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	October 28, 2019
Established Name	Calcipotriene
(Proposed) Trade Name	SORILUX™ (calcipotriene) Foam, 0.005%
Pharmacologic Class	Vitamin D analog
Code name	None
Applicant	Mayne Pharma LLC
Formulation(s)	Foam
Dosing Regimen	Twice daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of plaque psoriasis of the scalp and body in patients 4 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 4 years and older.

Consultant Reviews

Labeling Reviews

- Division of Medication Error Prevention and Analysis (DMEPA) Madhuri R. Patel, PharmD (Review dated 7/16/2019)
- Office of Prescription Drug Promotion (OPDP) Laurie Buonaccorsi, PharmD; Review of Prescribing Information (PI), patient package insert (PPI), and Instructions for Use (IFU) (Review dated 9/26/2019)
- Division of Medical Policy Programs (DMPP): Shawna Hutchins, MPH, BSN, RN; Review PPI and IFU (Review dated 9/25/2019)

Other Consultations

- Division of Pediatric and Maternal Health (DPMH), Pediatric División Consult Response: Erica Radden, M.D. (Review dated 10/8/2019)
- Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance I:
  - Jessica Weintraub, PharmD, BCPS, (Reviews dated 8/7/2019 and 9/12/2019).
  - Melissa Reyes, M.D. (Review dated 9/5/2019).

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Glossary

AE	adverse event
API	active pharmaceutical ingredients
BSA	body surface area
CMC	chemistry, manufacturing, and controls
DER	deferral extension request
EA	environmental assessment
eCTD	electronic common technical document
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IFU	instructions for use
iPTH	intact parathyroid hormone
ISGA	Investigator's Static Global Assessment
IND	investigational new drug
LLQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PeRC	Pediatric Review Committee
PI	prescribing information
PK	pharmacokinetics
PMR	postmarketing requirement
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT interval
SAE	serious adverse event
SDTM	Study Data Tabulation Model
sNDA	supplemental new drug application
SOC	system organ class
TE	treatment effect
TEAE	treatment-emergent adverse event
TEAR	treatment-emergent adverse reaction
VAS	visual analog scale

1. Executive Summary

SORILUX™ (calcipotriene) Foam, 0.005% is a topical product for the treatment of plaque psoriasis of the scalp and body in patients 12 years and older. The active ingredient is calcipotriene, a synthetic vitamin D3 analog. The Applicant, Mayne Pharma LLC, submitted a supplemental new drug application (sNDA) to support revisions to product labeling which provided for the use of SORILUX (calcipotriene) Foam, 0.005% in the population age 4 years and older. The Applicant conducted Trial STF115469 to address postmarketing requirement (PMR) 1944-3 under the Pediatric Research Equity Act (PREA) to evaluate the effects of SORILUX Foam, 0.005%, on calcium metabolism and safety in the pediatric population ages 2 to 11 years. In addition, the Applicant submitted draft labeling in response to a request (Prior Approval Supplement Request Letter dated 05/06/2019) to develop a Postmarketing Experience section 6.2 of labeling (S-008, SDN 363 dated 6/26/2019).

Trial STF115469 was an open-label, pharmacokinetic and safety trial enrolling 36 subjects ages 4 to 11 years with mild to moderate plaque psoriasis of the scalp and body. The Applicant intended to submit data from 75 evaluable subjects. However, recruitment challenges prevented the timely completion of the trial and the Food and Drug Administration (FDA) requested that the Applicant submit the available data for review. All analyzed pharmacokinetic (PK) samples were below the limit of quantitation; there were no clinically meaningful trends in the laboratory parameters related to calcium metabolism. The review team identified no new safety issues associated with the use of SORILUX Foam, 0.005% in this pediatric population. The trial was not designed to evaluate efficacy which was extrapolated from the adult population.

The Applicant did not achieve the target sample size and age range specified in PMR 1944-3. There is limited safety data in the pediatric population 4 to 6 years of age who received SORILUX Foam, 0.005%, 0.005%: adverse event data for four subjects, pharmacodynamic data for two subjects and PK data for zero subjects. Cases of hypercalcemia were observed in postmarketing data primarily in older adults with potential risk factors which increased exposure, who used the product for an unlabeled indication or extensive body surface area. However, the preponderance of evidence from more than 20 years of postmarketing data for the moiety suggested that the risk of hypercalcemia, the primary safety concern in patients using SORILUX Foam, 0.005%, 0.005%, is low. The Applicant provided sufficient data to confirm that the risk benefit conclusions in this pediatric population are similar to the adult population. This reviewer recommends an approval action for this application, NDA 22563 Supplement-007, to revise the current indication to the topical treatment of plaque psoriasis of the scalp and body in patients 4 years and older.

In addition, this reviewer recommends an approval action for Supplement-008 to revise the Postmarketing Experience section 6.2 of labeling.

As the labeling review is still in progress, these recommendations are contingent upon the successful completion of labeling negotiations with the Applicant.

1.1. Benefit-Risk Assessment

The Review Teams based the analysis of the benefits and risks of SORILUX Foam, 0.005%, 0.005% for the topical treatment of plaque psoriasis of the scalp and body in patients aged 18 years and older on data from 3 adequate, well-controlled Phase 3 clinical trials (Trials U0267-301, Trials U0267-302 and Trials U0267-303). See Clinical Reviews dated 09/17/2010 (Trials U0267-301 and U0267-302 evaluating plaque psoriasis on the body) and 09/03/2012 (Trial U0267-303 evaluating plaque psoriasis on the scalp.) The study populations included subjects 12 years of age and older; however, there was insufficient safety data (including bioavailability data) to support approval of SORILUX Foam, 0.005%, 0.005% for patients younger than 18 years of age.

In another supplement (S-006, approved 5/6/2019), the Applicant submitted results from Trial STF115750 which provided safety and bioavailability data for SORILUX Foam, 0.005%, 0.005% in the treatment of pediatric subjects age 12 to 16 years with plaque psoriasis of the scalp and body. The trial evaluated a total of 19 subjects with moderate plaque psoriasis defined as an Investigator's Static Global Assessment (IGSA) score of 3 on the scalp and body, at least 10% total body surface area (BSA) affected (excluding face and scalp) and at least 20% of the scalp affected. All subjects applied SORILUX Foam, 0.005%, 0.005% twice daily for 15 days. A total of six subjects experience eight adverse events (AEs). Five AEs [application site pain (two events), application site pruritus (two events) and pruritus (one event)] which occurred in three subjects were related to the study product. All analyzable pharmacokinetic samples were below the level of quantification, with the lower limit of quantification (LLQ) equal to 10 pg/mL. There were no clinically meaningful changes from Baseline in measures of calcium metabolism, the primary safety issue. The review identified no new safety signals. With the extrapolation of efficacy from the adult population, the safety and effectiveness of SORILUX Foam, 0.005%, 0.005% in the pediatric population age 12 to 16 years were established.

In this supplement (S-007), the Applicant submitted results from Trial STF115469 which provided safety and bioavailability data for SORILUX Foam, 0.005%, 0.005% in the treatment of pediatric subjects ages 4 to 11 years with plaque psoriasis of the scalp and body. The trial evaluated a total of 36 subjects with mild to moderate plaque psoriasis which was defined as an IGSA score of 2 or 3. Overall, 23 subjects (23/36, 64%) reported 29 AEs. A total of seven adverse reactions occurred in six subjects including application site pain, contact dermatitis and psoriasis.

All analyzed pharmacokinetic (PK) samples were below the limit of quantitation; there were no clinically meaningful changes in laboratory parameters related to calcium metabolism. The review team identified no new safety issues associated with the use of SORILUX Foam, 0.005%, 0.005% in this pediatric population.

The trial did not evaluate efficacy which was extrapolated from the adult population. However, the results demonstrate improvement of psoriasis severity on both the scalp and body according to the Investigator's Static Global Assessment (ISGA).

The Applicant stated, "Experience with other formulations has established topical calcipotriene as a safe and effective alternative to topical steroids in the treatment of plaque psoriasis, particularly for patients with mild to moderate disease… The results from Study STF115469 support the hypothesis that this positive benefit/risk ratio can be extended to patients 4 to 11 years of age, with no increase risks compared to the patient population 12 years and above" (SDN 354 dated 4/19/2019).

Despite the limitations of the data in this submission, the totality of the PK, pharmacodynamic (PD), and safety data in the pediatric population and postmarketing data related to the moiety indicate a favorable risk benefit conclusion and support approval of this sNDA which provides for the use of SORILUX Foam, 0.005%, 0.005% in the population age 4 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 (Mallbris et al. 2005). Chronic plaque psoriasis is the most common form of psoriasis in children and adults (Paller and Lund 2018). 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 (Shah 2013). The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, producing proinflammatory cytokines which trigger and perpetuate the inflammatory cascade.

The prevalence of psoriasis varies by geographic region. The estimated prevalence worldwide ranges from 0 to 1.37% of children and 0.51 to 11.3% of adults (Michalek et al. 2017). Studies of the United States population found prevalence rates of up to 4.6% (Paller and Lund 2018). Among the estimated 7.5 million Americans affected with psoriasis, 80% have mild to moderate disease, while 20% have moderate to severe disease affecting more than 5% of the body surface area.

The onset of psoriasis may occur at any age, but often occurs in childhood. In approximately 35% to 50% of individuals, psoriasis develops before the age of 20 years; in approximately 75%

of individuals, psoriasis develops before the age of 40 years (Paller and Lund 2018). 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 (Morris et al. 2001; Mercy et al. 2013). 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, and psychiatric and behavioral disorders (Elmets et al. 2019).

