per protocol analysis set (HPA-axis subgroup)- this analysis set was a defined as the subjects who provided results from the HPA-axis challenge.

In this trial, the full analysis set was the same as the safety analysis set. The safety analysis set included 107 subjects although for 2 subjects the application of the study product was not confirmed. Of the 33 subjects who were assigned to the HPA-axis subgroup, the Applicant excluded 2 subjects who did not provide results from the HPA-axis challenge testing. A total of 6 subjects did not meet the inclusion criterion concerning evidence of adrenal function suppression at baseline; 5 of 6 subjects participated in HPA axis testing. Therefore, the per protocol set (HPA-axis subgroup) included a total of 31 subjects.

Protocol Amendments
The Applicant submitted 6 versions of Protocol LP0076-1017. The key changes resulted from comments from regulatory agencies or strategies to increase recruitment of subjects. The key amendments are summarized below:

Version 2
In response to regulatory agency comments, the Applicant modified the protocol to permit subject from the United States performing HPA and PK assessments to apply non-steroid treatments to the face and skin folds and subjects not performing HPA and PK assessments to apply low-/mid -potency corticosteroids to the face and skin folds during the trial. In the protocol, the Applicant clarified the PK sampling timepoints, PK endpoints, and required weight at enrollment (at least 30 kg). The Applicant modified the entry criteria to allow the participation of subjects taking stable doses of Vitamin D and permitted subjects who were clear at Week 4 to discontinue treatment.

Version 3
The Applicant revised the locations of the study sites. In response to FDA comments, the Applicant removed the maximal weekly dose limits for subjects participating in the HPA and PK assessments and indicated that there were no anticipated risks to address with specific withdrawal criteria.

Version 4
The Applicant modified study population to enroll subjects with psoriasis of moderate severity involving 10-35% BSA (excluding lesions of psoriasis involving the face and sensitive areas) in the cohort performing HPA Axis and PK assessments and to enroll subjects with psoriasis of at

least mild severity involving at least 3% BSA (excluding lesions of psoriasis involving the face and sensitive areas) in the cohort not performing PK and HPA axis assessments.

Versions 5 and 6
In response to recruitment challenges, the Applicant increased the number of study sites by including new investigators in central and eastern Europe. In addition, the Applicant added Romania to the countries permitted to conduct HPA axis and PK assessments.

7.2.2. Results of Efficacy Assessment

Protocol LP0076-1017 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. The following are secondary efficacy endpoints:

- Subjects with *controlled disease* (*clear* or *almost clear*" for subjects with at least *moderate* disease at baseline, *clear* for subjects with *mild* disease at baseline) according to the **investigator's global assessment** of disease severity on the body at end of treatment.
- Percentage change in Psoriasis Area Severity Index (PASI) from baseline to end of treatment.
- Subjects with *controlled disease* (*clear* or *very mild*) according to the **patient's global assessment** of disease severity on the body at end of treatment.

The results of the assessments of treatment effect are presented below.

Table 6: Controlled Disease at the End of Treatment: Full Analysis Set

	Body	Scalp
	Number of Subjects (%)	**Number of Subjects (%)**
End of Treatment		
Investigator's Global Assessment of Disease Severity (IGA)		
Controlled Disease	62 (57.9)	74 (69.2)
Non-Controlled Disease	45 (42.1)	33 (30.8)
Patient's Global Assessment of Disease Severity (PGA)		
Controlled Disease	67 (62.6)	74 (69.2)
Non-Controlled Disease	40 (37.4)	33 (30.8)
Total	107 (100)	107 (100)

There was a greater proportion of subjects with controlled disease on the scalp than on the body at the end of treatment as assessed by both investigators and subjects**.** Compared with the results of other trials conducted by the Applicant, the percentage of subjects with controlled disease on the body according to IGA was greater in this trial while the percentage of subjects with controlled disease on the scalp was similar. See the tabulation below.

Table 7: Results of Assessments of Efficacy/Treatment Effect from Other Clinical Trials in the Development Program for Taclonex Topical Suspension

Clinical trial	Controlled disease[b] (IGA) (%)	
	Week 2 or 4	End of treatment
Trial in adolescents (scalp and body)		
LP0076-1017 (n=107)		
Scalp	49.0[d]	69.2
Body	43.3[d]	57.9
Trials in adolescents (scalp)		
MBL 0801 (n=31)	32.3	54.8
MBL 0412 INT (n=78)	47.4	84.6
Pivotal trials in adults (scalp)[c]		
MBL 0405 INT (n=494[a])	55.5	70.0
MBL 0406 INT (n=512[a])	47.1	67.2
Trials in adults (body)		
LEO 80185-G23 (n=482)	13.3[d]	29.0
MBL 0202 INT (n=162)	16.0d	27.2
LEO 80185-G21 (n=183)	18.6d	39.9

Abbreviation: IGA = Investigator's Global Assessment of Disease Severity
a In the LEO 80185 treatment group, only.
b Controlled disease by the IGA of disease severity defined as clear or almost clear disease (clear for subjects with mild disease at baseline) or absence of disease or very mild disease.
c This analysis was the Sponsor amended analysis, excluding subjects with mild disease (by IGA on severity) as presented in the USPI for the primary endpoint. Some of the numbers were not previously reviewed by the FDA but produced in order to make a parallel comparison to the data being presented for the adolescent population.
d These are Week 4 data for the primary endpoint.
Source: Module 2.7.3 Summary of Clinical Efficacy Panel 6

The percentage of subjects who had controlled disease by the end of treatment was higher for subjects who had moderate disease (63.2%) at baseline than for subjects with mild (50.0%) disease at baseline; none of the 6 subjects with severe disease at baseline were controlled at the end of treatment.

