CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-563

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
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Division / Office	DDDP/ ODE III
Reviewer Name(s)	Melinda McCord, M.D.
Review Completion Date	September 1, 2010
Established Name	Calcipotriene Foam, 0.005%
(Proposed) Trade Name	Sorilux Foam, 0.005%
Therapeutic Class	Vitamin D Analog
Applicant	Stiefel, a GSK Company
Formulation(s)	Foam
Dosing Regimen	Twice daily for 8 weeks
Indication(s)	Psoriasis Vulgaris
Intended Population(s)	(b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of Sorilux (calcipotriene foam, 0.005%) for the topical treatment of plaque psoriasis in patients age 18 and older.

1.2 Risk Benefit Assessment

Psoriasis is a chronic inflammatory disorder with an estimated prevalence in the United States of 2%. According to Menter et al. approximately 80% of psoriasis patients have mild to moderate disease. In this population topical corticosteroids are a mainstay of treatment. However, chronic treatment with corticosteroids may be limited by local cutaneous side effects and HPA axis suppression. Calcipotriene is a Vitamin D analog which has been available in various formulations for more than 15 years. There are multiple approved products containing calcipotriene with demonstrated efficacy in well controlled trials. Treatment options such as Vitamin D analogs serve as steroid sparing agents for patients with psoriasis.[1]

The applicant conducted 2 Phase 3 vehicle controlled trials with calcipotriene foam, 0.005%. The intent to treat analysis set includes 659 subjects in Phase 3 trials. The study design is adequate to support claims of efficacy. Although trial U0267-302 demonstrates the superiority of calcipotriene foam compared to vehicle foam, trial U0267-301 fails to meet the specified efficacy criteria with a p value of 0.058. Multiple factors may have contributed to the failure to achieve statistical significance for the primary endpoint. Subjects who missed the Week 8 evaluation are considered treatment failures even if they demonstrate treatment success prior to the 8 Week evaluation. The reclassification of a single subject who was a success at Day 44 as a “treatment success” rather than a “treatment failure” due to a missed visit at Week 8 results in a p value less than 0.05. Additional data from the Phase 2 comparative trial (CAL. 201) with Dovonex Ointment supports the efficacy of the drug product.

Subgroup analysis by baseline disease severity indicates that there is no difference in treatment response between calcipotriene foam and vehicle foam for any endpoint in subjects with mild disease at baseline. In fact, subjects in trial U0267-301 with mild disease treated with vehicle foam demonstrate a higher response rate than subjects treated with calcipotriene foam. Therefore, the difference in treatment response is driven by subjects with moderate disease. This result may reflect the effect of the

1 Menter A., Korman NJ, Elmets CA et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol 2009; 60: 643-659.

emollient properties of the vehicle in subjects with mild disease compared to subjects with moderate disease or the lack of measurable effect of the active ingredient in subjects with mild disease. Since disease severity lies on a continuum without standard criteria for “mild” and “moderate” disease the differential effect may not be clinically meaningful to the practicing physician. However, the totality of the data demonstrates that calcipotriene foam is efficacious for the treatment of mild to moderate psoriasis although the treatment effect is not robust.

The safety analysis is based on all randomized subjects who received calcipotriene foam or vehicle foam in the Phase 2 trial (CAL.201) and in the Phase 3 trials. Ninety percent of 731 subjects in the pooled safety data set completed the trial. At least one adverse event (AE) was reported by 17% of subjects in the calcipotriene group and 21% in the vehicle foam group. The most common adverse events (AEs) are application site irritation and nasopharyngitis reported by 2% of subjects in each group. There were no deaths among subjects in the development program. However, there are 3 subjects who experienced non-fatal serious adverse events (SAEs) unrelated to the study product. There are no treatment-related severe AEs in the calcipotriene foam group and 2 treatment-related severe AEs in the vehicle group.

Dermal safety is adequately evaluated with 4 provocative Phase 1 studies. One subject experienced contact sensitization but there is no difference in irritation, photoallergic or phototoxic potential between calcipotriene foam and vehicle foam.

