Clinical Review and Evaluation

PMR Final Study Report

Application Type	sNDA: Efficacy Supplement
Application Number(s)	NDA 22563/ S-006
Priority or Standard	Standard
Submit Date(s)	July 3, 2018
Received Date(s)	July 3, 2018
PDUFA Goal Date	May 3, 2019
Division/Office	Division of Dermatology and Dental Products (DDDP)
Review Completion Date	April 10, 2019
Established Name	Calcipotriene
(Proposed) Trade Name	SORILUX Foam
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 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 Medication Error Prevention and Analysis (DMEPA) Madhuri R. Patel, PharmD (Review dated 12/17/2018)
- Division of Medical Policy Programs (DMPP): Shawna Hutchins, MPH, BSN, RN and Office of Prescription Drug Promotion (OPDP): Lynn Panholzer PharmD; Review of Patient Information and Instructions for Use (Review dated 3/11/2019)
- OPDP: Lynn Panholzer PharmD; Review of Prescribing Information (Review dated 3/13/2019)

Division of Pediatric and Maternal Health (DPMH)

- Pediatric División Consult Response: Erica Radden, M.D. (Review dated 4/9/2019; 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 2/20/2019; comments included in Section 8 of labeling)

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1. Executive Summary

The Applicant, Mayne Pharma LLC, submitted a Supplemental NDA (sNDA) to support revisions to product labeling which provided for the use of SORILUX ™ (calcipotriene) Foam, 0.005% in the population age 12 years and older. To support the changes in labeling the Applicant submitted data from Trial STF115750. The Applicant conducted Trial STF115750 to address post marketing requirement (PMR) 1944-1 under the Pediatric Research Equity Act (PREA) to evaluate the effects of SORILUX Foam on calcium metabolism and safety in the pediatric population age 12 to 16 years. In addition, the Applicant submitted proposed labeling which is compliant with the Pregnancy and Lactation Labeling Rule (PLLR).

Trial STF115750 was an open-label, pharmacokinetic and safety trial enrolling 19 subjects age 12 to 16 years with moderate plaque psoriasis of the scalp and body who were treated under maximal use conditions. 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 in this pediatric population. The trial did not evaluate efficacy which was extrapolated from the adult population.

The Applicant provided sufficient data to confirm that the risk benefit conclusions in this pediatric population are similar to the adult population. The Applicant proposed labeling which was compliant with PLLR. This reviewer recommends an approval action for this

application, NDA 22563 Supplement-006, 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 benefits and risks of SORILUX Foam for the topical treatment of plaque psoriasis of the scalp and body in patients aged 18 years and older from 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 for patients younger than 18 years of age.

In this supplement, the Applicant submitted results from Trial STF115750 to provide safety and bioavailability data for SORILUX Foam in the treatment of pediatric subjects age 12 to 16 years with plaque psoriasis of the scalp and body. A total of 19 subjects with moderate plaque psoriasis defined as an Investigator's Static Global Assessment (IGSA) scores of 3 on the scalp and body and at least 10% total body surface area (BSA) affected (excluding face and scalp) and at least 20% of the scalp affected applied SORILUX Foam twice daily for 15 days. A total of 6 subjects experience 8 adverse events (AEs). Five AEs [application site pain (2 events), application site pruritus (2 events) and pruritus (1 event)] which occurred in 3 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. As the pathophysiology of plaque psoriasis and response to treatment are the same in the adult and pediatric populations, efficacy in the population age 12 to 16 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 SORILUX Foam in the population age 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.[1] Chronic plaque psoriasis is the most common form of psoriasis in children and adults.[2] 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.[3] The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, producing proinflammatory cytokines which trigger and perpetuate the inflammatory cascade.

The prevalence of psoriasis varies by geographic region. The estimated prevalence worldwide ranges from 0 to 1.37 percent of children and 0.51 to 11.3 percent of adults.[4] 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.[5,6] 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.[7]

[1] Mallbris L et al. J Invest Dermatol. 2005 Mar;124(3):499-504.
[2] Paller AS et al. Psoriasis in children: Epidemiology, clinical manifestations, and diagnosis. UpToDate. Accessed April 5, 2019.
[3] Shah KN. Diagnosis and treatment of pediatric psoriasis: current and future. Am J Clin Dermatol. 2013;14(3):195
[4] Michalek IM et al. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017;31(2):205.
[5] Morris A et al. Childhood psoriasis: a clinical review of 1262 cases. Pediatr Dermatol. 2001;18(3):188.
[6] 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.
[7] 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

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),[8] 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. [9]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

Based on the objectives of the trial, the Applicant evaluated only clinician reported outcomes.

	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	
	□ Patient reported outcome	
	□ 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)	

[8] 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.

[9] Paller AS et al. Psoriasis in children: Management of chronic plaque psoriasis. UpToDate> Accessed April 5, 2019.

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	The patient experience data that was submitted as part of the application includes:	Section where discussed, if applicable
□	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.	

3. Regulatory Background

Stiefel, a GSK Company, developed SORILUX Foam 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 ("prior Applicant") 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. Assessments in the pediatric population age 2 years 16 years were deferred because the product was ready for approval for use in adults and the pediatric studies were not complete.