Percent change in PASI score showed a trend toward improvement in severity. The mean PASI score at baseline was 10.7 (range 2.8-27.5) while the mean PASI score at the end of treatment was 1.9 (range 0-21.0). Percent change in PASI was -78.7.

Overall, there was a reduction in the maximal intensity of itching and sleep loss during the last 24 hours as assessed using the Itch and Sleep Questionnaire. However, in the absence of a

definition of a clinically meaningful change and vehicle comparator, the results are not interpretable.

7.3. Review of Safety

7.3.1. Safety Review Approach

The review of the safety of Taclonex Topical Suspension in the pediatric population age 12 to less than 17 years focused on data from a single trial, Trial LP0076-1017. 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

Investigators assessed extent of exposure and compliance with the dosing regimen by recording the duration of exposure and amount of investigational product (IP) applied.

Overall, the mean duration of exposure was 52.7 days (range 22 to 70 days). The mean weekly exposure by month is tabulated below. The mean weekly exposure in the first month (32.5) is comparable to the mean weekly exposure in the second month (26.7). The mean amount of IP used during the entire treatment period was 247.2 g [median 7.2 g (range 12.0 to 864.3 g)].

Table 8: Extent of Exposure: Average Weekly Amount of Investigational Product (IP) Used (g)

Weekly Amount of IP Used (g)	Statistics	Subjects/Results N=107
Visit 1 to Visit 3 (4 weeks)	N	92
	Mean (SD)	32.5 (21.5)
	Median	30.6
	Minimum/Maximum	1.4/111.8
Visit 3 to Visit 5 (4 weeks)	N	80
	Mean (SD)	26.7 (22.2)
	Median	22.2
	Minimum/Maximum	0.0/116.6
Visit 1 to End of Treatment	N	75
	Mean (SD)	30.8 (21.6)
	Median	26.6
	Minimum/Maximum	1.6/114.2

Source: Adapted from Panel 22 page 71; LP0076-1017 Clinical trial report

As indicated in the following table, subjects participating in the adrenocorticotropic hormone (ACTH) challenge (evaluation of potential for HPA Axis suppression) and PK assessments

experienced greater average exposure to the study product than subjects in the safety analysis set.

Table 9: Total Amount of Product Used (g): Safety Analysis Set Vs. HPA Axis / PK Subset

Amount of Product Used Through Week 4 (Timepoint for HPA/PK Evaluation)	Safety Analysis Set N=107	HPA Axis / PK Subset N=31
N (total subjects providing data)	92	31
Mean (SD)	136.2 (89.2)	157.0 (70.3)
Median	127.7	162.9
Minimum/Maximum	5.4/431.1	18.7/266.2

Abbreviations: HPA = hypothalamic-pituitary-adrenal axis, PK = pharmacokinetics, SD = standard deviation
Source: Adapted from SD 330 Panel 1 2/22/2019

Table 10: 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	84 (80.8%)	25 (80.6%)
Yes: <=10% applications missed	16 (15.4%)	6 (19.4%)
Yes: >10% to <=20% applications missed	3 (2.9%)	0 (0.0%)
Yes: >20% to <=30% applications missed	1 (1.0%)	0 (0%)
Total	104 (100.0%)*	31 (100.0%)

Abbreviations: HPA = hypothalamic-pituitary-adrenal axis, PK = pharmacokinetics
Source: Adapted from Panel 23 * data not available for all 107 subjects

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

Of 107 pediatric subjects, most were female (58%) and in the age group 14 to 16 years (mean 14.2 years). All subjects had a history of psoriasis with a mean duration of 4.1 years from diagnosis. At Baseline, the majority (81.3%) of subjects had psoriasis of the body of moderate intensity; the remainder of the subjects had psoriasis of severe intensity (5.6%) or mild intensity (13.1%). The mean Psoriasis Area Severity Index (PASI) score at baseline was 10.7 for the safety population. More than 70% of subjects rated their psoriasis as moderate on the Patient's global assessment. Among the 31 subjects participating in the HPA axis assessment, 84% rated their psoriasis as moderate.

Table 11: Demographic and Baseline Characteristics

Characteristics / Statistics	Subjects N (%) Total Population N=107	HPA Axis/PK Subgroup (Max Use) N=31
Sex [n (%)]		

Characteristics / Statistics	Subjects N (%) Total Population N=107	HPA Axis/PK Subgroup (Max Use) N=31
F	62 (57.9%)	17 (54.8%)
M	45 (42.1%)	14 (45.2%)
Age [n (%)]		
≥12 years and ≤13	33 (30.8%)	9 (29.0%)
≥14 years and ≤16	74 (69.2%)	22 (71.0%)
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	97 (90.7%)	29 (93.5%)
Black /African American	2(1.9%)	1 (3.2%)
Asian	6 (5.6%)	1 (3.2%)
Other	2 (1.9%)	0 (0.0%)
Hispanic/Latino	7 (6.5%)	4 (12.9%)
Not Hispanic/Latino	100 (93.5%)	27 (87.1%)
Extent of BSA (body)		
Mean (SD)	13.3 (10.3)	18.0 (4.7)
Median	11.0	18.0
Minimum/Maximum	3/68	10/26
Extent of BSA (Scalp)		
Mean (SD)	55.1 (29.5)	62.4 (26.4)
Median	50.0	75.0
Minimum/Maximum	10/100	20/100
Total BSA		
Mean (SD)	14.9 (8.3)	18.4 (5.4)
Median	13.0	18.0
Minimum/Maximum	4/68	10/29
Baseline PASI		
Mean (SD)	10.7 (4.41)	11.0 (3.43)
Median	10.2	11.5
Minimum/Maximum	2.6/ 27.5	6.0/20.1
Height (cm)		
Mean (SD)	164.1 (11.37)	161.2 (11.7)
Median	164.0	160.0
Minimum/Maximum	132.0/ 192.0	135.0/192.0
Weight (kg)		
Mean (SD)	60.1 (16.1)	56.4 (15.8)
Median	57.0	52.0
Minimum/Maximum	32.0/ 118.0	32.0/96.0
Duration of psoriasis (years)		
Mean (SD)	4.1 (3.2)	3.6 (2.8)
Median	3.0	3.0
Minimum/Maximum	1/15	1/12
Skin classification		