Calcium homeostasis is a particular safety concern with all vitamin D analogs. Although none of the subjects develop albumin adjusted serum calcium levels above the normal range in the Phase 2 trials, some of the baseline values are below the lower limit of normal. In addition, albumin adjusted serum calcium is not the most sensitive method of evaluating fluctuations in calcium.

The adverse event data and laboratory assessment demonstrate the safety of calcipotriene foam for the treatment of mild to moderate plaque psoriasis in subjects aged 18 years and older. The segment of the intended patient population between the ages of 12 and 18 has not been adequately evaluated. There is insufficient clinical pharmacology and safety data to support labeling in patients under age 18.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The standard post-marketing procedures are recommended for calcipotriene foam. The risk management plan proposed by the applicant includes updated spontaneous reporting and quarterly post-marketing periodic reports unless a safety signal is identified. The most important adverse events to follow are those related to hypercalcemia, application site reactions and exposure in children. The risk of adverse events due to exposure to the moiety, calcipotriene, is not adequately characterized in

children less than age 12. A risk evaluation and mitigation strategy is not necessary for this 505 (b)(2) application for which the adverse event profile is well known.

1.4 Recommendations for Postmarket Requirements and Commitments

The pharmacology and safety data are insufficient for subjects age 2 to 17. Since calcipotriene foam is ready for approval in adults and safety data is adequate to support initiation of studies in pediatric patients then deferral of PREA studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is appropriate. The required trials include:

1. PK/PD trial of calcipotriene foam under maximal use conditions in 20 evaluable pediatric subjects with plaque psoriasis age 12 to 16 years. The applicant should evaluate the effect of the product on calcium metabolism in all subjects.

2. PK/PD trial of calcipotriene foam under maximal use conditions in 25 evaluable pediatric subjects with plaque psoriasis age 2 to 11 years. The applicant should evaluate the effect of the product on calcium metabolism in all subjects.

3. Vehicle-controlled trial of the safety and efficacy of calcipotriene foam in 100 evaluable pediatric subjects with plaque psoriasis age 2 to 12 years. The applicant should evaluate the effect of the product on calcium metabolism in all subjects.

2 Introduction and Regulatory Background

2.1 Product Information

Stiefel submits a marketing application for a new calcipotriene formulation, calcipotriene foam, 0.005%. Calcipotriene is a synthetic vitamin D3 analog that inhibits keratinocyte proliferation and stimulates keratinocyte differentiation. The proposed indication is the topical treatment of plaque psoriasis in patients (b) (4) The recommended dosing regimen for calcipotriene foam, 0.005% is twice daily. The vehicle is an ethanol-free, aqueous based emulsion foam which is rapidly absorbed.2

2 Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature 2007;445:866-873.

2.2 Tables of Currently Available Treatments for Proposed Indications

Approved products for the treatment of mild to moderate psoriasis are indicated either for psoriasis or the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses. The products in Table 1 are FDA approved for the treatment of mild to moderate psoriasis and the products in Table 2 are approved for relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

Table 1: Approved Treatment Options for Mild to Moderate Psoriasis

Product Name	Sponsor	NDA #	Approval Date	Indication
Vectical Ointment	Galderma Laboratories	22087	1/23/2009	Plaque psoriasis
Taclonex Ointment	Leo Pharmaceuticals	21852	1/9/2006	Psoriasis vulgaris, ≥ 18 years
Tazorac Cream	Allergan	21184	9/29/2000	Plaque Psoriasis
Locoid lipocream	Triax Pharmaceuticals	20769	9/8/1997	Psoriasis
Tazorac Gel 0.05%, 0.1%	Allergan	20600	6/13/1997	Stable Plaque Psoriasis, up to 20% BSA
Dovonex Cream 0.005%	Leo Pharmaceuticals	20554	7/22/1996	Plaque Psoriasis

Table 2: Products indicated for the relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses

Product Name	Formulation	Age
Desonide	Cream 0.05% Ointment 0.05% Lotion 0.05%	
Hydrocortisone butyrate	Cream 0.1% Ointment 0.1% Solution 0.1%	
Fluticasone propionate	Cream 0.05% Ointment 0.005%	3 months and older Adults
Fluocinonide	Cream 0.1% Cream 0.05% Gel 0.05% Ointment 0.05%	12 years and older
Clocortolone pivalate	Cream 0.1%	
Halcinonide	Cream 0.1% Ointment 0.1% Solution 0.1%	
Betamethasone dipropionate	Cream 0.05% Ointment 0.05% Lotion 0.05%	13 years and older

Adapted from Table 1: Currently available treatments NDA 22087
Representative topical corticosteroids are included.