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) (Menter et al. 2019), inhibition of pro-inflammatory cytokines and chemokines (topical corticosteroids) and epidermal hyperproliferation and differentiation (vitamin D analogs) has been demonstrated in both children and adults. The response to both systemic and localized immunosuppression appears to be similar in all age groups (Paller and Lund 2019). For a discussion of the topical treatment options for chronic plaque psoriasis see the Clinical Reviews of NDA 22563 dated 09/17/2010 and 09/03/2012.

2.3. Patient Experience Data

The investigator or designated staff member conducted the primary assessments of treatment effect in Trial STF115469. However, the evaluation of tolerability included a patient reported outcome (PRO), an evaluation of pain using a 10-point Visual Analog Scale (VAS) and/or Faces Pain Scale. Although PROs may be important measures to evaluate treatment effect, the Applicant solicited no comments regarding the most appropriate tools for use in this age group to support labeling claims. Therefore, the results of the patient-reported outcome (PRO) assessment will be discussed only briefly in this review.

	The patient experience data that was submitted as part of the application includes:		Section where discussed, if applicable
X	Clinical outcome assessment data, such as		
	X	Patient reported outcome	Section 7.3.5
	□	Observer reported outcome	
	X	Clinician reported outcome	Section 7.2.2
	□	Performance outcome	
□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi panel, etc.)		
□	Patient-focused drug development or other stakeholder meeting summary reports		
□	Observational survey studies designed to capture patient experience data		
□	Natural history studies		
□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)	
□	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	
	□	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

The original Applicant, Stiefel, developed SORILUX Foam, 0.005%, 0.005% under IND 71198. SORILUX (calcipotriene) Foam, 0.005% (NDA 022563) was approved on October 6, 2010, for the topical treatment of plaque psoriasis (on the body) in patients aged 18 years and older. Stiefel received a waiver of assessments in the pediatric population ages 0 months to 2 years because necessary studies were impossible or impracticable because there are too few children with the condition to study. Required assessments under the Pediatric Research Equity Act (PREA) in

the pediatric population ages 2 years to 16 years were deferred because the product was ready for approval for use in adults and the pediatric studies were not complete.

The Applicant submitted an efficacy supplement (S-002) to revise the indication to "the topical treatment of plaque psoriasis of the scalp and body in patients aged 18 years and older" (November 29, 2011). With the extension of the indication to include plaque psoriasis of the scalp (S-002, approved September 27, 2012), the Applicant was released from the original postmarketing requirements (Letter dated 3/12/2013) under PREA which were replaced with the following required studies to evaluate SORILUX Foam, 0.005%, 0.005% for the treatment of plaque psoriasis on both the scalp and body:

> 1944-1: A Pharmacokinetics/Pharmacodynamics trial of SORILUX Foam, 0.005%, 0.005%, 0.005% under maximum-use conditions in 20 evaluable pediatric subjects with plaque psoriasis of the scalp and body age 12 years to 16 years and 11 months. The effect of the product on calcium metabolism will be evaluated in all subjects (STF115750).
>
> Final Report Submission: June 2015
>
> 1944-2: A vehicle-controlled trial of the safety and efficacy of SORILUX Foam, 0.005% in 150 evaluable pediatric subjects with plaque psoriasis of the scalp and body age 2 years to 11 years and 11 months. Pharmacokinetic/Pharmacodynamic parameters will be evaluated in a subset of at least 25 evaluable subjects under maximum-use conditions. Evaluate the effect of the product on calcium metabolism in all subjects (STF115469).
>
> Final Report Submission: December 2019

On November 25, 2015, the Applicant was released from conducting the required study under PMR 1944-2 because completion of the trial as designed (vehicle-controlled trial) was "no longer feasible." The FDA reissued the deferred study requirement (PMR 1944-3) for subjects ages 2 to 11 years and 11 months as follows:

> 1944-3: An open-label trial of the safety and treatment effects of SORILUX Foam, 0.005% in 75 evaluable pediatric subjects with plaque psoriasis of the scalp and body age 2 years to 11 years and 11 months. Pharmacokinetic/Pharmacodynamic parameters will be evaluated in a subset of at least 25 evaluable subjects under maximum use conditions. The effect of the product on calcium metabolism will be evaluated in all subjects. (STF115469)[1]
>
> Trial Completion: March 2018
> Final Report Submission: September 2018

[1] The vehicle-controlled design of PMR 1944-2 was replaced with the open-label design of 1944-3 in 2015 (Letter dated 11/25/2015).

The Division provided advice regarding the study population, assessments and design of Trial STF115469 during three guidance meetings (Meeting Minutes dated 6/20/2011, 6/30/2015 and 7/14/2017) with Stiefel and the current Applicant, Mayne Pharma LLC (acquired January 2017). To accelerate enrollment, the Division agreed that the PK cohort could enroll subjects with at least 3% body surface area (BSA) and some scalp involvement and the general cohort could enroll subjects with psoriasis of the body with or without scalp involvement. (Meeting Minutes dated 7/14/2017.)

Mayne Pharma LLC submitted a Deferral Extension Request (DER) on March 14, 2018, to extend the milestone date to provide the final study report for Trial STF115469 to August 30, 2019. The basis for this request was ongoing recruitment challenges. The Applicant indicated that the population of subjects in this age group with psoriasis of moderate severity on both the scalp and body was very limited. In addition, caregivers/ children were unwilling to enroll in a study which required frequent sampling of the blood and urine. In view of the substantial delay in receiving data in this pediatric population, the Division denied the DER (August 22, 2018) and requested that the Applicant submit the data for FDA review that was available to date.

On October 1, 2018, the Applicant submitted an efficacy supplement (S-007). However, the submission was not sufficiently complete due to the absence of PK data, bioanalytical method validation and bioanalysis reports. In addition, the submission contained only data from the final version of the protocol. On November 21, 2018, the FDA notified the Applicant of the Refuse to File action.

On resubmission (January 4, 2019) of S-007, the Applicant included data from all versions of the protocol and both vehicle-controlled and open-label designs.

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 sites.

4.2. Product Quality

The Applicant determined that the formulation of SORILUX Foam, 0.005%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. 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 CMC Review by Rajiv Agarwal, Ph.D. dated 09/07/2010.

The Office of Product Quality Reviewer, Steve Hathaway, Ph.D., analyzed the request for categorical exclusion from the requirement to conduct an environmental assessment (EA). The Applicant stated that SORILUX Foam, 0.005%will not increase the use of active moiety and the amount of waste to be generated is expected to be small. The Applicant anticipated that "no extraordinary circumstances exist with regard to this action" (SDN 354 dated 4/19/2019). The FDA granted a categorical exclusion from the EA requirement which was submitted to support the expansion of the patient population to include adolescents 12 years of age or older (SDN 318).

The quality reviewer stated, "Based on previous EA categorical exclusion information, and the low concentration of the active ingredient in the drug product, there is little to no likelihood of the proposed change causing the environmental exposure of the API to reach the EA reporting threshold. The request for categorical exclusion from the EA requirement is acceptable."

The Applicant proposed no changes to the CMC-related sections of the Prescribing Information, Patient Information, or carton and container labeling. Dr. Hathaway stated that "the proposed package insert is acceptable from the perspective of CMC" and concluded, "This supplement is recommended for approval." See review by Joel Hathaway, Ph.D., dated 3/20/2019.

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 SORILUX Foam. For an analysis and discussion of the nonclinical data, refer to the review by Carmen Booker, Ph.D. dated 8/24/2010.

During the review of NDA 22563 S-006, the Pharmacology/Toxicology Reviewer provided comments regarding the relevant subsections of labeling, Sections 8 Use in Specific Populations and 13 Nonclinical Toxicology (review by Carmen Booker, Ph.D. dated 3/19/2019.)

6. Clinical Pharmacology

The Clinical Pharmacology Reviewer, Soo Hyeon Shin, Pharm.D., Ph.D., evaluated the pharmacokinetics (PK) and effects of twice daily administration of SORILUX Foam, 0.005% for up to 8 weeks on calcium metabolism. Dr. Shin indicated that the trial results suggest that "the

systemic absorption of calcipotriene from SORILUX in pediatric subjects down to 7 years old is minimal." In addition, she concluded that "based on the totality of data in addition to the lack of clear correlation between urine calcium/creatinine ratio and the presence of hypercalciuria (or urinary calcium excretion measured by a 24 hr urine collection) it was determined that there is no clinically significant effect on indices of calcium metabolism."

The Clinical Pharmacology Reviewer determined that the bioanalytical methods used to evaluate the PK samples were adequate with acceptable sensitivity (10 pg/mL =0.023nM). To assess the calcium concentrations in serum and urine, the Applicant used an acceptable commercially available system reagent that was cleared with a 510(k) application.

Dr. Shin concluded that "The Office of Clinical Pharmacology finds the NDA 022563/S-007 acceptable."

A summary of analyses and conclusions from the clinical pharmacology review are provided below.

6.1. Pharmacokinetics

The Applicant conducted a pharmacokinetic (PK) assessment in 16 subjects

A total of 14 subjects received SORILUX Foam, 0.005%and 2 subjects received vehicle foam. However, only 11 subjects who received SORILUX Foam, 0.005%had both pre- and postdose assessments. These subjects ranged in age from 7 to 11 years (mean age 9.9 years) and had a BSA of 6% to 37%. See the review by Soo Hyeon Shin, Pharm.D., Ph.D. dated 10/2/2019 for the key Baseline characteristics of the PK population.

Per protocol, investigators evaluated the plasma concentration of calcipotriene at Baseline, Week 2, and Week 8 for subjects under Version 5 of the protocol and at screening and Week 2 for subjects in the "maximum use cohort" under Version 7 of the protocol. All samples had calcipotriene plasma concentrations below the limit of quantitation (<10.0 pg/mL) at all time points.