Characteristics / Statistics	Subjects N (%) Total Population N=107	HPA Axis/PK Subgroup (Max Use) N=31
Type I	2 (1.9%)	0 (0.0%)
Type II	47 (43.9%)	12 (38.7%)
Type III	34 (31.8%)	13 (41.9%)
Type IV	20 (18.7%)	5 (16.1%)
Type V	2 (1.9%)	0 (0.0%)
Type VI	2 (1.9%)	1 (3.2%)
Screening Body ISGA* Score		
Mild (2)	14 (13.1%)	0 (0.0%)
Moderate (3)	87 (81.3%)	29 (93.5%)
Severe (4)	6 (5.6%)	2 (6.5%)

Abbreviations: HPA = hypothalamic-pituitary-adrenal axis, PK = pharmacokinetics, SD = standard deviation, BSA = body surface area, ISGA = Investigator Global Assessment Scale, SD = standard deviation
Source: Adapted from Final Study Report LP0076-1017, Tables 1-4 to 1-9

The majority of subjects were White (91%) and enrolled from 6 foreign countries (95/107, 89%). The tabulation below presents the distribution of subjects by country.

Table 12: Distribution of Subjects by Country of Enrollment

Country	Number of subjects
United States	12
Canada	6
France	5
United Kingdom	8
Poland	14
Romania	42
Germany	20

Source: NDA 22185, SD 329 dated 2/13/2019

The Applicant indicates that the submitted foreign data is applicable to the United States population because the prevalence of psoriasis is highest among Caucasians of European origin (3.6%).[13] In addition, to support the extrapolation of findings derived from a White study population to other populations in the United States, the Applicant conducted a vehicle-controlled trial (MBL 0502 US) which investigated the efficacy and safety of Taclonex Topical Suspension on the scalp and Taclonex Ointment on the body in African American and Hispanic subjects in US with psoriasis, who were not well represented in the Phase 3 trials in adults. Safety and efficacy in these non-White populations were similar to the findings from the Phase 3 trials. See Reviews by Dr. Brenda Carr dated 9/14/2005 and 4/23/2008.

[13] Rachakonda TD et al. Psoriasis prevalence among adults in the United States. JAAD. 2014 Mar; 70(3) 512-6. https://www.ncbi.nlm.nih.gov/pubmed/24388724#

Concomitant Medications at Baseline

The Applicant coded concomitant medications according to WHODRUG. At Baseline, a total of 25 (23.4%) subjects in the safety population and 7 (22.6%) subjects in the HPA/PK subgroup reported the use of concomitant medications. The most common classes of medications were "dermatologicals" including corticosteroids and emollients and "respiratory system" products including antihistamines.

Disposition

Investigators screened a total of 125 subjects which included 17 screening failures and one subject who was lost to follow-up after the screening visit. Of 107 subjects who received treatment at Visit 1 (Week 0), 3 withdrew prior to Visit 2 (Week 2) [1 lost to follow-up and 2 voluntarily withdrew] and 14 withdrew after Visit 3 (Week 4) [1 AE; 1 voluntarily withdrew; and 12 who were clear and withdrew per protocol.] A total of 90 subjects completed Visit 4 (Week 6) and Visit 5 (Week 8).

Table 13: Reasons for Discontinuation During the Treatment Phase

Disposition		Safety Analysis Set N=107	HPA Axis / PK Subset N=31
Disposition [N (%)]	Completed	102 (95.3%)	29 (93.5%)
	Adverse event*	1 (0.9%)	1 (3.2%)
	Lost to follow-up	1 (5%)	0 (0.0%)
	Non-compliance	0 (0%)	0 (0%)
	Withdrawal by subject	3 (0%)	1 (3.2%)
	Other	0 (0%)	0 (0%)
	Total withdrawn	5 (4.7%)	2 (6.5%)

Abbreviations: HPA = hypothalamic-pituitary-adrenal axis, PK = pharmacokinetics
Source: Adapted from Table 1-3, Clinical Study Report *Serum cortisol level at 30 min. below 18 mcg/l on Day 40

Protocol Deviations

Per Applicant, the protocol deviations did not impact the validity of the data or overall conclusions. The most common protocol deviations related to the trial procedures. The primary categories of protocol deviations are listed below:

- Informed Consent: not signed by a medically qualified individual (4 subjects), not signed by both parents (1 subject)
- Administration of Trial Medication: subject not applying the product per protocol/ missed applications, subjects dispensed the wrong number of bottles, bottles not returned, or applications not documented (2 subjects)

- Procedures:
  - Laboratory assessments: Incorrect timing or amount of urine collection, laboratory assessments not performed, 7 subjects consumed more than the allowed calcium
  - Visits: missing visit dates, delayed visits due to delayed lab results,
  - HPA Axis Evaluation: 6 subjects included in the analysis did not have normal HPA axis function at screening (5 subjects completed the trial with evaluable data). See Clinical Pharmacology Review for a discussion of the potential impact.
  - Concomitant medications: 7 subjects used other corticosteroids; concomitant medications initiated

Adequacy of the Safety Database
The size of the safety database was sufficient for the evaluation of Taclonex Topical Suspension applied once daily for up to 8 weeks in the pediatric population. The demographics of the study population are adequately representative of the target population. Therefore, the safety database presented by the Applicant is sufficient to characterize the pharmacokinetics, pharmacodynamics and safety profile of Taclonex Topical Suspension for the treatment of plaque psoriasis in the pediatric population age 12 to 17 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 Taclonex Topical Suspension applied once daily for up to 8 weeks. The review team discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events
Per ICH E6 (R1), the Applicant defined an adverse event (AE) as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, 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". 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 will refer 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).