The prior Applicant submitted an efficacy supplement (S-002) to modify the indication to "the topical treatment of plaque psoriasis of the scalp and body in patients aged 18 years and older." (November 29, 2011). The Pediatric Review Committee (PeRC) (Meeting 7/18/2012), concurred with the approach to utilize two trials to meet both the existing post-marketing requirements to evaluate SORILUX Foam for the treatment of plaque psoriasis on the body as well as the current post-marketing requirements to evaluate SORILUX Foam for the treatment of plaque psoriasis on the scalp. With the extension of the indication to include plaque psoriasis of the scalp (S-002, approved September 27, 2012), the prior Applicant was released from the original postmarketing requirements (Letter dated 3/12/2013) which were replaced by the following:

> 1944-1: A Pharmacokinetics/Pharmacodynamics trial of SORILUX Foam, 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 2017

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)[10]

On December 20, 2012 the prior Applicant submitted the final version of protocol STF115750 (IND 071198 SD 71, v.6), which was intended to address postmarketing requirement 1944-1. On January 30, 2013 (NDA 22563, SD 133), the prior Applicant notified the Agency that Trial STF115750 had been initiated on January 15, 2013 in accordance with the milestone date specified in the Supplement Approval Letter (dated September 27, 2012.)

The Agency granted 3 Deferral Extension Requests (Letter dates 12/30/2014 and 2/16/2018 with verbal communication of the final extension to June 2018) based on the challenge of recruiting pediatric subjects with psoriasis of moderate severity on both the scalp and body.

The Division provided advice regarding the study population, assessments and design of Trial STF115750 during 3 Guidance Meetings, (Meeting Minutes dated 6/20/2011, 6/30/2015 and 7/14/2017) with Stiefel and the current Applicant, Mayne Pharma LLC (acquisition January 2017). Division recommended that the trial enroll subjects with moderate psoriasis (Investigator's Static Global Assessment [ISGA] of 3) and at least 20% body surface area (BSA) with an adequate number of subjects across the lowest age range. Although the target sample size was 20 evaluable pediatric subjects per PMR 1944-1, the Division agreed that that data on 16 completers was adequate to characterize the pharmacokinetics and pharmacodynamics of SORILUX Foam in this population. (Meeting Minutes dated 7/14/2017.)

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. OSI recently inspected the site (4/16/2018-4/19/2018) that enrolled the largest number of subjects (N=6). This site (Dr. Lawrence Eichenfield, listed in Table 4) received a Compliance Classification of "no deviation from regulations" (NAI).

[10] 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).

4.2. Product Quality

The Applicant determined that the formulation of SORILUX Foam which was approved for use in adult population was acceptable for use in the target pediatric populations. Therefore, the Applicant submitted no new product quality data. For the analysis of the 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, PhD. 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 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." (SD 318 dated 8/24/2018) 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 to the CMC-related sections of the Prescribing Information, Patient Information, or carton and container labeling. Dr. Hathaway states 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 10/31/2018.

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

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 determined that the bioanalytical methods to assess calcipotriene and calcium concentrations were acceptable. The Applicant used a validated liquid chromatography process followed by tandem mass spectrometric detection (LC-MS/MS) to evaluate calcipotriene concentration in plasma. To determine calcium concentrations in

serum and urine, the Applicant used a commercially available system reagent that was cleared with a 501(k) application.

6.1. Pharmacokinetics

The Applicant conducted a pharmacokinetic (PK) assessment in 17 subjects. Blood samples for assessment of calcipotriene concentration were collected on Day 1 (pre-dose) and on Day 15 (pre-dose, 1h, 2h, 3h, 4h, and 6 h) after the morning dose of study product. The mean treated body surface area excluding face and scalp was 24.1% and the mean treated scalp was 42.6%. Among the 8 subjects who missed doses on the scalp and/or body, 3 subjects missed ≥14 doses on the scalp. All analyzed samples had calcipotriene concentrations below the limit of quantification (LOQ, 10 pg/mL).

The Clinical Pharmacology Reviewer, Soo Hyeon Shin, Pharm.D., Ph.D. concluded that

> "*Given that the bioanalytical method was reasonably sensitive with the LOQ in the sub-nanomolar range (10 pg/mL =0.023 nM), it appears that the systemic absorption of calcipotriene from SORILUX in adolescent subjects is minimal… Although several subjects reported missed dose(s), the available data include two subjects aged 12, the youngest age from the study population, under the agreed-upon maximal-use conditions... Overall, the submitted PK data in terms of quality and quantity appear acceptable."* (Review dated 3/29/2019)

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 levels of albumin adjusted serum calcium, iPTH, alkaline phosphatase, magnesium, phosphorus, and calcium/creatinine ratio on Day 1, Day 15 and Day 22 (when available). In 18 subjects with evaluable data, the Applicant assessed the relative change from Baseline to Day 15/22 by calculating geometric mean ratios. The Clinical Pharmacology Reviewer, Soo Hyeon Shin, Pharm.D., Ph.D., indicated that the majority of the geometric mean ratios were close to 1 and within the 90% confidence interval.[11] In view of the small sample size, parameters characterized by a high degree of variability, such as iPTH and phosphorous, had geometric mean ratios which deviated from 1. Dr. Shin concluded that "There was no significant effect on indices of calcium metabolism." (Review dated 3/29/2019)

The Clinical Pharmacology Reviewer indicated that Trial STF115750 "*provides sufficient evidence to conclude fulfillment of the PMR."*

[11] Although the geometric mean ratio (Day 15/Day 1) of calcium/creatinine was slightly higher than 1 (1.27), urinary calcium excretion is highly variable from a spot urine sample. Jones AN, et al. Fasting and postprandial spot urine calcium-to-creatinine ratios do not detect hypercalciuria. Osteoporosis Int. 2012;23(2):553-62.