The results of the PK assessments will be conveyed to the prescriber in Sections 8.4 Pediatric Use and 12.3 Pharmacokinetics of the Prescribing Information (PI) for SORILUX Foam.

6.2. Pharmacodynamics

The Applicant evaluated changes in calcium metabolism by measuring urine calcium/creatinine ratio, albumin-adjusted serum calcium, intact parathyroid hormone (iPTH), alkaline phosphatase, magnesium, and phosphorus. The timepoints and assessments varied with the version of the protocol. A total of 23 subjects provided PD data. Of these, 21 subjects received

SORILUX Foam, 0.005%and 2 subjects received vehicle. In the PD population the mean and median age was 9 years (range 4 to 11 years) including two subjects age 4 years. See the review by Soo Hyeon Shin, Pharm.D., Ph.D. dated 10/2/2019 for the key Baseline characteristics of the PD population.

No subjects had albumin corrected serum calcium values above the normal range and no subjects had calcium/ creatinine (ca/cr) ratios above the normal range at Week 2. However, two male subjects had slight elevations of ca/cr ratios above the normal range (240 mg/g creatinine) at Week 8 (245 mg/g creatinine and 285 mg/g creatinine). Neither subject reported symptoms or adverse events related to calcium metabolism. These results were not considered clinically meaningful based on the totality of the data.

The results of the pharmacodynamic assessments will be incorporated into Section 8.4 Pediatric Use and 12.2 Pharmacodynamics of the prescribing information (PI).

7. Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

To address PMR 1944-3 and support the use of SORILUX Foam, 0.005%in younger pediatric patients with plaque psoriasis of the scalp and body, the Applicant conducted a single, open-label Trial STF115469. Trial STF115469 was entitled, *"A multicenter, open-label, Phase 1 study of the safety, tolerability, systemic exposure, pharmacodynamics, and treatment effect of calcipotriene foam, 0.005% in pediatric subjects (ages 2 to 11 years) with plaque psoriasis."* The final study design (Version 7.0 dated October 20, 2017) is summarized below.

Table 1: Clinical Trial STF115469

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects	Intended Study Population	No. of Sites and Countries
Studies to Support Safety							
STF115469	Multicenter, open-label, repeat-dose safety, PK and PD	Twice daily up to 8 weeks	PD: effect of SORILUX on calcium metabolism PK Safety: AEs, VS, local tolerability	8 weeks with a 7-day follow up by telephone	36	Mild to moderate plaque psoriasis with ≥10% scalp and ≥3% BSA affected ages 2 to 11 years	16 sites in U.S.

Abbreviations: PK = pharmacokinetic; PD = pharmacodynamic; AE = adverse event; BSA = body surface area; no. = number; VS = vital signs

Source: Reviewer's Table

7.1.2. Review Strategy

The focus of this review was the local and systemic safety of SORILUX Foam, 0.005% which included the PK and PD findings. As the pathophysiology of plaque psoriasis and response to treatment are similar in the adult and pediatric populations (Paller and Lund 2018; Paller and Lund 2019), efficacy in the population ages 12 to 16 years was extrapolated from data in the adult population.

Data Sources

The sources of data used for the evaluation of the efficacy and safety of SORILUX Foam, 0.005%for the proposed indication included final a study report submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model] and literature references.

This application was submitted in electronic common technical document (eCTD) format and entirely electronic. The electronic submission including the protocol, clinical study reports, SDTM, and Analysis Data Model format are located in the following network path: \\CDSESUB1\evsprod\NDA 022563\022563.enx

Data and Analysis Quality

In general, the data submitted by the Applicant to support the safety of SORILUX Foam, 0.005%for the proposed indication appeared adequate.

7.2. Review of Relevant Trial

7.2.1. Study Design and Endpoints

Clinical Trial STF115469

Objective

The primary objective of the trial was to evaluate the local and systemic safety of SORILUX Foam, 0.005% in subjects ages 2 to 11 years with mild to moderate plaque psoriasis. The secondary objectives were to characterize the pharmacodynamic effects (i.e., calcium metabolism), pharmacokinetics and treatment effects in this target pediatric population.

Study Population

The Applicant intended to enroll a sufficient number of subjects to ensure 50 evaluable subjects in a 'general use' cohort and 25 evaluable subjects in a 'maximum-use' cohort. The key entry criteria that defined the study population for the final version of the protocol (v 7) are as follows:

Key inclusion criteria:

- Male or female subjects, ages 2 to 11 years, inclusive, at the time of consent.
- General use cohort:
  - Investigator's Static Global Assessment (ISGA) score of 2 or 3 on a scale of 0 to 4 at Screening with no minimum Body Surface Area (BSA) requirement.
- Maximum-use cohort:
  - Investigator's Static Global Assessment (ISGA) score of $\geq$3 on a scale of 0 to 4 at Screening.
  - Plaque psoriasis involving at least 3% total BSA with some scalp involvement.
  - "Napkin" psoriasis (psoriasis in the diaper area) can be included in the BSA calculation for this age group.

Key exclusion criteria:

- Any inflammatory skin disease in the treatment area that may confound the evaluation (e.g., atopic dermatitis, contact dermatitis, tinea corporis).
- Current diagnosis of unstable forms of psoriasis in the treatment area, including guttate, erythrodermic, exfoliative, or pustular psoriasis.
- Use of prohibited topical of systemic concomitant medication (see list below).
- Any serious skin disorder or any chronic medical condition that is not well controlled.
- Average daily ingestion of more than 2000 mg of elemental calcium or more than 1000 IU of vitamin D within 2 weeks prior to enrollment.
- History of hypersensitivity, known allergy, or other adverse reaction to calcipotriene or other vitamin D analogs or to any component of the study product.
- Current or history of hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders.

- Pregnant, breastfeeding, or sexually active female subjects of childbearing potential (after menarche) who are not practicing an acceptable method of contraception.
- Albumin-adjusted serum calcium at Screening that is outside the normal reference range (may retest once).

Study Design

Trial STF115469 was a multicenter, open-label (after v 5), repeat-dose trial to evaluate the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of SORILUX Foam, 0.005%, in subjects ages 2 to 11 years with mild to moderate plaque psoriasis. After confirmation of eligibility, investigational staff identified treatment sites and instructed subjects/ primary caregivers to apply a thin layer of SORILUX Foam, 0.005% (or vehicle per 2:1 randomization in v 5 of the protocol) with gentle message twice daily to all affected areas except the face. Investigational staff instructed subjects/caregivers to apply SORILUX Foam, 0.005% to any new lesions and all prespecified lesions, even those which cleared with treatment, for up to 8 weeks. Subjects avoided bathing the treatment sites within 4 hours of administration of the investigational product. After the first supervised administration of the study product, subjects applied all doses at home. Investigational staff applied the final dose on Day 15.

The dose applied was "the smallest amount of study product necessary to cover all treatable lesions (excluding the face)." The dose depended on the BSA as follows:

- For those subjects with psoriasis covering between 5% and 10% total body surface area (BSA), the estimated dose was <0.5 to 1.5 capfuls.
- For those subjects with ≥10% body involvement and ≥10% scalp involvement, the estimated dose was 0.5 to 5 capfuls.

Screening assessments included medical history, height and weight, complete skin examination for determination of percent BSA of involvement and ISGA of the scalp and body, blood sampling for serum 25-OH vitamin D concentration and spot urine sampling for urine calcium/creatinine ratio and pregnancy testing.

During Trial STF115469, investigators conducted an evaluation of safety including effects on calcium metabolism, PK, and treatment effect. The key safety measures which were obtained at all visits (Screening, Week 2 and Week 8) included adverse events, vital signs [temperature, blood pressure, pulse], local safety assessments (erythema assessed by the investigator on a 5-point scale and pain assessed by the subject), and concomitant medications. Interim phone contacts occurred at Week 4 and 9. In version 5 of the protocol, investigators monitored subject safety at Week 4 during a clinic visit, while in version 7 investigators monitored subjects during a telephone interview.

Pharmacodynamic measures included the following:

- urine calcium/creatinine ratio (in all subjects)

- albumin-adjusted serum calcium (in maximum-use cohort only in current version and all subjects prior to Amendment #5)
- intact PTH (iPTH) (in maximum use cohort only in current version and all subjects prior to Amendment #5)
- alkaline phosphatase (in maximum use cohort only in current version and all subjects prior to Amendment #5)
- magnesium (in maximum use cohort only in current version and all subjects prior to Amendment #5)
- phosphorus (in maximum use cohort only in current version and all subjects prior to Amendment #5)
- serum 25-OH vitamin D concentrations (Baseline: maximum use cohort only in current version and all subjects prior to Amendment #5)

Table 2: Pharmacodynamic and Pharmacokinetic Assessments V 7

	Screening		Week 2		Week 8
	Blood	**Urine**	**Blood**	**Urine**	**Urine**
Maximum-use cohort	albumin-adj serum calcium	calcium/ creatinine ratio	albumin-adj serum calcium	calcium/ creatinine ratio	calcium/ creatinine ratio
	intact PTH (iPTH)		intact PTH (iPTH)		
	alkaline phosphatase		alkaline phosphatase		
	magnesium		magnesium		
	phosphorus		phosphorus		
	25-OH vit D				
	calcipotriene plasma conc		calcipotriene plasma conc		
General-use cohort	albumin-adj serum calcium	calcium/ creatinine ratio		calcium/ creatinine ratio	calcium/ creatinine ratio
	intact PTH (iPTH)				
	alkaline phosphatase				
	magnesium				
	phosphorus				
	25-OH vit D				

Abbreviations: iPTH = intact parathyroid hormone; vit D = vitamin D

Source: Reviewer's Table

In version 7 of the protocol, the Applicant evaluated the pharmacokinetics of SORILUX Foam, 0.005%at Screening and Week 2 in the maximal use cohort with sparse sampling, approximately 1 to 5 hours after the morning dose. In version 5 of the protocol, all subjects provided samples for analysis at Screening, Week 2 and Week 8.