Routine Clinical Tests
Subjects provided blood and urine samples for routine clinical laboratory testing at screening, Week 4 and Week 8. Laboratory tests included hematology (complete blood count and differential count), biochemistry (including calcium, phosphate, albumin, and parathyroid hormone), urine pregnancy testing, urinalysis (from spot urine sample for glucose and ketones) and 24- hour urine collection (calcium, phosphate, creatinine and volume).

7.3.4. Safety Results

Deaths, Serious Adverse Events (SAEs), and Discontinuations Due to Adverse Events (AEs)
There were no deaths in Trial LP0076-1017. One subject experienced a serious adverse event (suicide attempt) and one subject withdrew from the trial due to an adverse event (mild blood cortisol decreased which was assessed as possibly related.) Brief narratives are as follows:

- A 13-year-old White, Hispanic female subject (b) (6) with mild psoriasis (IGA on body 3, BSA of 4-10%) and a history of anxiety and depression attempted suicide by overdosing on a combination of ibuprofen, acetaminophen, diphenhydramine hydrochloride, and tinidazole/ norfloxacin after receiving Taclonex for 8 weeks. Concomitant medications were folic acid, Montelukast sodium, and salbutamol. Approximately 70 days after first dose of the study product, the subject returned to the study site for re-evaluation of an elevated parathyroid hormone level (Day 56 assessment). When the subject revealed that she had taken an overdosed of “painkillers” on the previous day, she was sent to the emergency department for evaluation and later hospitalized in a psychiatric facility for 3 days. The AE was assessed as severe, not related and resolved with sequelae (need for ongoing therapy for depression).
- A 13-year-old, White, non-Hispanic, male subject (b) (6) with moderate psoriasis on scalp and body (IGA 3 on body, total BSA of 28%) and normal results from the physical examination, had a low value for plasma cortisol (<18 mcg/dL) at 30 min (mild, non-serious) following ACTH-challenge at Visit 3/Day 28 (17.4 mcg/dL at 30.) Plasma cortisol returned to normal on repeat assessment (Day 56). There was no relevant medical history or concomitant medications. The event was assessed as possibly related.

Adverse Events
A total of 38 (35.5%) subjects in Trial LP0076-1017 experienced 62 adverse events (AEs). All AEs were mild or moderate except 1 (suicide attempt) which was severe (see narrative above). A

total of 3 AEs occurred in a lesional or perilesional location (folliculitis, arthropod sting and pruritus.) The most common adverse events occurred within the infections and infestations system organ class (SOC)(12.1% of subjects). Most adverse events (AEs) 61/62 (98%) were non-serious and reported by a single subject. Tabulated below are the AEs reported by SOC and preferred term (PT) [if the PT was reported by more than 1 subject]. The most common adverse events were nasopharyngitis and headache which were reported by 6 subjects each (5.6%). In the Skin and subcutaneous tissue disorders SOC, one subject each reported acne, erythema, pruritus and sunburn.

Table 14: Treatment-Emergent Adverse Events by Organ System Class (Preferred Terms Included if Reported by More Than 1 Subject) in Trial LP0076-1017

System Organ Class Preferred Term	No. Subjects N=107	No. TEAEs
Overall	38 (35.5%)	62
Infections and infestations	13 (12.1%)	14
Nasopharyngitis	6 (5.6%)	6
Rhinitis	2 (1.9%)	2
Investigations	7 (6.5%)	8
Blood parathyroid hormone	4 (3.7%)	5
Blood cortisol	2 (1.9%)	2
Nervous System Disorders	7 (6.5%)	11
Headache	6 (5.6%)	8
Respiratory, thoracic & mediastinal disorders	7 (6.5%)	7
Cough	2 (1.9%)	2
Oropharyngeal pain	2 (1.9%)	2
Skin and subcutaneous tissue disorders	4 (3.7%)	4
Gastrointestinal disorders	3 (2.8%)	3
Musculoskeletal & conn tissue disorders	3 (2.8%)	4
Reproductive system and breast disorders	3 (2.8%)	3
Dysmenorrhea	3 (2.8%)	3
Injury, poisoning & procedural complications	2 (1.9%)	2
Psychiatric disorders	2 (1.9%)	2

TEAEs = treatment-emergent adverse events
Source: Adapted from Panel 2; Module 2.7.4 Summary of Clinical Safety page 12

Adverse Reactions (AR)

Investigators assessed 8 AEs (13%) which occurred in 7 subjects as possibly or probably related to the study product. Among those treatment emergent adverse reactions (TEAR), 3 were of moderate intensity (blood parathyroid hormone increased, erythema, and folliculitis); the remaining treatment emergent ARs were mild in intensity. The 2 AEs of blood cortisol decreased were laboratory findings from HPA axis assessments of subjects in the maximal use cohort. The adverse reactions are tabulated below.