The results of the pharmacodynamic assessments will be incorporated into Section 8.4 *Pediatric Use* and 12.2 *Pharmacodynamics* of the PI. Refer to the Clinical Pharmacology Review by Dr. Shin (dated 3/29/2019) for detailed labeling comments.

7. Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

To address PMR 1944-1 and support the indication for patients 12 years and older with plaque psoriasis of the scalp and body, the Applicant conducted a single, open-label Phase 1 trial (STF115750) entitled, *"A Phase 1, Open Label, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacodynamics, Pharmacokinetics of Calcipotriene Foam, 0.005%, Applied under Maximal-Use Conditions in Adolescent Subjects (Ages 12 to 16 Years) with Plaque Psoriasis."* The trial is tabulated and summarized below.

Table 1: Clinical Trial STF115750

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							
STF115750 Conducted 4/2012-8/2015	Multicenter, open-label, repeat-dose safety, PK and PD	Twice daily X 14 days, 1 X on Day 15	PD: effect of SORILUX Foam on calcium metabolism PK Safety: AEs, VS, local tolerability	2 weeks and 7- day follow up	19	Moderate plaque psoriasis with ≥20% scalp and ≥10% BSA affected age 12 to 16 years	9 sites in U.S.

Abbreviations: PK = pharmacokinetic; PD = pharmacodynamic; AE = adverse event; 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 SORILUX Foam 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[12], efficacy in the population age 12 to 16 years was extrapolated from data in the adult population.

[12] UpToDate *Psoriasis in children: Epidemiology, clinical manifestations, and diagnosis & Management of chronic plaque psoriasis* accessed 3/20/2019

Data Sources
The sources of data used for the evaluation of the efficacy and safety of SORILUX Foam for the proposed indication included final study report submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] 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\NDA 022563\022563.enx

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

7.2. Review of Relevant Trial

7.2.1. Study Design and Endpoints

Clinical Trial STF115750

Study Population
The key entry criteria that defined the study population are as follows:

Key inclusion criteria:
- Male or female subjects, ages 12 to 16 years, inclusive, at the time of consent.
- Plaque psoriasis involving at least 10% total BSA (excluding the face and scalp).
- Plaque psoriasis with at least 20% scalp involvement
- Clinical diagnosis of moderate plaque psoriasis, as defined by an ISGA score at Screening of 3 on a scale of 0 to 4.

Key exclusion criteria:
- Current diagnosis of unstable forms of psoriasis in the treatment area, including guttate, erythrodermic, exfoliative, or pustular psoriasis
- 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 enrolment.
- 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.

Study Design

Trial STF115750 was a multicenter, open-label, repeat-dose trial to evaluate the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of SORILUX Foam, 0.005%, in subjects age 12 to 16 years with moderate plaque psoriasis. After confirmation of eligibility, investigational staff identified treatment sites and instructed subjects to apply a thin layer of SORILUX Foam with gentle message twice daily. Investigational staff instructed subjects/caregivers to apply SORILUX Foam to any new lesions and all prespecified lesions, even those which cleared with treatment. The dose applied was "a sufficient amount of the drug product to cover all areas affected with psoriasis." After the first supervised administration of the study product, subjects applied 27 doses at home. Investigational staff applied the final dose on Day 15.

During Trial STF115750, investigators conducted an evaluation of PK, PD, safety, disease severity and compliance. Investigators performed PK and PD assessments prior to treatment and on Day 15. Safety monitoring included adverse events, local safety assessments, concomitant medications, and laboratory parameters to evaluate the effects of SORILUX Foam on calcium metabolism (serum albumin, calcium, intact parathyroid hormone (iPTH), alkaline phosphatase, magnesium, phosphorus, Baseline Serum 25-OH vitamin D concentrations and urinary calcium and creatinine). Investigators documented disease severity and body surface area (BSA) at screening and during the treatment period. To assess compliance, study personnel documented the weight of the study product containers when dispensed and returned and reviewed logs of the number of applications completed by each subject.

Concomitant Medications

Permitted concomitant medications included stable use of inhaled/intranasal corticosteroids and treatments for other medical conditions, sunscreens on non- treatment areas and emollients. Washout periods prior to first application of the study product are tabulated below:

Table 2: Prohibited Products

Product	Washout period prior to first application of study product
Use of topical products to affected areas, sunscreen, moisturizers, creams, ointments, lotions, and powders	48 hours
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. alefacept, etanercept, efalizumab)	4 weeks
Phototherapy (UVA, 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

Source: Clinical Study Report for STF 115750, Table 5

Objectives and Related Endpoints

The endpoints and related objectives are tabulated below.

Table 3: Objectives and Endpoints

Objectives	Endpoints
Primary Objective (Pharmacodynamic)	**Primary Endpoints (Pharmacodynamic)**
• The primary objective of this study is to evaluate the PD effect of calcipotriene foam, 0.005%, on calcium metabolism under maximal-use conditions in adolescent subjects (ages 12 to 16 years, inclusive) with moderate plaque psoriasis	• Relative change from Day1 to Day15 (Day 15/Day 1 ratio) of: Albumin adjusted serum calcium Intact parathyroid hormone (iPTH) Alkaline phosphatase Magnesium Phosphorus Urinary calcium/creatinine ratio (Day 15 minus Day 1) • Day 22/Day 15 and Day 22/Day 1 ratios of these PD endpoints will only be evaluated if at least 30% of the subjects have abnormal result at Day 15.