The treatment effect was assessed on the ISGA at Screening, Week 2 and Week 8. The endpoints included the proportion of subjects with:

- ISGA Score of 1 or 0 at Week 8
- ≥1 grade improvement on ISGA at Week 8, compared with Baseline

- ≥2 grade improvement on ISGA at Week 8, compared with Baseline

To assess compliance, study personnel documented the weight of the study product canisters when dispensed and returned, reviewed logs of the number of applications completed by each subject and queried caregivers regarding the number of missed doses. For each subject, there was a summary of missed doses by location (body, scalp, both) and percent BSA and deviations from administration instructions.

Criteria for early withdrawal from treatment or assessment:

- Subject withdrew consent
- Investigator concluded that it is not in the best interest of the subject to continue in the trial.
- Occurrence of an AE/SAE, which the Investigator assessed as warranting discontinuation of the subject from the trial
- Pregnancy
- Significant noncompliance with standard of care treatment or that would interfere with the study results or increase the subject's risks in the trial
- Subjects assessed as treatment failures, defined as subjects whose condition worsened and who require alternative or supplemental therapy)

Concomitant Medications

Permitted concomitant medications included stable use of inhaled/intranasal corticosteroids and treatments for other medical conditions, sunscreens and bland emollients on non-treatment areas. No other topical or systemic therapy including phototherapy that may impact psoriasis was permitted. Prohibited medications and their washout periods prior to first application of the study product are tabulated below:

Table 3: Prohibited Products and Washout Periods for All Subjects

Product	Washout period prior to first application of study product
Use of topical treatments that have a known beneficial effect including but not limited to corticosteroids, retinoids, vitamin D derivatives, coal tar, medicated shampoos, tazarotene, or anthralin	2 weeks
Nonbiologic systemic antipsoriatic therapy (e.g., corticosteroids, psoralen, retinoids, methotrexate, cyclosporine, other immunosuppressive agents) or biological therapies (e.g., adalimumab, etanercept, golimumab, infliximab, ustekinumab)	4 weeks
Phototherapy (PUVA, UVB)	4 weeks
Medications that affect or change calcium and PTH concentrations or that interfere with the measurement of calcium or PTH concentrations are not allowed during the study.	4 weeks
Nonpsoriatic therapy, including antimalarials, β- blockers, interferon, or lithium	4 weeks
Investigational drugs or treatments other than the study product during the study	4 weeks

Abbreviations: UVB = ultraviolet B; PTH = parathyroid hormone; PUVA = psoralen plus ultraviolet A

Source: Clinical Study Report for STF 115469, Table 4, page 47

Investigator(s)

There was a total of 16 participating study sites in the United States. As tabulated below, sites with two site numbers recruited subjects under the oversight of both clinical research organizations, (b) (4) and (b) (4) Sites with a single site number recruited subjects under the oversight of (b) (4) only.

Table 4: Study Sites and Enrollment

Site Numbers	Investigator	Location	Product		Total
			SORILUX N=32	Vehicle N=4	N=36
200647/61140	Andrea Zaenglein	Hersey, PA	1 (3.13)	0 (0.00)	1 (2.78)
100101/65438	Vivian Laquer	Fountain Valley, CA	3 (9.38)	0 (0.00)	3 (8.33)
100102/65439	Lorley Mendez	Miami, FL	2 (6.25)	0 (0.00)	2 (5.56)
100103/65440	Melody Stone	St. Joseph, MO	1 (3.13)	0 (0.00)	1 (2.78)
100104/65441	Mark Amster	Brighton, MA	1 (3.13)	0 (0.00)	1 (2.78)
100107/65444	John Browning	San Antonio, TX	2 (6.25)	0 (0.00)	2 (5.56)
100109/65445	Diamondis Papadopoulos	Atlanta, GA	1 (3.13)	0 (0.00)	1 (2.78)
100069/_____	Suzanne Bruce	Houston, TX	1 (3.13)	0 (0.00)	1 (2.78)
100372/65446	Adelaide Hebert	Houston, TX	6 (18.75)	1 (25.00)	7 (19.44)
100508/65447	David Pariser	Norfolk, VA	0 (0.00)	1 (25.00)	1 (2.78)
100536/65448	Elaine Siegfried	St. Louis, MO	6 (18.75)	0 (0.00)	6 (16.67)
100537/_____	Amy Paller, MD	Chicago, IL	0 (0.00)	1 (25.00)	1 (2.78)
100539/65449	Jamie Weisman	Sandy Springs, GA	1 (3.13)	0 (0.0)	1 (2.78)
100547/_____	Aida Lugo-Somolinos, MD	Chapel Hill, NC	1 (3.13)	1 (25.00)	2 (5.56)
201121/65450	Shahram Jacobs, MD	Sherman Oaks, CA	1 (3.13)	0 (0.00)	1 (2.78)
201352/61139	Alfons Krol/Tracy Funk	Portland, OR	5 (15.63)	0 (0.00)	5 (13.89)

Source: NDA 22563 SDN 360 dated May 31, 2019.

Table 5: Schedule of Assessments: STF115469

Parameter	Study Visit				
	Baseline Day 1	Phone Call Week 1 Day 7-9	Week 2 Day 13-16	Phone Call Week 4 Day 28-31	Week 8/ET Day 56-59
Inclusion/exclusion criteria	X				
Vital sign measurements: temperature, BP, pulse	X		X		X
Complete skin examination (% BSA involvement)	X		X		X
Record Prior/concomitant medications	X	X	X	X	X
Urine sampling for calcium/creatinine ratio (See Note)	X		X		X
Urine pregnancy test	X		X		X
ISGA of body and scalp	X		X		X
Blood sampling for PK/PD parameters (See Note)			X		
Record adverse events	X	X	X	X	X
Record serious adverse events	X	X	X	X	X
Local tolerability assessments	X	X	X		
Record time of previous dose			X		
Weigh and dispense study product canisters	X		X		X
First application of study product	X				
Dispense study product compliance log	X		X		
Collect/review study product compliance log			X		X
Schedule next visit	X		X	X	
	Phone Call Follow-up – Week 9 – Day 63-66				
Prior/concomitant medications query	Adverse events query				

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic

Source: Clinical Study Report for STF 115469 Protocol, STUDY FLOWCHART, Synopsis page 19

Data Analysis

Several different datasets were used to conduct analyses. Safety population, which was used to analyze tolerability and safety, consisted of all subjects who received at least one application of study product. PD population consisted of all subjects who received study treatment and had at least one postdose urinary calcium/creatinine ratio. Maximum-use PD population consists of all subjects who received study treatment and had at least one postdose plasma sample for plasma PD assessments. The PK population consisted of all subjects who received active treatment and had at least one blood sample collected for the determination of calcipotriene concentration. The treatment effect (TE) population consists of all subjects who received active treatment and had a Baseline and 8-week ISGA score.

Protocol Amendments

The original design of Trial STF115469 was a vehicle-controlled trial evaluating the safety and efficacy of SORILUX Foam, 0.005% in 150 subjects ages 2 years to 11 years with plaque psoriasis of the scalp and body. The protocol included assessment of PK/PD parameters in a subset of at least 25 evaluable subjects with greater body surface area involvement, with the assessment of the effect of the product on calcium metabolism in all subjects. There were six amendments to Protocol STF 115469 following the initial agreement. No subjects enrolled in the first three versions of the protocol which incorporated FDA comments.

Per Summary of Changes, Version 4 of the protocol specified enrollment of 120 subjects with mild to moderate plaque psoriasis defined as a score of 2 or 3 on a scale of 0 to 4 and involving 5% to 30% of total BSA and a target lesion with a score of 2 or 3 at Baseline. Most key revisions to the final versions of the protocol were designed to enhance enrollment and increase the likelihood of completing the study as required under Pediatric Research Equity Act (PREA):

Version 5:

- Increased the target sample size to 180 to account for dropouts
- Decreased required BSA range to ≥5% BSA involvement on the body and ≥5% scalp involvement (excluding the face)
- Increased the subset of subjects with more extensive disease to 'a minimum of 75 subjects will have at least 10% BSA on the body and a minimum of 10% scalp involvement with an ISGA score of moderate'
- Added maximum dose of 5.5 capfuls to method of administration
- Added application site tolerability assessments

Version 6:

- Changed the study design and objectives from a vehicle-controlled to an open-label design for the evaluation of safety
- Reduced the sample size from 150 evaluable subjects to 75 evaluable subjects
- Redefined the study population to include a " a general use" cohort enrolling 50 evaluable subjects with plaque psoriasis and an ISGA score of 2 or 3 at Baseline and a 'maximum-use' cohort enrolling 25 evaluable subjects with plaque psoriasis and an ISGA score of 3 or higher at Baseline
- Defined the 'maximum-use' cohort to include 15 subjects ages 7 to 11 years with at least 10% total BSA with some scalp involvement and 10 subjects ages 2 to 6 years with at least 3% total BSA with some scalp involvement. Revised the BSA calculation for ages 2 to 6 years to include "Napkin" psoriasis (i.e., psoriasis in the diaper area)
- Reduced the number of blood sampling timepoints

Version 7:

- Redefined the 'maximum-use' cohort to include 25 evaluable subjects aged 2 to 11 years of age with at least 3% BSA with some scalp involvement
- Increased the number of study sites to 16 to expedite enrollment

7.2.2. Results of Efficacy Assessment

As an open-label safety trial, STF115469 was not designed to evaluate efficacy. There was no formal hypothesis testing. As the pathophysiology of plaque psoriasis and response to treatment are similar in the pediatric and adult populations, efficacy in the pediatric population was extrapolated from the adult population (Dunne et al. 2011). Per protocol, investigators estimated the percentage of BSA involvement (methodology of the calculation is described in Appendix 1 Protocol STF115469 v 7) and documented ISGA scores separately for the scalp and body at Baseline, Week 2 and Week 8 using the following scale:

Table 6: Investigator's Static Global Assessment Scale

Score	Category	Description
0	Clear	Minor residual discoloration; no erythema, scaling, or plaque thickness
1	Almost Clear	Occasional fine scale, faint erythema, and barely perceptible plaque thickness (possible but difficult to ascertain whether there is a slight elevation above normal skin)
2	Mild	Fine scales predominate with light red coloration and mild plaque thickness (slight but definite elevation, typically edges are indistinct or sloped)
3	Moderate	Coarse scales predominate with moderate red coloration and moderate plaque thickness (moderate elevation with rough or sloped edges)
4	Severe	Thick tenacious scale predominates with deep red coloration and severe plaque thickness (very marked elevation typically with hard sharp edges)

Source: Reviewer's summary table, modified from Investigator's Static Global Assessment - Body and Scalp Appendix 2 Protocol STF115469 v 7

The results demonstrate improvement of psoriasis severity on both the scalp and body according to ISGA. From Baseline to Week 8, there were reductions in the numbers of subjects with moderate (3) and severe disease (4) on both the body and the scalp as summarized below.