Table 15: Drug-Related Treatment Emergent Adverse Events (Adverse Reactions)

System Organ Class Preferred Term	Subjects N=107	Events
Overall	7 (6.5%)	8
Investigations	3 (2.8%)	3
Blood cortisol	2 (1.9%)	2
Blood parathyroid hormone	1 (0.9%)	1
Skin and subcutaneous tissue disorders	2 (1.9%)	2
Acne	1 (0.9%)	1
Erythema	1 (0.9%)	1
Endocrine disorders	1 (0.9%)	1
Hyperparathyroidism	1 (0.9%)	1
Infections and infestations	1 (0.9%)	1
Folliculitis	1 (0.9%)	1
Nervous system disorders	1 (0.9%)	1
Headache	1 (0.9%)	1

Source: Adapted from Module 2.5 Clinical Overview, Panel 3 page 23

There is low biologic plausibility that hyperparathyroidism and increased blood parathyroid hormone (PTH) are related to the proposed product because elevations in serum calcium concentrations result in decreased PTH not increased PTH. In addition, headache is a common finding among all clinical trial subjects. For a topical product, headache is more likely to represent an AE rather than AR. Therefore, the events of hyperparathyroidism/ PTH increased will not be conveyed as ARs in labeling. In addition, the findings of adrenal suppression (depressed blood cortisol) which were observed with maximal doses of the study product will be conveyed in Sections 8 and 12 of labeling rather than Section 5.

Laboratory Findings

Examination of shift tables for laboratory values demonstrated no clinically meaningful changes from Baseline. No subjects developed elevated albumin-corrected calcium levels or elevated 24-hour urinary calcium excretion. A total of 2 subjects (2/83) who had normal urinary calcium: creatinine ratios at Baseline developed elevated ratios at Week 4 but findings in both subjects normalized by Week 8.

See Analysis of Submission-Specific Safety Issues for the discussion of the laboratory findings.

Vital Signs

Investigators evaluated systolic and diastolic blood pressure (BP: mmHg) and heart rate (HR: beats per minute) at Baseline and at Weeks 4 and 8. The mean systolic blood pressure declined less than 2 mmHg from Baseline to Week 4 and 8 while the mean diastolic blood pressure declined 1 mmHg or less from Baseline to Week 4 and 8. In addition, the mean heart rate increased by less than 2 bpm during the course of the trial. Vital sign data indicated no clinically meaningful changes from Baseline; there were no adverse events related to vital sign abnormalities.

Electrocardiograms (ECGs) and QT
The Applicant did not conduct ECG monitoring during Trial LP0076-1017. The pro-arrhythmic potential of the components of this fixed combination product, calcipotriene and betamethasone, were 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 Taclonex Topical Suspension investigators performed cardiovascular monitoring in Maximal Use Trial (MUsT) MBL 0404 FR. 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

Taclonex Topical Suspension is a fixed combination product containing calcipotriene hydrate and betamethasone dipropionate. Class specific safety issues are addressed in labeling for all formulations and dosage forms of topical corticosteroid products and vitamin D analogs.

Calcipotriene is a synthetic analog of vitamin D. Vitamin D is a fat-soluble vitamin which promotes calcium absorption in the gut and enables bone growth and remodeling.[14] Treatment with topical calcipotriene products may be associated with the development of hypercalcemia and cutaneous reactions including contact dermatitis.

Betamethasone dipropionate is a potent corticosteroid[15] with the potential to cause reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, hyperglycemia and local reactions. Per labeling, these local reactions may include allergic contact dermatitis, atrophy, striae, telangiectasias, itching, dryness, hypopigmentation, perioral dermatitis, secondary infection, and miliaria.

Local Tolerability
The Applicant evaluated local reactions as lesional/perilesional AEs occurring less than or equal to 2 cm from the border of the treatment areas. There were 3 adverse events captured as lesional/perilesional events (folliculitis, arthropod sting, and pruritus) which were reported by 3 subjects (2.8%.) There were no reports of allergic contact dermatitis, atrophy, striae, telangiectasias, itching, dryness, hypopigmentation or perioral dermatitis.

[14] Holick MF. Vitamin D Deficiency. N Engl J Med 2007; 357:266-281.
[15] According to the World Health Organization Classification of Topical Corticosteroids

Systemic Safety

Pharmacokinetics

At pre-dose on Day 14 and post-dose on Day 28 (pre-trough), subjects provided samples for the evaluation of plasma levels of calcipotriene and betamethasone and their respective major metabolites MC1080 and betamethasone 17-propionate (B17P). Most samples were below lower limit of quantification (LLOQ). See Section 6.1 of this review.

HPA Axis Suppression

Investigators conducted ACTH challenge tests using 2 commercial cosyntropin products, CORTROSYN® and Synacthen®, in United States and European sites, respectively. There were 5 of 31 subjects (16.1%) who demonstrated adrenal suppression (serum cortisol $\leq$ 18 mcg/dL) in response to ACTH challenge at 30 minutes. One case was classified as an adverse event because the subject withdrew from the trial at Week 4. Two subjects had minimal decreases (17.4 and 17.8 mcg/dL) in serum cortisol. None of the subjects had a decrease in cortisol response at 60 minutes. See Section 6 Clinical Pharmacology of this review and the Clinical Pharmacology Review by Jihye Ahn, PharmD dated June 17, 2019 for a detailed analysis of these systemic safety assessments.