Objectives	Endpoints
Secondary Objectives (Safety)	**Secondary Endpoints (Safety)**
• To evaluate the safety of calcipotriene foam, 0.005%, in adolescent subjects (ages 12 to 16 years, inclusive) with moderate plaque psoriasis.	• Adverse events • Clinical laboratory test results • Vital signs • Concomitant medications
Secondary Objective (Tolerability)	**Secondary Endpoints (Tolerability)**
• To evaluate local tolerability at application area.	• Investigator assessment of erythema • Subject assessment of pain
Secondary Objective (PK)	**Secondary Endpoints (PK)**
• To determine the pharmacokinetics of calcipotriene foam, 0.005%, in adolescent subjects (ages 12 to 16 years, inclusive) with moderate plaque psoriasis.	• Plasma concentrations of calcipotriene
Other Objectives (Other)	**Other Endpoints (Other)**
• To establish baseline disease state and to evaluate changes in Investigator Static Global Assessment (ISGA) score • To evaluate changes in extent of psoriatic involvement	• ISGA (Body) • ISGA (Scalp) • Extent of psoriatic involvement

Source: Clinical Study Report for STF 115750, Table 2

Investigator(s)

There were 9 participating study sites in the United States. Of these, 8 study sites enrolled subjects as tabulated below.

Table 4: Study Sites and Enrollment

Site Number	Site Name	Principal Investigator	Site Address	Subjects Enrolled (N)
097957	Derm Research, LLC	Leon Kircik, MD	1169 Eastern Parkway Suite 2310 Louisville, KY 40217	1 (5%)*
098745	Dawes Fretzin Clinical Research Group, LLC	Dawes, Kenneth W.	8103 Clearvista Parkway Suite 260 Indianapolis, IN 46256	0 (0%)
098893	Paddington Testing Company Inc	Parish, Lawrence C.	1845 Walnut Street Suite 1650 Philadelphia, PA 19103	5 (26%)
099146	Ameriderm Research	Solomon, James A.	725 West Granada Blvd Suite 44 Ormond Beach, FL 32174	1 (5%)
099147	Pediatric & Adolescent Dermatology	Eichenfield, Lawrence E.	8010 Frost Street Suite 602 San Diego, CA 92123	6 (32%)
099222	U of Texas Houston Medical School	Hebert, Adelaide A	6655 Travis Street Suite 600 Houston, TX 77030	2 (11%)

Site Number	Site Name	Principal Investigator	Site Address	Subjects Enrolled (N)
099328	Northwestern University	Paller, Amy	676 N. Saint Clair St. Suite 1200 Chicago, IL 60611	2 (11%)
099583	Academic Alliance in Dermatology	Vasiloudes, Panos	4238 W Kennedy Blvd Tampa, FL 33609	1 (5%)*
212694	Marietta Derm Clinical Research Inc	Espy, Paul D.	111 Marble Mill Road Marietta, GA 30060	1 (5%)

Subjects were enrolled prior to the final protocol (subject (b) (6) and (b) (6) and did not apply drug to the scalp and do not have PK).
Source: Reviewer's Table with data from Final Study Report Appendix 16.1.4

Table 5: Schedule of Assessments

Parameter	Screening	Treatment Period			Follow-up
	Visit 1 Day -14 to -1	Visit 2 Day 1	Visit 3 Day 8 (by phone)	Visit 4/ET Day 15[a]	Visit 5 Day 22 (±1 day)
Written informed consent/assent	X				
Signed HIPAA authorization form	X				
Inclusion/exclusion criteria	X	X			
Demographics	X				
Medical history/review of systems	X				
Vital sign measurements: temperature, BP, pulse	X	X		X	X
Height and weight measurement	X				
Complete skin examination (% BSA involvement)[b]	X	X		X	
Prior/concomitant medications query[c]	X	X	X[d]	X	X
Urine drug screen[e]	X				
Urine sampling for calcium/creatinine ratio		X		X	
Urine pregnancy test[f]	X	X		X	

Source: Clinical Study Report for STF 115750, Table 6

Data Analysis

Safety population, which was used to analyze tolerability and safety, consists of subjects who received at least one application of study product. PD population comprised subjects in the Safety population who provided at least one blood sample on Day 1 and Day 15 for albumin-adjusted serum calcium PD assessments. The PK population comprised subjects in Safety population who provided at least 1 blood sample for PK assessment after dosing. PD and PK populations excluded subjects with important protocol deviations.

Protocol Amendments

There were 6 versions of the Protocol STF 115750. The Applicant submitted all versions to the Division for review. Key amendments to the final versions of the protocol included: increasing the number of study sites to expedite enrollment; clarifying the percent of affected body surface area (BSA) required for entry into the trial (at least 10% of the body and 20% of the scalp); removing the maximal total BSA to be treated; enrolling only subjects graded as

"moderate" on the Investigator's Static Global Assessments (ISGA); excluding subjects with both low and high albumin-adjusted serum calcium at Screening; conducting local tolerability assessments; permitting discontinuation from the trial due to pain; adding a follow-up assessment for ongoing AEs on Day 22; and including in the protocol a specific cardiovascular event collection tool.