Table 7: Investigator's Static Global Assessment Scores for Subjects Receiving SORILUX Foam: Treatment Effect (TE) Population

Anatomical Site	No. (%) of Subjects				
Visit	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ISGA: Body N=32					
Baseline (Day 1)	2 (6%)	0 (0%)	13 (41%)	14 (44%)	3 (9%)
Week 8	2 (6%)	12 (39%)	8 (26%)	8 (26%)	1 (3%)
ISGA: Scalp N=31					
Baseline (Day 1)	8 (25%)	3 (9%)	6 (19%)	13 (40%)	2 (6%)
Week 8	12 (39%)	7 (23%)	6 (19%)	6 (19%)	0 (0%)

Source: Adapted from Table 37 Clinical Study Report Protocol STF115469 Table 14.3.1

In the treatment effect population, a total of 14 subjects (45%) receiving SORILUX Foam, 0.005%achieved a score of 0 (clear) or 1 (almost clear) on the body at Week 8; a total of 19 subjects (61%) achieved a score of 0 (clear) or 1 (almost clear) on the scalp at Week 8. However, only three subjects (10%) achieved a score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement on the body at Week 8; only four subjects (13%) achieved a score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement on the scalp at Week 8.

7.3. Review of Safety

7.3.1. Safety Review Approach

The review of the safety of SORILUX Foam, 0.005% in the pediatric population ages 4 to 11 years focused on data from a single trial, STF STF115469. The analyses included treatment-emergent adverse events (TEAEs), serious AEs (SAEs), AEs leading to discontinuation, treatment-emergent adverse reactions (TEARs) and AEs associated with the product class, vitamin D analogs.

7.3.2. Review of the Safety Database

Exposure

Extent of Exposure

A total of 32 subjects received SORILUX Foam, 0.005% and 4 subjects received vehicle. Although most of these subjects achieved ≥95% compliance with twice daily applications to both the body and scalp, one subject (232001) missed almost 45% of the prespecified doses (56 doses) to the scalp. Overall, subjects missed more doses to the scalp than to the body.

Table 8: Extent of Exposure: Safety Population Receiving SORILUX Foam, 0.005%

Statistic	Amount of Product Used (g) Overall (N=29)	Average Dose (g/day) (N=28)	No. of Doses Applied to Scalp (N=31)	No. of Doses Applied to Body (N=31)	% Overall Compliance N=30
Mean (SD)	321 (260)	8 (5)	71 (54)	95 (41)	97 (8)
Median	264	7	108	112	100
Range	2, 979	0, 20	0, 138	0, 138	65,100

Abbreviation: SD = standard deviation

Source: Adapted form Table 15 Clinical Study Report for STF STF115469;

Table 9: Duration of Exposure (Days)-Safety Population

	Statistic	SORILUX	Vehicle	Total
Duration of Exposure (Days)	**N**	**32**	**4**	**36**
	Mean (SD)	50 (19)	45 (26)	50 (20)
	Median	57	56	57
	Min/Max	3/71	6/61	3/71

Abbreviation: SD = standard deviation

Source: Modified from NDA 22563 Clinical Study Report for STF STF115469 Table 19, page 84

Table 10: Duration of Exposure (Days)-Pharmacodynamic Population

	Statistic	SORILUX	Vehicle	Total
Duration of Exposure (Days)	**N**	**21**	**2**	**23**
	Mean (SD)	51 (18)	56 (1)	51 (17)
	Median	57	56	57
	Min/Max	5/64	55/57	5/64

Abbreviation: SD = standard deviation

Source: Modified from NDA 22563 Clinical Study Report for STF STF115469 Table 20 page 84

Characteristics of the Safety Population

Demographic and Baseline Characteristics

Most of the subjects were female (53%), white (78%), not Hispanic/Latino (60%) and in the age group 7 to 11 years (mean 9 years). The median ISGA score for the body and scalp at Baseline was 3 (moderate on a 4-point scale). At Baseline, the mean percent body surface (body and scalp) involved with psoriasis was 13% (median 9%).

Table 11: Demographic and Baseline Characteristics

Characteristics	Statistics	Subjects/Results N=36
Sex [n (%)]	F	19 (53%)
	M	17 (47%)
Age cat 12-13 [n (%)]	≥4 years and ≤6	5 (14%)
Age cat 14-16 [n (%)]	≥7 years and ≤11	31 (86%)
Age (years)		
	Mean (SD)	9
	Median	9
	Minimum/maximum	4/11
Race [n (%)]	White	28 (78%)
	Black/ African American	4 (11%)
	Asian	1 (3%)
	Other	3 (8%)
Ethnicity [n (%)]	Hispanic/Latino	14 (40%)
	Not Hispanic/Latino	21 (60%)
Height (cm)		
	Mean (SD)	135 (14)
	Median	136
	Minimum/maximum	104/ 159
Weight (kg)		
	Mean (SD)	42 (15)
	Median	40
	Minimum/maximum	18/ 77
BSA (%) (body + scalp)		
	Mean (SD)	13 (10)
	Median	9
	Minimum/maximum	1/37
Baseline body ISGA score		
	Mean (SD)	3 (1)
	Median	3
	Minimum/maximum	0/ 4
Baseline scalp ISGA score		
	Mean (SD)	2 (1)
	Median	3
	Minimum/maximum	0/ 4

Abbreviations: BSA = body surface area; SD = standard deviation; ISGA = Investigator's Static Global Assessment

Source: Adapted form Table 16 Clinical Study Report for STF

Concomitant Medications at Baseline

The Applicant coded concomitant medications according to WHODRUG (September 2016 and March 2017 Release). Overall, 56% (18/32) of subjects who received calcipotriene used

concomitant medications. The most common class of medications was "topical dermatologicals." However, the most common single drug used in the safety and PD populations was ibuprofen (three subjects).

Disposition

Of the 39 subjects who were screened for participation in Trial STF115469, investigators assessed 3 subjects as screening failures and enrolled 36 subjects in the trial. A total of 30 subjects completed the trial and 6 subjects discontinued treatment prior to Week 8. The following tables summarize enrollment by amendment number/ protocol version number and provide disposition data.

Table 12: Summary of Subjects Enrolled by Amendment/ Protocol Version

Amendment/Protocol Version	Number Receiving Calcipotriene	Number Receiving Vehicle
1-2/1-3	0	0
3/4 (double-blind)	0	0
4/5 (double-blind)	8	4
5/6 (open-label)	9	0
6/7 (open-label)	15	0

Source: Clinical Study Report; Table 9, page 57

Table 13: Summary of Disposition

Disposition	Statistic	SORILUX Foam N=32	Vehicle Foam N=4	Total N=39
Reason for Discontinuation	n (%)			
Screen failure	n (%)	NA	NA	3 (8%)
Completed	n (%)	27 (84)	3 (75)	30 (77)
Adverse event	n (%)	5	0	5 (13)
Lost to follow-up	n (%)	0	0	0
Non-compliance with study treatment	n (%)	0	0	0
Withdrawal of consent	n (%)	0	0	0
Progression/ lack of efficacy	n (%)	0	0	0
Death	n (%)	0	0	0
Other	n (%)	0	1	1

Source: Modified from Clinical Study Report; Table 10, page 58

Protocol Deviations

The Applicant documented 41 protocol deviations of which 33 were major and 8 were minor. The most common protocol deviations were related to testing, procedures or assessments (29 subjects). A total of 18 subjects had major protocol deviations due to temperature excursions in the storage of the study product; one subject had a minor protocol deviation due to a temperature excursion; and 3 subjects had protocol deviations due to temperature excursions

which were poorly documented. Other minor protocol deviations were recorded as issues with informed consent and investigator site files. The protocol deviations are categorized below.