Effects on Calcium Metabolism

Subjects performed assessments of the effects of Taclonex Topical Suspension on calcium metabolism at screening (SV2) and Day 28 and Day 56. The evaluation included measurements of serum calcium, albumin, phosphate, plasma parathyroid hormone (PTH) level and calculation of the albumin corrected serum calcium concentration. In addition, subjects provided a 24-hour urine sample for urinary volume, calcium-, phosphate-, and creatinine excretion for the calculation of calcium: creatinine and phosphate: creatinine ratios.

The mean changes from baseline for albumin- corrected calcium levels[16] and 24-hour urine calcium excretion at Week 4, and at Week 8 were small. Review of shift tables for albumin-corrected calcium levels and 24-hour urine calcium excretion showed no shifts from normal or low to high through the end of treatment. However, 2 subjects who had high urinary calcium: creatinine ratios at baseline had normal values at Week 4 and 2 subjects with normal values at baseline had elevated values at Week 4. By the end of treatment only 1 subject remained in the high category.

The results from Trial LP0076-1017 in the pediatric population do not indicate a safety signal for HPA Axis suppression or effects on calcium metabolism from topical application of Taclonex

[16] There were 4 cases in which the 24 hour-urine calcium rates were not calculable because urine calcium levels were greater than upper limit of quantification (7.5 mmol/L). Three of these subjects had normal 24 hour-urine calcium rates at screening. For these subjects, the corrected serum calcium was within normal limits and there were no other signs of hypercalcemia. Because other factors may impact the measurement of 24 hour-urine calcium rates including calcium in the diet (excess calcium consumption accounted for at least 7 protocol deviations), it is not possible to draw definitive conclusions regarding the findings in these 3 subjects.

Topical Suspension when compared with results from comparable exposures in the adult population (See Section 12 of current labeling).

7.3.6. Safety Analyses by Demographic Subgroups

In view of the small sample size, the utility of analyzing TEAE by demographic subgroup is limited. However, trends in incidence rates may be observed with sex and age group.

Treatment Emergent Adverse Events by Sex

Overall, a greater proportion of female subjects reported TEAEs (40.3%) than male subjects (28.9%). Female subjects experienced more headaches (8.1% compared with 2.2%) than male subjects and male subjects experienced more nasopharyngitis (8.9% versus 3.2%) than female subjects. See the tabulation below.

Table 16: Treatment Emergent Adverse Events by Sex

Treatment Emergent Adverse Events				
System Organ Class Preferred Term	**Males N=45**		**Females N=62**	
	Subjects	Events	Subjects	Events
Overall	13 (28.9%)	19	25 (40.3%)	43
Infections and infestations	6 (13.3%)	6	7 (11.3%)	8
Nasopharyngitis	4 (8.9%)	4	2 (3.2%)	2
Rhinitis	0 (0.0%)	0	2 (3.2%)	2
Investigations	2 (4.4%)	2	5 (8.1%)	6
Blood parathyroid hormone ↑	1 (2.2%)	1	3 (4.8%)	4
Blood cortisol ↓	1 (2.2%)	1	1 (1.6%)	1
Nervous System Disorders	2 (4.4%)	2	5 (8.1%)	9
Headache	1 (2.2%)	1	5 (8.1%)	7
Respiratory, thoracic & mediastinal disorders	2 (4.4%)	2	5 (8.1%)	5
Cough	0 (0.0%)	0	2 (3.2%)	2
Oropharyngeal pain	0 (0.0%)	0	2 (3.2%)	2
Skin and subcutaneous tissue disorders	2 (4.4%)	2	2 (3.2%)	2
Gastrointestinal disorders	2 (4.4%)	2	1 (1.6%)	1
Musculoskeletal & conn tissue disorders	1 (2.2%)	1	2 (3.2%)	3
Reproductive system and breast disorders	0 (0.0%)	0	3 (4.8%)	3
Dysmenorrhea	0 (0.0%)	0	3 (4.8%)	3
Injury, poisoning & procedural complications	1 (2.2%)	1	1 (1.6%)	1
Psychiatric disorders	0 (0.0%)	0	2 (3.2%)	2

Source: Adapted from Table 3-43; Clinical Study Report LP0076-1017

Treatment Emergent Adverse Events by Age Group

The proportion of subjects in the youngest age group (2-14 years) who reported TEAEs (38.3%) was greater than the proportion of subjects in the older age group (15-17 years) who reported TEAEs (31.9%). See the tabulation below.

Table 17: Treatment Emergent Adverse Events by Age Group

Treatment Emergent Adverse Events				
System Organ Class **Preferred Term**	**12-14 years N=60**		**15-17 years N=47**	
	Subjects	**Events**	**Subjects**	**Events**
Overall	23 (38.3)	37	15 (31.9%)	25
Infections and infestations	8 (13.3%)	8	5 (10.6%)	6
Nasopharyngitis	6 (10.0%)	6	0 (0.0%)	0
Rhinitis	1 (1.7%)	1	1 (2.1%)	1
Investigations	5 (8.3)	5	2 (4.3%)	3
Blood parathyroid hormone ↑	3 (5.0%)	3	1 (2.1%)	2
Blood cortisol ↓	1 (1.7%)	1	1 (2.1%)	1
Nervous System Disorders	3 (5.0%)	4	4 (8.5%)	7
Headache	3 (5.0%)	4	3 (6.4%)	4
Respiratory, thoracic & mediastinal disorders	5 (8.3)	5	2 (4.3%)	2
Cough	1 (1.7%)	1	1 (2.1%)	1
Oropharyngeal pain	1 (1.7%)	1	1 (2.1%)	1
Skin and subcutaneous tissue disorders	3 (5.0%)	3	1 (2.1%)	1
Gastrointestinal disorders	2 (3.3%)	2	1 (2.1%)	1
Musculoskeletal & conn tissue disorders	3 (5.0%)	4	0 (0.0%)	0
Reproductive system and breast disorders	2 (3.3%)	2	1 (2.1%)	1
Dysmenorrhea	2 (3.3%)	2	1 (2.1%)	1
Injury, poisoning & procedural complications	2 (3.3%)	2	0 (0.0%)	0
Psychiatric disorders	1 (1.7%)	1	1 (2.1%)	1

Source: Adapted from Table 3-42; Clinical Study Report LP0076-1017

Adverse Events by Race

A total of 31/97 (32.0%) White subjects reported 50 TEAEs and 7 /10 (70.0%) non-White subjects (African American, Asian and other) reported 12 TEAEs. In view of the small number of non-White subjects, the analysis of TEAE by race has limited utility and will not be presented.