7.2.2. Results of Efficacy Assessment

There was no formal efficacy assessment. As the pathophysiology of plaque psoriasis and response to treatment are the similar in the pediatric and adult populations, efficacy in the pediatric population was extrapolated from the adult population. [13]Per protocol, the investigators documented separate ISGA scores for the scalp and body at Baseline and Day 15 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

The results support a trend toward improvement of psoriasis severity of both the scalp and body according to ISGA during the trial. At Baseline, the majority of subjects had moderate (Grade 3) psoriasis of the scalp (17/18, 94%); while at Day 15, less than 50% (7/18, 44%) had moderate (Grade 3) psoriasis of the scalp. At Baseline, all subjects (19/19, 100%) had moderate psoriasis of the body; while at Day 15, less than 60% (11/19, 57.9%) had moderate psoriasis of the body.

Table 7: Investigator's Static Global Assessment Scores

Anatomical Site	No. (%) of Subjects				
Visit	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ISGA: Body					
Baseline (Day 1)	0 (0.0%)	0 (0.0%)	0 (0.0%)	19 (100.0%)	0 (0.0%)
Day 15	0 (0.0%)	2 (10.5%)	6 (31.6%)	11 (57.9%)	0 (0.0%)
ISGA: Scalp					
Baseline (Day 1)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (94.4%)	1 (5.6%)
Day 15	0 (0.0%)	3 (16.7%)	7 (38.9%)	8 (44.4%)	0 (0.0%)

Source: Adapted from Table 37 Clinical Study Report STF 115750

[13] Dunne J et al. Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs. *Pediatrics* 2011;128: e1242–e1249

7.3. Review of Safety

7.3.1. Safety Review Approach

The review of the safety of SORILUX Foam in the pediatric population age 12 to 16 years focused on data from a single trial, STF 115750. The analyses included treatment emergent adverse events (TEAEs), serious AEs (SAEs), AEs leading to discontinuation, adverse reactions (ARs) and AEs associated with the product class, vitamin D analogs.

7.3.2. Review of the Safety Database

Exposure

Extent of Exposure

All 19 subjects received SORILUX Foam for 15 days. Most of the subjects achieved full compliance with the twice daily dosing instructions for the study product (total of 29 doses). However, a greater percentage of subjects were compliant with dosing of the study product to the body (99%) than to the scalp (85%). A total of 7 subjects missed both morning and evening doses to the scalp. Two subjects missed a dose to the body in the morning and 3 subjects missed a dose to the body in the evening.

Table 8: Extent of Exposure (N=19)

Statistic	Amount of Product Used (g)	Average Dose (g)	No. of Doses Applied to Scalp	No. of Doses Applied to Body
Mean (SD)	144.9 (113.0)	5.0 (3.9)	24.7 (8.2)	28.7 (0.6)
Median	116.9	4.2	29.0	29.0
Range	63.7, 556.0	2.2, 19.2	0.0, 29.0	27.0, 29.0

Source: Adapted form Table 18 Clinical Study Report for STF 115750

Characteristics of the Safety Population

Demographic and Baseline Characteristics

Most of the subjects were female (53%), White (63%), not Hispanic/Latino and in the age group 14 to 16 years (mean 14.4 years). The mean and median ISGA score for the body and scalp at screening was 3 (moderate on a 4- point scale). All subjects had a history of psoriasis with a disease duration ranging from 0.3 to 13.2 years from diagnosis (mean 5.1 years, median 4.3 years). At Baseline, the mean percent body surface (body and scalp) involved with psoriasis was 26% (median 23%) while the mean percent of the scalp involvement was 43% (median 30%).

Table 9: Demographic and Baseline Characteristics

Characteristics	Statistics	Subjects/Results N=19
Sex [n (%)]	F	10 (53%)
	M	9 (47%)
Age Cat 12-13 [n (%)]	≥12 years and ≤13	5 (26%)
Age Cat 14-16 [n (%)]	≥14 years and ≤16	14 74%)
Age (years)		
	Mean (SD)	14.4
	Median	14.0

Characteristics	Statistics	Subjects/Results N=19
	Minimum/Maximum	12/16
Race [n (%)]	White	12 (63%)
	Black /African American	4 (21%)
	Asian	2 (11%)
	Other	1 (5%)
Ethnicity [n (%)]	Hispanic/Latino	6 (32%)
	Not Hispanic/Latino	13 (68%)
Total BSA [cm^2]		N=19
	Mean (SD)	18245.3 (3317.13)
	Median	18112.8
	Minimum/Maximum	14434.4/25537.7
Height (cm)		N=19
	Mean (SD)	165.3 (6.81)
	Median	163.5
	Minimum/Maximum	154.9/ 181.6
Weight (kg)		N=19
	Mean (SD)	74.1 (25.47)
	Median	67.1
	Minimum/Maximum	47.0/ 129.3
BSA (%) (Body + Scalp)		N=19
	Mean (SD)	26.0 (12.3)
	Median	22.7
	Minimum/Maximum	11.8/56
Screening Body ISGA Score		N=19
	Mean (SD)	3.0 (0.00)
	Median	3.0
	Minimum/Maximum	3.0/ 3.0
Screening Scalp ISGA Score		N=17
	Mean (SD)	2.8 (0.39)
	Median	3.0
	Minimum/Maximum	2.0/ 3.0

Abbreviations: BSA = body surface area; SD = standard deviation; ISGA = Investigator's Static Global Assessment
Source: Adapted form Table 16 Clinical Study Report for STF 115750

Concomitant Medications at Baseline

The Applicant coded concomitant medications according to WHODRUG (Q1 2017 Release). A total of 14 (74%) subjects used 42 concomitant medications. The most common class of medications was "topical dermatologicals". In this class, the most frequently reported products were corticosteroids [e.g. Clobetasol propionate (5/19, 26%), and fluocinonide (2/19, 11%)] and calcipotriol (4/19, 21%). Other classes of concomitant medications included systemic anti-infectives, alimentary tract and metabolism (e.g. vitamins), genitourinary and sex hormones and nervous system drugs.