2.3 Availability of Proposed Active Ingredient in the United States

Generic Name and formulation	Brand Name	Applicant/Sponsor	NDA or ANDA number	FDA Approval Date
Calcipotriene foam 0.005%	Sorilux	Stiefel Laboratories, Inc	22563	*Approval Pending*
Calcipotriene ointment 0.005%	Generic	Glenmark Generics	90633	March 24, 2010
Calcipotriene cream 0.005%	Dovonex	Leo Pharmaceuticals	20554	July 22, 1996
Calcipotriene solution 0.005%	Dovonex and generics	Leo Pharmaceuticals, Tolmar, Hi Tech Pharma, Nycomed US	20611, 77029, 77579, 78305	March 3, 1997
Calcipotriene 0.005% and Betamethasone 0.064% ointment	Taclonex	Leo Pharmaceuticals	21852	January 9, 2006
Calcipotriene 0.005% and Betamethasone 0.064% suspension	Taclonex Scalp	Leo Pharmaceuticals	22185	May 9, 2008
Calcipotriene ointment 0.005%	*Dovonex*	*Leo Pharmaceuticals*	*20273*	*Discontinued*

Source: Adapted from a review by Tracy M. Salaam, Division of Pharmacovigilance

Three formulations of topical calcipotriene are marketed in Europe and Russia under the trade names Daivonex and Psorcutan. Calcipotriene products are approved in Australia, New Zealand, Japan and Korea.

2.4 Important Safety Issues with Consideration to Related Drugs

The adverse event profile of calcipotriene is well documented. The most frequently reported adverse events are local cutaneous reactions including itching, burning and irritation. These reactions occur with all formulations and are documented in labeling. Erythema, rash, dermatitis, dry skin, peeling and exacerbation of psoriasis are observed less frequently. Hypercalcemia, skin atrophy, hyperpigmentation and folliculitis are reported in less than 1% of subjects in clinical trials. Hypercalcemia is more likely to be reported in individuals who apply the product to large surface areas and pediatric patients with a higher ratio of skin surface area to body mass. Symptomatic hypercalcemia may be observed with serum calcium concentrations greater than 11 mg/dl and is characterized by fatigue, depression, nausea, vomiting, constipation and polyuria.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This marketing application is submitted under section 505(b)(2) of the Food, Drugs, and Cosmetics Act. Dovonex Ointment (calcipotriene 0.005%) is the listed drug for this

development program for "biopharmaceutic purposes". There is extensive post-marketing and non-clinical data concerning the listed drug.

Dovonex Ointment was approved on December 29, 1993 (NDA 20-273) and withdrawn for business reasons from the United States and European markets in April 2007. The product was not discontinued or withdrawn for safety or efficacy reasons according to the Federal Register. The applicant established the clinical bridge with the 2 Phase 2 trials which were completed prior to the withdrawal of the listed drug.

The clinical trials in this development program are submitted under IND 71,198.

There are three Type B Presubmission meetings associated with this New Drug Application (NDA):

- Pre-Investigational New Drug Application Meeting (PIND) held on March 7, 2005
- End of Phase 2 Meeting (EOP2) held on October 24, 2007.
- Pre-NDA Meeting held on October 21, 2009.

The most significant issues are summarized for the following meetings:

Pre-IND Meeting: March 7, 2005

Chemistry, Manufacturing and Controls

Many issues are discussed including overages, drug substance and drug product specifications, analytical methods, acceptance limits, and the stability program.

Clinical Pharmacology and Biopharmaceutics

The Agency recommends that pharmacokinetic studies that are intended to compare systemic exposures of different formulations of a drug substance need to be conducted in patients under maximal usage conditions.

Clinical

The applicant agrees to utilize a single efficacy time point at 8 weeks.