Adverse Events by Exposure to the Study Product

A total of 51 subjects applied less than 40 grams of the study product per week; 24 subjects applied 40 grams or more per week. Among subjects applying less than 40 grams of the study product, 18 subjects (35.3%) experienced 32 TEAEs; among subjects applying 40 grams or more per week 9 subjects (37.5%) experienced 13 TEAEs.

7.3.7. Supportive Safety Data From Other Clinical Trials

120-Day Safety Update

During the reporting period (July 2018 to September 2019) for the 120-day safety update report (SUR), the Applicant indicated that there were no ongoing clinical trials and no new safety information to inform labeling. (SD 336 dated March 7, 2019)

7.3.8. Safety in the Postmarket Setting

Expectations on Safety in the Postmarket Setting
Analysis of safety data from Trial LP0076-1017 identified no additional safety signals in the population age 12 to less than 17 years with exposure to the Taclonex Topical Suspension.

7.4. Summary and Conclusions

Statistical Issues
This trial was not designed to establish efficacy. There were no statistical issues affecting the overall conclusions.

Conclusions and Recommendations
In this supplement, the Applicant submitted results from Trial LP0076-1017 to provide safety and bioavailability data for Taclonex Topical Suspension for the treatment of pediatric subjects age 12 years to less than 17 years with plaque psoriasis of the scalp and body. This open label trial enrolled a total of 107 subjects with plaque psoriasis on the scalp and body 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 3% total BSA affected. All subjects applied Taclonex Topical Suspension once daily for up to 8 weeks and provided an assessment of calcium metabolism. In a subset of 31 subjects with psoriasis of at least moderate severity and 10-35% body surface area (BSA) affected, the Applicant evaluated the pharmacokinetics and the potential for HPA axis suppression under maximal use conditions.

The data indicated no new safety signals. There were no deaths; one subject experienced a serious adverse event (suicide attempt) and one subject withdrew from the trial due to an adverse event (mild blood cortisol decreased which was assessed as possibly related.) Overall, a total of 38 (35.5%) subjects experienced 62 adverse events (AEs). The most common adverse events were nasopharyngitis and headache which were reported by 6 subjects each (5.6%). Investigators identified 8 adverse reactions (13%) which occurred in 7 subjects and included both local and systemic effects. Local safety findings included erythema and folliculitis, while systemic findings included decreased blood cortisol in 2 subjects in the maximal use cohort who participated in HPA axis testing.

All analyzable samples for calcipotriol and its metabolite were below the level of quantification; there were no clinically meaningful changes from Baseline in measures of calcium metabolism, the primary safety issue. Among the subjects participating in HPA axis assessments, 5 (16%) of 31 subjects experienced adrenal suppression. These pharmacodynamic findings in the pediatric population are similar to the labeled findings in adult population.

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 less than 17 years was extrapolated from data in the adult population.

The submitted PK, PD and safety data in the pediatric population support approval of this sNDA which provides for the use of Taclonex Topical Suspension in the population 12 years and older with plaque psoriasis of the scalp and body.

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

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 Applicant conducted Trial LP0076-1017 to address the required assessment under PREA and support the use of Taclonex Topical Suspension in the target pediatric population with mild to moderate plaque psoriasis. The Pediatric Review Committee (PeRC) agreed with the Division that PREA PMR 1935-1 was fulfilled and the data was sufficient to support amended labeling (PeRC Meeting 6/ 5/2019, Meeting Minutes dated 6/20/2019).

Amy M. Taylor, MD, MHS, the Division of Pediatric and Maternal Health (DPMH), Pediatric Team, agreed with expanding the age group for which Taclonex Topical Suspension 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 Taclonex Topical Suspension have been established in pediatric patients 12 to 17 years. Dr. Taylor recommended that 8.4 Pediatric Use section of labeling convey a limited amount of information with reference to other sections of labeling for the data. To optimize access to the necessary prescribing information, the clinical team recommended all the key findings be included in the Pediatric Use section. Refer to the Review by Dr. Amy Taylor dated June 17, 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) and Instructions for Use (IFU) for Taclonex Topical Suspension. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed PI, PPI, IFU and carton labeling for Taclonex Topical Suspension and did not identify areas of vulnerability that may lead to medication errors (Review dated 7/18/2019). However, Dr. Patel recommended that the team consider inserting the product strength "0.005%/0.064%" to the HOW SUPPLIED SECTION of the PI.