Disposition
A total of 19 subjects enrolled and completed assessments through Day 15 and 1 subject was lost to follow up on Day 22.

Protocol Deviations
Per Applicant, no protocol deviations resulted in exclusion of subjects from the safety population. However, the 2 subjects who enrolled prior to the last amendment of the protocol, did not have scalp involvement and did not participate in PK sampling (14-year-old female subject (b) (6); 15-year-old male subject (b) (6)). Other protocol deviations related to improper consenting (16-year-old male subject (b) (6)), multiple missed scalp applications (15-year-old female subject (b) (6)) and use of "demo" canisters and investigational product canisters (12-year-old male (b) (6). The key protocol deviations are summarized below.

Table 10: Protocol Deviations Occurring in ≥1 Subject

Deviation	No. (%) of Subjects
Any deviation occurring in ≥1 subject	13 (68.4%)
Product issues	10 (52.6%)
Informed consent issues	5 (26.3)
Laboratory issues	4 (21.1%)
Out of visit window	3 (15.8)
Inadequate source documents	1 (5.3%)
Other	1 (5.3%)

Source: Adapted form Table 14 Clinical Study Report for STF 115750

Adequacy of the Safety Database
The total subject exposure to SORILUX Foam applied twice daily for 15 days, provides adequate data for the evaluation of pharmacokinetics and safety. The demographics of the study population are sufficiently representative of the target population. Therefore, the safety database presented by the Applicant is sufficient to characterize the pharmacokinetics, pharmacodynamics and safety profile of SORILUX Foam for the treatment of plaque psoriasis in the pediatric population age 12 16 years.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
Overall, the quality of the data submitted is adequate to characterize the safety of SORILUX Foam applied twice daily for 14 days and once on Day 15. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events
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 adverse events (AEs) using MedDRA, version 20.1. 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 (TEAE) or treatment emergent adverse reactions (AR). The focus of this review is TEAE and AR 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 ICH and EU 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
Throughout the treatment period and a 7-day follow-up period, investigators monitored adverse events, concomitant medications, local safety and effects on calcium metabolism. The laboratory and pharmacokinetic assessments occurred at Screening and on Day 1 (before the first dose), Day 15 (3 to 9 hours after dosing), and on Day 22 if the results from Day 15 showed any abnormalities. 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.

Investigators performed no formal efficacy assessments but documented ISGA scores at the Screening, Day 1, and Day 15.

7.3.4. Safety Results

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

Adverse Events
One subject (1/19, 5.3%) reported a "pre-therapy" AE, viral gastroenteritis (Subject (b) (6)) which was graded as mild in severity and did not result in changes in product administration. Most TEAEs were in the General disorders and administration site conditions system organ class (SOC) (3/19 subjects, 15.8%). The remaining TEAEs were in Infections and infestations SOC, Respiratory, thoracic and mediastinal disorders SOC and the Skin and subcutaneous tissue disorders SOC (1/19 subjects, 5.3% each).

A total of 6 subjects experience 8 AEs. These AEs are tabulated below by system organ class and preferred term.

Table 11: Treatment Emergent Adverse Events

System Organ Class Preferred Term	Number of Subjects	Number of TEAEs
Overall	6 (31.6%)	8
General disorders and administration site conditions	3 (15.8%)	5
Application site pain	1 (5.3%)	2
Application site pruritus	2 (10.5%)	2
Vessel puncture site pain	1 (5.3%)	1
Infections and infestations	1 (5.3%)	1
Ear infection	1 (5.3%)	1
Respiratory, thoracic and mediastinal disorders	1 (5.3%)	1
Nasal congestion	1 (5.3%)	1
Skin and subcutaneous tissue disorders	1 (5.3%)	1
Pruritus	1 (5.3%)	1

Source: Adapted form Table 29: Summary of Adverse Events by Treatment Period, (page 53)

Adverse Reactions

Investigators assessed 5 AEs which occurred in 3 subjects as related to the study product. The adverse reactions are tabulated below.

Table 12: Drug-Related Treatment Emergent Adverse Events (Adverse Reactions)

System Organ Class Preferred Term	Subjects	Events
Overall	3 (16%)	5
General disorders and administration site conditions	2 (11%)	4
Application site pain	1 (5.3%)	2
Application site pruritus	2 (11%)	2
Skin and subcutaneous tissue disorders	1 (5.3%)	1
Pruritus	1 (5.3%)	1

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

Section 6.1 *Clinical Trials Experience* of SORILUX Foam labeling will include the adverse reactions of application site pain, application site pruritus and pruritus which were observed in adolescent subjects under the conditions of this trial.

Laboratory Findings

See Analysis of Submission-Specific Safety Issues for the discussion of the 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 (ECGs) and QT

The Applicant did not conduct ECG monitoring during Trial STF 115750. 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 to

submit data from 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.[14] Calcipotriene, the active ingredient in SORILUX Foam 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.