Table 14: Protocol Deviations Occurring in ≥1 Subject

Deviation	No. (%) of Subjects
Number of subjects with ≥1 deviation	29 (81%)
Tests/assessments/procedures	14 (25%)
Product management/accountability	10 (18%)
Out of visit window	9 (16%)
Informed consent issues	8 (14%)
Other	7 (12%)
Subject dosing	6 (11%)
Concomitant medications	2 (4%)
Inclusion/exclusion criteria	1 (2%)

Source: Adapted form Table 14 Clinical Study Report for STF115469

Adequacy of the Safety Database

The Applicant did not achieve the enrollment size specified in PMR-3. However, review of data supporting the use of SORILUX Foam, 0.005% in the pediatric population ages 12 to 16 years indicated that the safety profile of SORILUX Foam, 0.005% in adults and children is similar. In the current trial, there were five subjects in the youngest pediatric age group, 4- to 6-year-old subjects; of these, four received SORILUX Foam. Two of the subjects with worsening disease withdrew or discontinued treatment prior to Week 8. None of the four subjects had an elevated postbaseline laboratory value related to calcium metabolism or experienced an unexpected adverse event. However, only two subjects had calcium assessments at both predose and postdose. In addition, none of the five subjects had a PK sampling at Baseline and Week 2 (postdose.)

Table 15: Data in the Age Group: 4 to 6 Years Old

Subject ID	Age	%BSA at Baseline	Applied doses	TEAE	Action With Drug/Relatedness	Ca/Cr: Baseline and Week 2
			SORILUX Foam			
(b) (6)	5	14	76			Normal
	4	34	28	Psoriasis	Withdrawn/related	*
	4		18	Psoriasis	Withdrawn/related	**
	6		114	URI	None/not related	Normal
			VEHICLE Foam			
	5	22	88			***

*normal Screening and Baseline

**normal at Week 8 but withdrawn and missed Week 2 assessment

*** high at Screening and normal at Baseline

Abbreviations: TEAE = treatment-emergent adverse event; ca/cr = calcium / creatinine ratio; URI = upper respiratory infection

Source: Reviewer's Table

Although the data in the youngest age group was limited, there were no safety signals, elevations in parameters related to calcium metabolism or unexpected AEs or ARs. Therefore, the safety database presented by the Applicant is sufficient to characterize the safety and

treatment effects of SORILUX Foam, 0.005% applied once daily for up to 8 weeks in the population ages 4 to 11 years with plaque psoriasis.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted was adequate to characterize the safety of SORILUX Foam, 0.005% applied twice daily for up to 8 weeks. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

Per ICH E6 (R1), the Applicant defined an adverse event (AE) as "any untoward medical occurrence in a subject or study subject temporally associated with the use of a study product, which does not necessarily have a causal relationship with the treatment." This includes any unintended or unfavorable sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated), worsening of psoriasis, abuse, or misuse of the study drug or occurrences resulting from study procedures.

AEs were categorized by system-organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The Applicant coded AEs using MedDRA, version 20.0. The Applicant classified AEs as "pre-therapy" or "on-therapy." In this review, "on-therapy" AEs will be referred to as treatment-emergent adverse events (TEAEs) or treatment-emergent adverse reactions (TEARs). The focus of this review is TEAEs and TEARs, not events which occurred prior to the initiation of the study drug.

Investigators graded AEs by seriousness, intensity (mild, moderate, or severe), causality, and action taken with the study product. The definition of serious adverse event (SAE) was based on International Conference on Harmonization (ICH) and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use. If there was a reasonable possibility that a causal relationship existed between the study product and the AE, investigators assessed the AE as related.

Routine Clinical Tests

Investigators monitored adverse events, concomitant medications, local safety and effects on calcium metabolism. The timepoints for laboratory and pharmacokinetic assessments varied with the version of the protocol. The key timepoints were Screening/ Day 1 (predose), and Day 15 (3 to 9 hours after dosing). Some subjects had laboratory assessments at the end of treatment. Measures to evaluate calcium metabolism included albumin adjusted calcium, intact parathyroid hormone (iPTH), alkaline phosphatase, magnesium, phosphorus, Baseline Serum 25-OH vitamin D concentrations and urinary calcium/creatinine ratios.

7.3.4. Safety Results

Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

There were no deaths, serious adverse events (SAEs) or AEs assessed as severe. Of the six subjects who discontinued treatment, five subjects experienced adverse events [worsening of psoriasis (3 subjects), application site pain (1 subject), contact dermatitis (2 subjects)]. In addition, one of the subjects (b) (6)) withdrew from the trial prior to Week 8 ("early termination.")

Table 16: Number of Subjects and TEAEs by SOC PT

System Organ Class Preferred Term	Number of Subjects N=32	Number of TEAEs
Number of adverse events leading to discontinuation of treatment	5 (16%)	6
General disorders and administration site conditions	1 (3%)	1
Application site pain	1 (3%)	1
Skin and subcutaneous tissue disorders	5 (16%)	5
Dermatitis contact	2 (6%)	2
Psoriasis	3 (9%)	3

Source: Modified from Clinical Study Report Table 14.1.1.1.2, 14.4.2.3 and Table 23

One subject (# (b) (6)) in the vehicle group discontinued treatment and withdrew from the trial ("early termination ") due to "other" reason.

Adverse Events

The Applicant defined treatment-emergent adverse events as all AEs that occurred after the first dose of the study product. The majority of the TEAEs were in the skin and subcutaneous tissue disorders system organ class (SOC) (8/32 subjects, 25%), infections and infestations SOC (4/32 subjects, 13%), and the injury, poisoning and procedural complications (4/32 subjects, 13%). The remaining TEAEs were distributed in the SOCs as summarized below. None of the four subjects receiving vehicle foam experienced any adverse events.

Table 17: Treatment-Emergent Adverse Events

System Organ Class Preferred Term	Number of Subjects N=32	Number of TEAEs
Overall	17(53%)	23
Skin and subcutaneous tissue disorders	8 (25%)	8
Dermatitis contact	3 (9%)	3
Psoriasis	3 (9%)	3
Alopecia	1 (3%)	1
Pruritus	1 (3%)	1
Infections and infestations	4 (13%)	6
Upper respiratory infection	3 (9%)	3
Ear infection/ otitis media	2 (6%)	2
Lice Infestation	1 (3%)	1

System Organ Class Preferred Term	Number of Subjects N=32	Number of TEAEs
Injury, poisoning and procedural complications	4 (13%)	4
Exposure to toxic agent	1 (3%)	1
Lower limb fracture/ upper limb fracture	2 (6%)	2
Road traffic accident	1 (3%)	1
Metabolism and nutrition disorders	3 (9%)	3
Vitamin D deficiency	2 (6%)	2
Increase Appetite	1 (3%)	1
General disorders and administration site conditions	2 (6%)	2
Application site pain	2 (6%)	2
Respiratory, thoracic and mediastinal disorders	2 (6%)	2
Oropharyngeal pain	2 (6%)	2
Gastrointestinal disorders	2 (6%)	2
Toothache	1 (3%)	1
Vomiting	1 (3%)	1
Ear and labyrinth disorders	1 (3%)	1
Ear pain	1 (3%)	1
Investigations	1 (3%)	1
Streptococcus test positive	1 (3%)	1

Source: Adapted form Table 21: Summary of Adverse Events by Safety population page 86

Adverse Reactions

A total of six subjects experienced seven TEAEs that were considered to be related to the use of SORILUX Foam, 0.005% [psoriasis (three events), application site pain (two events) and contact dermatitis (two events)]. These AEs are tabulated below by system organ class and preferred term. The adverse reactions (AR) are tabulated below.

Table 18: Drug-Related Treatment-Emergent Adverse Events (Adverse Reactions)

System Organ Class Preferred Term	Subjects (N=32)	Events
Overall	6 (19%)	7
Skin and subcutaneous tissue disorders	5 (16%)	4
Dermatitis contact	2 (6%)	2
Psoriasis	3 (9%)	3
General disorders and administration site conditions	2 (6%)	1
Application site pain	2 (6%)	2

Source: Adapted from Table 32, Clinical Study Report for STF 115750, page 55

Section 6.1 Clinical Trials Experience of SORILUX Foam, 0.005% labeling will include the adverse reactions of application site pain and contact dermatitis which were observed in this pediatric population. Exacerbation of psoriasis represents a treatment failure and will not be described as an AR.

Laboratory Findings

The mean values for corrected serum calcium, magnesium and phosphorus were consistent over the duration of the trial. Some parameters such as iPTH and alkaline phosphatase demonstrated substantial variability during the trial with no consistent trends. See 7.3.5 Analysis of Submission-Specific Safety Issues for the discussion of the other laboratory findings.

Vital Signs

Examination of shift tables of vital signs demonstrated no clinically meaningful changes from Baseline and no adverse events related to vital sign abnormalities.

Electrocardiograms and QT

The Applicant did not conduct electrocardiogram monitoring during Trial STF115469. Refer to the Clinical Review of the original application (dated 9/17/2010) for a discussion of the cardiac safety of SORILUX Foam. In the original application, the Division granted the request for a waiver from conducting a thorough QT/QTc study based on low systemic exposure and lack of a cardiac safety signal for the moiety.

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

Vitamin D is a fat-soluble vitamin which promotes calcium absorption in the gut and enables bone growth and remodeling (Holick 2007). Calcipotriene, the active ingredient in SORILUX Foam, 0.005% and other products indicated for the treatment of plaque psoriasis, is a synthetic analog of vitamin D. Treatment with calcipotriene products is associated with the development of local cutaneous reactions including contact dermatitis and the potential for hypercalcemia. These class specific safety issues are included in labeling for all formulations and dosage forms of vitamin D analogs.

<u>Effects on Calcium Metabolism</u>

The primary pharmacodynamic analyses to evaluate the effects of SORILUX Foam, 0.005% on calcium metabolism, were the relative change in the following laboratory parameters in the pharmacodynamic (PD) population:

- Urinary calcium/creatinine ratio
- Calcium corrected
- Intact parathyroid hormone (iPTH)
- Alkaline phosphatase

- Magnesium
- Phosphorus

Among these assessments of calcium metabolism, the key parameter included in the final versions of the protocol was the urinary calcium/creatinine ratio obtained from spot urine samples. Blood sampling needed for the for the assessment of albumin corrected serum calcium represented a barrier to the recruitment of subjects in this age group.