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 18: Reviewers Providing Labeling Comments and Location in the Document

Section of Labeling	Reviewers Providing Comments & Location in This Review
1 Indications and usage	Clinical Team, Amy Taylor: (b) (4)
5.2 Effects on Endocrine System	Clinical Team, Amy Taylor:
6 Adverse reactions	Clinical Team: (b) (4)
8 Use in specific populations	Amy Taylor, Jane Liedtka: (b) (4)
11 Description	Joel Hathaway: (b) (4)
12 Clinical pharmacology	Jihye Ahn, Chinmay Shukla: (b) (4)
13 Nonclinical toxicology	Norman See, Barbara Hill: (b) (4)
17 Patient Counseling Information	Review team: Jane Liedtka, Eric Brodsky, Clinical Team: (b) (4)

Source: Reviewer's Table

Revisions to the PI were extensive. Associate Directors for Labeling (ADLs), Debra Beitzell, MD, Eric Brodsky, MD, and Nancy Xu, MD provided comments regarding current labeling policy throughout the PI. The team incorporated those recommendations which contributed to greater accessibility to information and clarity of findings to the healthcare provider. The review team inserted headings and revised Section 17 Patient Counseling Information to reflect the revisions to other sections of the PI.

(b) (4)

(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

The other marketed dosage form of calcipotriene and betamethasone dipropionate, Taclonex Ointment, is in PLLR format (revised December 2018). Therefore, the Applicant submitted changes to labeling which were consistent with the labeling of the other dosage form. Jane Liedtka M.D., from the Maternal Health Division of Pediatric and Maternal Health (DPMH), provided recommendations for labeling (Review by Dr. Jane Liedtka dated June 17, 2019). Revisions to Taclonex Topical Suspension in Section 8.1 and 8.2 were intended to reflect current best practices.

Limited data is available with the use of Taclonex Topical Suspension 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 (b) (4)
The revised 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 the PPI and IFU. The Patient Labeling Team concluded that the IFU was acceptable as submitted and provided comments on the PPI. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Ruth Mayrosh, PharmD, (dated 6/20/2019.)

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 Taclonex Topical Suspension. 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 19: Covered Clinical Study LP0076-1017

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 30		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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: Data from Form FDA 3454 and Attachment A

Table 20: Study Sites and Enrollment

Site Number	Principal Investigator	Site Location	Subjects (N) Treated	Subjects (N) completed
DEU01	Dr. Dagmar Wilsmann-Theis	Sigmund-Freud-Strass, Germany	6	6
DEU02	Dr. Ulrike Blume-Peytavi	Berlin, Germany	7	7
DEU03	Dr. A Pinter	Frankfurt am Main, Germany	7	7
FRA01	Dr. Jean-Philippe Lacour	Nice, France	4	4
FRA02	Dr. Mireille Ruer Mulard	Martigues, Bouchesdu- Rhône, France	1	1
FRA03	Dr. Patrice Plantin	Quimper, Finistère, France.	0	0
GB04/GBR18	Dr. Anthony Bewley	Leytonstone, London, UK	2	2
GB08/GBR19	Dr. James Halpern	Walsall, West Midlands, UK	2	1
GB09/GBR08	Dr. Evmorfia Ladoyanni	Dudley, West Midlands, UK	2	1
GB11/GBR21	Dr. Aruni Ranasinghe	Bury St Edmunds, Suffolk, UK	2	2
CAN01	Dr. Jill Keddy-Grant	Winnipeg, Manitoba, Canada	1	1
CAN03	Dr. C Lynde	Markham, Ontario, Canada	2	2
CAN04	Dr. Kamal Ohson	Newfoundland /Labrador, Canada	0	0
CAN06	Dr. Marcoux	Montreal, Quebec, Canada	3	3
US01	Dr. Christopher G. Nelson	Tampa, Florida, USA	2	2
US02	Dr. Elizabeth Tichy	San Antonio, Texas, USA	5	5
US03	Dr. Joel Schlessinger	Omaha, Nebraska, USA	1	1
US04	Dr. Jeffrey M. Weinberg	Forest Hills, New York, USA	1	1
US05	Dr. Lawrence Eichenfield	La Jolla, CA USA	3	3
POL01	Dr. Jolanta Weglowska	Wroclaw, Poland	1	1
POL02	Dr. Adam Borzecki	Lublin, Poland.	1	1
POL03	Dr. Dagmara Maranska	Karczew, Poland.	6	6
POL04	Dr. Joanna Piskorz-Wapinska	Ostroda, Poland.	2	2
POL05	Dr. Joanna Kolinek	Warszawa, Poland.	4	4
ROU01	Dr. Sorin Tiplica	Bucharest, Romania.	1	1
ROU03	Dr. Anca Jian	Brascov, Romania	2	2
ROU4	Dr. Caius Solovan	Timisoara, Romania.	5	5
ROU5	Dr. Silviu Morariu	Targu-Mures, Romania	9	7
ROU06	Dr. Remus Orasan	Cluj-Napoca, Romania	4	4
ROU07	Dr. Dorin Mihalache	Iasi, Romania	21	20

Melinda McCord, M.D.
Medical Officer/Dermatology

12. Appendices

12.1. Efficacy Assessment Scales

Table 21: Investigator's Global Assessment of Disease Severity for the Body and Scalp

(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 coloration
(3) Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
(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 coloration; extreme red coloration; or deep red coloration

Source: Clinical trial report Panel 7

Table 22: Patient's Global Assessment of Disease Severity for the Body and Scalp

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 Panel 10

12.2. Labeling Comments

Labeling Comments Section 8.2
Associate Director of Labeling (ADL) Nancy Xu, MD commented:

(b) (4)

Examples include:

- Breo Ellipta (fluticasone furoate and vilanterol inhalation powder) labeling revised 12.2017
- Xhance (fluticasone propionate) nasal spray labeling revised 09.2017
- Armonair Respiclick (fluticasone propionate) labeling revised 03.2018

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/s/

MELINDA L MCCORD
07/24/2019 04:34:23 PM

GORDANA DIGLISIC
07/25/2019 12:00:35 AM