Effects on Calcium Metabolism
To evaluate the effects of SORILUX Foam on calcium metabolism, the Applicant analyzed albumin adjusted serum calcium, iPTH, alkaline phosphatase, magnesium, and phosphorus and the urine calcium/creatinine ratio under maximal use conditions. Examination of shift tables for laboratory values demonstrated no clinically meaningful changes from Baseline. At Baseline 18/19 (95%), subjects had normal calcium levels and 1 (5%) subject had an elevated calcium level. On Day 15 and 22, all subjects had normal calcium levels. Corrected calcium was normal for all subjects at all timepoints. Calcium/creatinine ratios were normal for all subjects at Baseline; at Day 15, 1 (5%) subject had an elevated value and 1 (5%) subject had a low value. At Baseline, 14/17 (82%) subjects had low 25-OH Vitamin D levels while 3/17 (18%) had normal levels.

Under the conditions of this trial, SORILUX Foam use produced no significant effects on indices of calcium metabolism. These results and conclusions will be conveyed to the prescriber in Section 8.4 *Pediatric Use* and 12.2 *Pharmacodynamics* of the Prescribing Information (PI).

Local Tolerability
Investigators evaluated erythema and pain as the primary measures of tolerability to calcipotriene Foam during the trial. Erythema assessments were based on a 4- point scale [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.] The mean tolerability at baseline was 1.1 (min: 0 and max: 3) and the mean tolerability at Day 15 was 1.4 (min: 0 and max: 3). Faint red or pink coloration was slightly more evident at Day 15 than Baseline.

[14] Holick MF. Vitamin D Deficiency. N Engl J Med 2007; 357:266-281.

Investigators evaluated pain using a 10- point numerical rating scale (NRS). In the majority of subjects, pain decreased during the trial as presented below. By Day15, 13/16 (81.3%) subjects report no pain.

Table 13: Subject Pain Assessment Scores With Exposure to Calcipotriene Foam, 0.005%

Pain Score	Baseline (Day 1) (N=17)	Day 8 (N=17)	Day 15 (N=16)
0	4 (23.5%)	8 (47.1%)	13 (81.3%)
1	4 (23.5%)	3 (17.6%)	0 (0.0%)
2	3 (17.6%)	2 (11.8%)	1 (6.3%)
3	1 (5.9%)	1 (5.9%)	2 (12.5%)
4	1 (5.9%)	1 (5.9%)	0 (0.0%)
5	2 (11.8%)	1 (5.9%)	0 (0.0%)
6	2 (11.8%)	0 (0.0%)	0 (0.0%)
7	0 (0.0%)	1 (5.9%)	0 (0.0%)
8	0 (0.0%)	0 (0.0%)	0 (0.0%)
9	0 (0.0%)	0 (0.0%)	0 (0.0%)
10	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Adapted from Table 36 Clinical Study Report STF 115750

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. However, greater number of female subjects (40%) reported TEAEs than male subjects (22%). Only White subjects reported any TEAEs.

Table 14: Treatment Emergent Adverse Events by Sex

System Organ Class Preferred Term	Females		Males	
	Subjects	Events	Subjects	Events
Overall	4 (40%)	6	2 (22%)	2
General disorders and administration site conditions	2 (20%)	4	1 11%)	1
Application site pain	1 (10%)	2	0 (0.0%)	0
Application site pruritus	2 (20%)	2	0 (0.0%)	0
Vessel puncture site pain	0 (0.0%)	0	1 (11%)	1
Infections and infestations	1 (10%)	1	0 (0.0%)	0
Ear infection	1 (10%)	1	0 (0.0%)	0
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	0	1 (11%)	1
Nasal congestion	0 (0.0%)	0	1 (11%)	1
Skin and subcutaneous tissue disorders	1 (10%)	1	0 (0.0%)	0
Pruritus	1 (10%)	1	0 (0.0%)	0

Source: Adapted from Table 30, Clinical Study Report for STF 115750

Table 15: Adverse Events by Race

Treatment Emergent Adverse Events System Organ Class Preferred Term	White N=12 Subjects / Events	Black/ African American N=4 Subjects/ Events	Asian N=2 Subjects/ Events	Other N=1 Subjects/ Events
	N (%)/ n	N (%)/ n	N (%)/ n	N (%)/ n
Overall	6 (50%) 8	0 (0.0%) 0	0 (0.0%) 0	0
General disorders and administration site conditions	3 (25%) 5	0 (0.0%) 0	0 (0.0%) 0	0
Application site pain	1 (8.3%) 2	0 (0.0%) 0	0 (0.0%) 0	0
Application site pruritus	2 (17%) 2	0 (0.0%) 0	0 (0.0%) 0	0
Vessel puncture site pain	1 (8.3%) 1	0 (0.0%) 0		
Infections and infestations	1 (8.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0
Ear infection	1 (8.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0
Respiratory, thoracic and mediastinal disorders	1 (8.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0
Nasal congestion	1 (8.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0
Skin and subcutaneous tissue disorders	1 (8.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0
Pruritus	1 (8.3%) 1	0 (0.0%) 0	0 (0.0%) 0	0