Hypercalciuria is one of the earliest signs of vitamin D toxicity and precedes occurrence of hypercalcemia. Unless calcium excretion is included in routine safety monitoring, hypercalciuria may easily be missed. Normal urinary calcium-to-creatinine values are age-related, decreasing with age in the first few years of life, and may also be impacted by other factors such as differences in climate and sunlight exposure, cultural variability in diet, mineral composition of drinking water, and race. Because of the diurnal variation in urinary calcium excretion with higher excretion at night, the first morning urine sample may not be as accurate as the second morning urine sample. In addition, children with low muscle mass will have lower urinary creatinine excretion which may lead to an over estimation of the calcium-to-creatinine ratio from a spot urine sample (b) (4) All of these factors may contribute to variability in the results of calcium creatinine ratios.

Interpretation of the results of calcium to creatinine ratios in this trial was challenging due to the small number of samples, variability in the data2 and the uncertainty about whether the Applicant was able to control for the factors with potential impact on the results (e.g., time of sample collection, adequate sample, muscle mass, nutritional content of calcium etc.).

Because of the limitations of data regarding the impact of SORILUX Foam, 0.005% on calcium metabolism, especially in subjects ages 4 to 6 years, the review team requested an analysis of postmarketing data by the Pharmacovigilance team. Jessica Weintraub, PharmD, BCPS, conducted a review of FDA Adverse Event Reporting System (FAERS) and the medical literature for reports of hypercalcemia or hypercalciuria in association with vitamin D analogs (calcipotriene, calcipotriol and calcitriol) from January 2006 to the present (review dated 8/7/2019).

Dr. Weintraub identified 22 cases of hypercalcemia and no cases of hypercalciuria with the use of topical calcipotriene or topical calcitriol. One case was an infant exposed through secondary transfer from an adult. These cases were primarily from foreign sources and reported in an older adult population. Of the 11 cases reporting use for the indication of plaque psoriasis, psoriasis vulgaris, or unspecified psoriasis, seven cases reported other potential factors that may have contributed to the risk of hypercalcemia. Of the remaining four cases, one reported

[2] Most values remained within the normal range but trended upward. One subject, a 7-year-old Hispanic male, had an elevated calcium creatinine level at Week 2. However, at Week 8 his level decreased to the screening level while on treatment. He was excluded from the PD population due to a major protocol deviation.

use of 250 g calcipotriene in 4 days (exceeding the standard dosing recommendations) and the remaining three cases provided limited information for case assessment, including no information on the amount of calcipotriene or calcitriol used or the area of application. See the Review by Jessica Weintraub, PharmD, BCPS dated 8/7/2019.

In a second analysis of postmarketing data from 1992 through 2005, Dr. Weintraub identified 12 cases from FAERS and the medical literature in patients with psoriasis reporting hypercalcemia, hypercalciuria, or both with topical use of calcipotriene. All cases occurred in adults. As in the previous review, the majority of cases reported one or more factors that could have contributed to increased absorption of the vitamin D analog or to the risk for hypercalcemia or hypercalciuria (e.g., chronic kidney disease, application to large body surface areas, osteoporosis (treatment not indicated), use of topical and systemic corticosteroids and diabetes (Liamis et al. 2014).

Dr. Weintraub noted that there were two studies which reported the use of "high-dose" calcipotriene in patients with chronic plaque psoriasis. Most of these subjects used the ointment dosage form of calcipotriene. Approximately one third experienced hypercalciuria and up to one quarter experienced hypercalcemia. However, these data are difficult to interpret because the maximum weekly doses for single-agent calcipotriene products are not specified in approved labeling in the United States. In contrast, the maximum weekly doses specified in labeling in the United Kingdom are 100 g in adults, 75 g in children >12 years of age, 50 g in children 6 to 12 years, with no maximum safe dose established in children less than 6 years. See the Review by Jessica Weintraub, PharmD, BCPS dated 9/12/2019.

Graphs with age stratification which were generated in Empirica Signal suggested no elevated risk of hypercalcemia in the pediatric population >1-year-old. In conjunction with postmarketing information and the literature, this data supports the view that the risk of hypercalcemia with the use of SORILUX Foam, 0.005% in pediatric patients with psoriasis is low. (Empirica Signal analysis conducted by Natalia Chalmers, DDS, MHSc, PhD.) In addition the geometric mean ratios for all PD markers approached 1.0 and most were within the 90% confidence intervals.

Labeling is data driven. The results of the evaluation of the available PD data will be conveyed to the prescriber in Section 8.4 Pediatric Use and 12.2 Pharmacodynamics of the Prescribing Information (PI).

Local Tolerability

The primary measures of tolerability were erythema and pain. Investigators evaluated erythema using the following 5-point scale:

Table 19: Investigator Assessment of Tolerability – Erythema

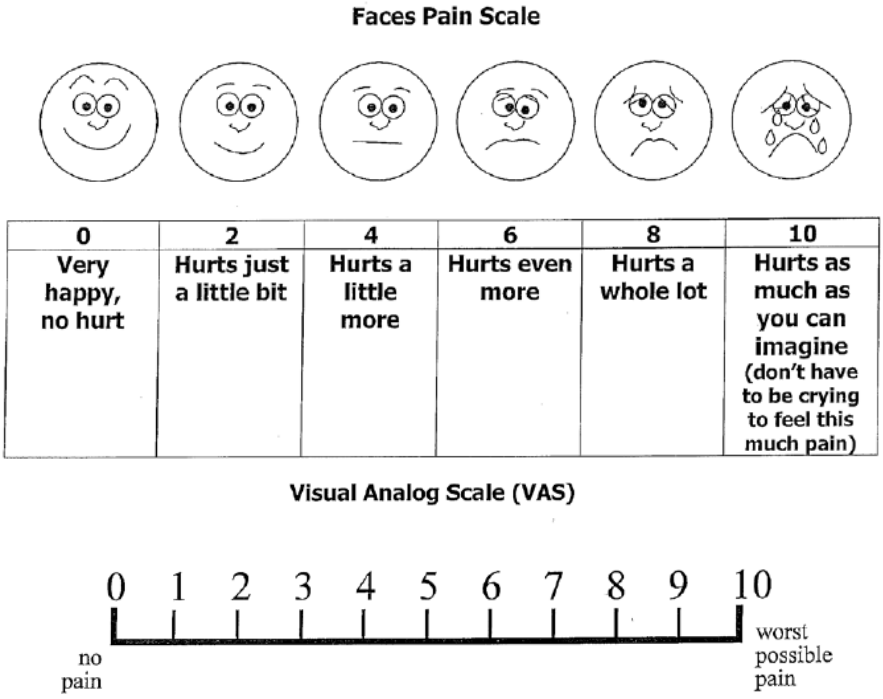
Score	Severity	Erythema
0	None/Absent	No redness
1	Slight	Faint red or pink coloration, barely perceptible
2	Mild	Light red or pink coloration
3	Moderate	Medium red coloration
4	Severe	Beet red coloration

Source: STF115469 Clinical Study Report Table 1 page 45

The timepoints for the conduct of assessment of erythema and pain varied with the protocol version. Investigators conducted tolerability assessments at baseline and Week 2 in all versions of the protocol; investigators also conducted tolerability assessments at Week 4 and 8 in version 5. Overall, the majority of subjects provided responses of 0 or 1 at any timepoint.

Subjects or their caregivers evaluated pain using a 10-point visual analog scale (VAS) and/or the Faces Pain Scale. The Applicate stated that "there were no instructions used during the trial" to standardize the evaluation of pain. Generally, the Faces Pain Scale is used for children 4 to 8 years old and a VAS for children 8 years and older. Most subjects reported no pain during participation in the trial (score of 0). By the end of treatment at Week 8, only one subject in the SORILUX group (score of 10) and one subject in the vehicle group (score of 6) reported any pain.

Figure 1: Scales for the Assessment of Pain: FACES and Visual Analog Scale



Source: NDA 22563 SD 366 dated 8/7/2019

7.3.6. Safety Analyses by Demographic Subgroups

In view of the small sample size, the analysis of TEAE by demographic subgroup has limited utility. There were insufficient numbers of subjects receiving SORILUX Foam, 0.005% of non-White races to provide a meaningful comparison [African American (4/32), American Indian or Alaska Native (1/32) and other (2/32.)] As previously indicated, the majority of the subjects were in the 7 to 11-year age group (31 subjects), only 5 subjects were in the 4 to 6-year-old age group. Therefore, this review will not address adverse events by race and age.

A greater proportion of female subjects (65%, 17/32) reported AEs than male subjects (53%, 15/32). The distribution of AEs by SOC was similar for males and females except for Skin and subcutaneous tissue disorders in which females reported a greater number of events.

7.3.7. Supportive Safety Data From Other Clinical Trials

120-Day Safety Update

In the 120-day safety update report (SUR), the Applicant provided no new safety information that would inform labeling (SDN 367 dated 8/23/2019).

7.3.8. Safety in the Postmarket Setting

Expectations on Safety in the Postmarket Setting

The analysis of the safety data from Trial STF115469 identified no additional safety signals in the population ages 4 to 11 years.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

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

7.4.2. Conclusions and Recommendations

In this supplement, the Applicant submitted results from Trial STF115469 to provide safety and bioavailability data for SORILUX Foam, 0.005% for the treatment of pediatric subjects age 4 years to 11 years with plaque psoriasis of the scalp and body. The Applicant intended to submit data from 75 evaluable subjects, 50 subjects in a “general use” cohort [mild (2) or moderate (3) on ISGA] and 25 subjects in a “maximum use” cohort [≥ moderate (3) on ISGA with ≥3% BSA affected]. When multiple revisions to the study design and modifications to the study population, did not result in timely completion of the trial, the FDA agreed to review the available data from 36 pediatric subjects with mild to moderate plaque psoriasis.