Source: Adapted from Table 31; Clinical Study Report STF 115750

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 a summary of the data from Trial STF115469 (15 subjects from version 7 of the protocol) as the only new available safety information. Trial STF115469 was a multicenter, open-label, Phase 1 trial to evaluate the safety, PK and PD of SORILUX Foam applied twice daily for 8 weeks in pediatric subjects age 2 to 11 years. The majority of these subjects were White (87%), Hispanic/Latino (53%) and male (67%) with a mean age of 9 years old (range 7-11 years). There were no deaths or serious adverse events (SAEs). A total of 3 subjects discontinued treatment due to adverse events (AE)

(i.e., one subject due to pain after application and psoriasis aggravated; one subject due to contact dermatitis, exposure to poison ivy, and a sore throat; and one subject due to contact dermatitis). Overall, 5 subjects reported 11 AE (traffic accident, upper limb fracture, ear infection, oropharyngeal pain and upper respiratory infection) which were assessed as unlikely to be related. The results of the tolerability assessments showed a decrease in erythema and pain with treatment. There were no clinically meaningful changes from Baseline in vital signs or laboratory assessments. The data indicated no new safety signals.

7.3.8. Safety in the Postmarket Setting

Expectations on Safety in the Postmarket Setting
The analysis of the SORILUX Foam safety data identified no additional safety signals in the population age 12 to 16 years.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

There were no statistical issues affecting overall conclusions.

7.4.2. Conclusions and Recommendations

To establish the safety of SORILUX Foam in the pediatric population age 12 to 16 years and address PMR 1944-1, the Applicant conducted Trial STF115750. This was an open-label, pharmacokinetic and safety trial enrolling 19 subjects with moderate plaque psoriasis who were treated under maximal use conditions. 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 in this pediatric population. The trial did not evaluate efficacy which was extrapolated from the adult population.

The Applicant assessed the safety of SORILUX Foam in the target pediatric population. 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 for the topical treatment of plaque psoriasis of the scalp and body in patients 12 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

In Trial STF115750, the Applicant evaluated the pharmacokinetics and safety of SORILUX Foam in the target pediatric population with mild to moderate plaque psoriasis. The Pediatric Review Committee (PeRC) agreed with the Division that this assessment was sufficient to address PMR 1944-1 and support labeling (PeRC Meeting 1/30/2019.) The DPMH Reviewer, Erica Radden, M.D., supported the decision to revise the indication to include the use of the product in the adolescent population (Review dated 4/9/2019). A description of the trial and results will be included in Sections 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 have been established in pediatric patients 12 years and older.

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) 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 and did not identify areas of vulnerability that may lead to medication errors (Review dated 12/17/2018). In addition, Lynn Panholzer, PharmD from the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the PI (Review dated 3/13/2019). She raised concerns about lack of data to support statements of low risk of adverse pregnancy outcomes and comparison of safety profiles in adults and adolescents. 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 Jane Liedtka (dated 2/20/2019), Soo Hyeon Shin (dated 3/28/2019) and Erica Radden, M.D. (dated 4/09/2019). Comments from the team will be reflected in the final labeling and the approval letter.

Table 16: 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
8 Use in specific populations	DPMH: Erica Radden (Pediatrics): 9, 10.1 Jane Liedtka (Maternal Health) Section: 10.1 Pharmacology/Toxicology: Carmen Booker/Barbara Hill: Section 5 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 Clinical team: Section 6; 7.3.5
13 Nonclinical toxicology	Pharmacology/Toxicology: Carmen Booker/Barbara Hill: Section 5

Source: Reviewer's Table

Pregnancy and Lactation Labeling Rule (PLLR) Conversion

In this submission, the Applicant revised Section 8 *Use in Specific Populations* of SORILUX Foam labeling to comply with the Pregnancy and Lactation Labeling (PLLR) format. Support for the proposed language was based on a review of the published literature from 2014 through 2018 in EMBASE, PubMed, Google Scholar and SciFinder and cases from a Pharmacovigilance Database (SD 313 dated 8/7/2018). Jane Liedtka M.D., from the Maternal Health Division of Pediatric and Maternal Health (DPMH), provided an analysis of the submitted data, confirmation of the content of the proposal through an independent review of the literature and recommendations for labeling. For a detailed discussion of these findings, refer to the consult review by Jane Liedtka dated 2/20/2019. Carmen Booker, PhD reviewed the "Nonclinical Experience" subsections and revised the content and language to conform to current FDA practice.

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) and OPDP reviewed and provided comments on the PPI and IFU. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Shawna Hutchins, MPH, BSN, RN and Lynn Panholzer, PharmD (dated 3/11/2019.)

11. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for SORILUX Foam (FDA Form 3454). Prior to trial initiation, the 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). Principal Investigator, (b) (6),

reported significant payments of $156,240.00 in grants to fund ongoing research and $59,157.00 as honoraria for a total of $215,397.00 in 2011 (FDA Form 3455).

The current Applicant, Mayne Pharma, was not involved with the conduct of Trial STF115750 at the time of the active participation of Dr. (b) (6). However, the Applicant concluded that the requirements of 21 CFR 54 were met because the investigator enrolled (b) (6), used objective measures to evaluate the primary endpoint (changes in calcium metabolism), and received standardized training in the data collection procedures (SD 318, dated 8/24/2018)

Table 17: Covered Clinical Study STF- 115750

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9		
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): 1		
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: 1 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:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	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:	Yes ☐	No ☐ (Request explanation from Applicant) NA

Forms: FDA 3454 and 3455 submitted 2/11/2019 (SD 345)

Melinda McCord, M.D.
Medical Officer/Dermatology

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/s/

MELINDA L MCCORD
04/10/2019 09:32:36 PM

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