There were no deaths, serious adverse events (SAEs) or AEs assessed as severe. Of the six subjects who discontinued treatment, five subjects experienced adverse events [worsening of psoriasis (3 subjects), application site pain (1 subject), contact dermatitis (2 subjects). A total of six subjects experienced seven TEAEs that were considered to be related to the use of SORILUX Foam, 0.005% [psoriasis (three events), application site pain (two events) and contact dermatitis (two events)].

All analyzed pharmacokinetic (PK) samples were below the limit of quantitation. Despite the variability in the parameters associated with the effects of SORILUX Foam, 0.005% on calcium metabolism, there were no clinically meaningful changes in laboratory parameters. The review team identified no new safety issues associated with the use of SORILUX Foam, 0.005% in this pediatric population. The trial did not evaluate efficacy which was extrapolated from the adult population.

Although the data were limited, the safety of the moiety is well characterized and the safety evaluation of the drug product in another pediatric subgroup age 12 to 17 years demonstrated no new safety concerns. The size of the safety database and the safety evaluations were sufficient to identify local and systemic treatment-emergent adverse reactions. The submitted PK, PD and safety data support approval of this sNDA which provides for the use of SORILUX Foam, 0.005% for the topical treatment of plaque psoriasis of the scalp and body in patients 4 years and older.

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 STF115469 to address the required assessment under PREA and support the use of SORILUX Foam, 0.005% in the target pediatric population with mild to moderate plaque psoriasis.

The Pediatric Review Committee (PeRC) and the Division discussed whether there was sufficient data in this supplement and for the moiety to support the use of SORILUX Foam, 0.005% in patients 4 years and older. In view of the lack of any postmarketing safety signals in

the population 2 to 4 years of age, PeRC suggested labeling SORILUX Foam, 0.005% for use in patients 2 years of age and older. However, PeRC emphasized that this recommendation was based on extensive experience with this particular class of products and should not be extrapolated to other applications. PeRC agreed with the Division that PREA PMR was fulfilled and the data were sufficient to support amended labeling (PeRC Meeting 8/28/2019).

The review team acknowledged that there is an unmet medical need for an approved product for the treatment of plaque psoriasis in the population ages 2 to 4 years of age. The extrapolation of efficacy in this population from adequate and well controlled adult studies is reasonable based on a similar pathophysiology and response to treatment. Although the data are not available for SORILUX Foam, the systemic exposure to calcipotriene is likely to be low. Per labeling of calcipotriene ointment, studies with radio-labeled ointment indicated absorption of approximately 6% (±3%, SD) following topical application to psoriasis plaques or 5% (±2.6%, SD) following topical application to normal skin. Much of the absorbed active drug is converted to inactive metabolites within 24 hours of application. Thus, the likelihood of systemic adverse events in this population appears low.

However, as labeling is data driven, the review team concluded that the data only supported the use of SORILUX Foam, 0.005% in the population age 4 years and older. The safety data in the youngest evaluated pediatric age group (age 4 to 6 years) was sparse. The small sample size and missing PK, PD and safety information, limits generalization of the safety conclusions to children 2 to 4 years of years of age. In addition, there are inherent limitations of postmarketing data from FAERS (voluntary submission, uncertain causality, incomplete information) and the literature (incomplete information). The absence of a safety signal from postmarketing data is insufficient to support the safety in the population ages 2 to 4 years. Thus, there is inadequate information to leverage in support of a recommendation for use of SORILUX Foam, 0.005% in the population ages 2 to 4 years.

Erica Radden, M.D., the Division of Pediatric and Maternal Health (DPMH), Pediatric Team, agreed with expanding the age group for which SORILUX Foam, 0.005% is indicated. Dr. Radden concluded that "the pediatric assessment along with supportive postmarketing safety data from use of calcipotriene (and other vitamin D analogs) in pediatric patients for plaque psoriasis and other indications are adequate to support approval of SORILUX down to 4 years of age." See Division of Pediatric and Maternal Health Review dated 10/9/2019 for a discussion of the factors which supported this conclusion.

Dr. Radden provided recommendations for labeling (Sections 1, 6, 8 and 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 SORILUX Foam, 0.005% have been established in pediatric patients 4 to 11 years. To optimize access to the necessary prescribing information, the review team included the key findings in the Pediatric Use section.

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)). The Applicant will be released from the pediatric assessments in subjects 2 to 4 years old. The population of patients in this age group is small and the current off-label use and potential use of SORILUX is unknown.

10. Labeling Recommendations

10.1. Prescribing Information

The Applicant submitted proposed Prescribing Information (PI) for SORILUX Foam. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed Prescribing Information (PI) for SORILUX Foam, 0.005% and did not identify areas of vulnerability that may lead to medication errors (Review dated 7/16/2019). In addition, Buonaccorsi, Laurie, PharmD from the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the PI, PPI, and instructions for use (IFU) (Review dated 9/26/2019). She indicated that OPDP had no comments on the proposed labeling. Erica Radden, M.D. from the Division of Pediatric and Maternal Health (DPMH), reviewed the proposed labeling and provided recommendations regarding the pediatric population in accordance with 21 CFR 201.57(c)(9)(iv). Clinical comments regarding the content of labeling are integrated into the relevant sections of this review.

The members of the primary review team who provided recommendations regarding PI are tabulated below. Refer to the Reviews by Soo Hyeon Shin (dated 10/2/2019) and Erica Radden, M.D. (dated 10/9/2019). Comments from the team will be reflected in the final labeling and the approval letter.

Table 20: Reviewers Providing Labeling Comments and Location in the Document

Section	Reviewers Providing Comments & Location in This Review
1 Indications and usage	Clinical team Section: 7.4.1
6 Adverse reactions	Clinical team Section: 7.3.4; Melissa Reyes 10.1
8 Use in specific Populations	DPMH: Erica Radden (Pediatrics): 9, 10.1 Clinical Pharmacology Reviewer: Soo Hyeon Shin /Chinmay Shukla: Section 6 Clinical team 7.3.5
12 Clinical pharmacology	Clinical Pharmacology: Soo Hyeon Shin/Chinmay Shukla: Section 6

Source: Reviewer's Table

Postmarketing Experience Supplement-008

Per FDA Prior Approval Supplement Request (dated 5/6/2019), the Applicant submitted a tabulation of spontaneous postmarketing adverse event reports and proposed labeling to capture postmarketing experience information (NDA 22563 S-008; SDN 363 dated 6/26/2019). The Applicant submitted 16 cases including 2 duplicates. Among these cases, the most common preferred terms were application site erythema and application site pain (labeled events) and rash (unlabeled event). Other preferred terms reported by 1 or two patients were application site exfoliation, application site pruritus, application site papules, application site vesicles, erythema, hyperpigmentation, application site discharge and pruritus. There was one poorly documented case of hypersensitivity with insufficient detail to support a causality conclusion. There were also reports of drug ineffective, off-label use and condition aggravated. The Applicant proposed the following language for section 6.2 Postmarketing Experience:

> 6.2 Postmarketing Experience
> The following adverse reactions (b) (6) use of SORILUX have been identified post-approva (b) (6) (b) (6). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Melissa Reyes, M.D., Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance I, conducted an analysis of the submitted data and an independent review of the literature. Dr. Reyes searched the FDA Adverse Event Reporting System (FAERS) database for all reports through July 23, 2019. There were 33 unique cases of adverse events related to SORILUX Foam, 0.005% identified in FAERS or by the Applicant. The FAERS cases included 8 application site reactions [erythema, pain, reaction, discharge, exfoliation, papules, pruritus, and vesicles/blister(two cases)], of which three (application site erythema, application site pain, and application site pruritus) are included in labeling as adverse reactions. Dr. Reyes indicated that "the adverse event of application site vesiculation is not currently captured in labeling and has clinical significance." In addition, Dr. Reyes searched the medical literature from 2010 to August 7, 2019, using Embase, PubMed@FDA, Web of Science, and PharmaPendium, and identified no additional cases of adverse events associated with SORILUX Foam. Dr. Reyes concluded, "The adverse events of application site pain and application pruritus are already included in the Clinical Trials Experience subsection. The adverse events of rash and skin irritation are less specific terms and inclusion is unlikely to enhance safe use of SORILUX." Based on her review, Dr. Reyes recommended the following language for section 6.2:

> 6.2 Postmarketing Experience
> The following adverse reactions have been identified during post approval use of SORILUX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous: application site vesicles.

For a detailed discussion of these findings, refer to the consult review by Dr. Reyes dated 9/05/2019.

Other formulations of calcipotriene include warnings regarding contact dermatitis and precautions regarding transient irritation. However, the cases identified in this postmarketing analysis contained insufficient detail to support a causality assessment. (See OSE review dated 2/13/2013 and Clinical Review dated 3/1/2013.)

10.2. Patient Labeling

The Applicant submitted a proposed patient package insert (PPI) and instructions for use (IFU). Shawna Hutchins, MPH, BSN, RN from the Division of Medical Policy Programs (DMPP) and Laurie Buonaccorsi, OPDP reviewed the PPI and IFU and concluded that the proposed PPI and IFU were acceptable. Refer to the Patient Labeling Reviews by Shawna Hutchins (dated 9/25/2019) and Laurie Buonaccorsi (dated 9/26/2019).

11. Financial Disclosure

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

Table 21: Covered Clinical Study Trial STF115469

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 16		
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

Forms: FDA 3454 and Financial disclosures for all principal investigators from Appendix 16.1.4.(SDN 354 dated 4/19/2019)

Melinda McCord, M.D.
Medical Officer/Dermatology

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