The Division recommends that a clinically meaningful primary endpoint should include an investigator global assessment score of 0 or 1 and at least a two grade improvement from baseline. The target lesion assessment may be included as a secondary endpoint

The applicant proposes to use Dovonex ointment as the listed drug for their product. The applicant plans to establish a clinical bridge to Agency findings of safety using a bioequivalence study with the listed drug and at least one pivotal trial comparing calcipotriene foam, the listed drug and vehicle foam. The Division asked the applicant to consider adding a fourth arm with the listed drug vehicle.

The Agency recommends an adequate dose ranging study to characterize the proposed drug product more completely.

Biostatistics

Since it is preferable to pre-specify power and sample size, the Division recommends that the applicant conduct the Phase 2 studies prior to the Phase 3 studies and use the estimate of treatment effects from the Phase 2 studies to ensure that the Phase 3 studies are adequately powered.

The analysis of efficacy should be conducted on the ITT population. Imputing missing data with LOCF is acceptable. The applicant is encouraged to use other imputation techniques.

End of Phase 2 Meeting (EOP2): October 24, 2007.

Chemistry, Manufacturing and Controls

The Agency states that the proposed drug substance specifications, finished drug product specifications and stability program are not acceptable.

Pharmacology/Toxicology

The Agency emphasizes that an adequate clinical bridge must be established to allow reference to the safety findings and labeling as approved for Dovonex® ointment. If it is determined that an adequate clinical bridge has not been established, then complete nonclinical toxicology information per ICH M3 guidelines is needed to support a NDA submission.

Clinical Pharmacology and Biopharmaceutics

The Agency indicated that the acceptability of CAL. 201 study outcomes is a review issue since the study may not meet the definition of “maximal usage conditions.” The study product was applied to less than 10% BSA.

Clinical/Biostatistics

As presented in the briefing package, the study designs (population, endpoints, and evaluations) for the proposed Phase 3 trials appear to be acceptable and the proposed development program appears to support a 505(b)(2) application.

To ensure that the results are not driven by the primary method of data imputation, the applicant should propose a sensitivity analysis using an alternate method of imputing missing data.

The Agency recommends incorporating multiplicity control for the set of key secondary endpoints.

The applicant is informed that long-term safety data needs outlined in the ICH E1A Guideline may be fulfilled by construction of an adequate clinical bridge and

literature. However, long-term safety data from another product does not address any safety signals that are unique to the formulation. The Agency is not aware of any unique safety issues at this time.

(b) (4)

Pre NDA Meeting: October 21, 2009

Discussion continues about the construction of an adequate clinical bridge, the requirements for an acceptable pediatric waiver and the adequacy of safety data.

Clinical/Biostatistics

The Agency expresses concern regarding efficacy data from study U0267-301. The study does not meet the specified efficacy criteria and does not replicate the findings of study U0267-302.

Chemistry, Manufacturing and Controls

The Agency states that the formulation change (b) (4) may pose additional safety concerns and may require additional studies.

The Agency confirms that data regarding the color of the collapsed foam is necessary for the NDA review since it contributes to the determination of the shelf life and could not be a post approval commitment.

Discussion:

The applicant incorporates many of the Agency recommendations in the development program. However, the applicant includes no dose ranging studies and plans no post-marketing trials for long term safety. The rationale is that the effective dose and long term safety are well established for the moiety after 15 years of marketing.

2.6 Other Relevant Background Information

There are two additional issues which impact the review of the calcipotriene foam application: the pediatric plan and the formulation modification.

(b) (4)

(b) (4)

Refer to Section 7.6.3 for further discussion of this issue.

Second, at the pre-NDA meeting on October 21, 2009, the applicant describes two formulations of calcipotriene foam, 0.005%: the original formulation that is used in the clinical trials and (b) (4)

The Agency informs the applicant that the clinical trials for dermal safety and pharmacokinetics must be conducted with the to-be-marketed formulation. In a letter dated December 18, 2009 the applicant responds that the product described in the new drug application and intended for marketing is "identical to the formulation used in the clinical and non-clinical studies" (not the reformulated product). Refer to Section 4.1 and 4.2.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Division is concerned about site specific efficacy data since trial U0267-301 does not meet the specified efficacy criteria and does not replicate the findings of trial U0267-302. The Division requests that the Department of Scientific Investigations (DSI) conduct clinical inspections of 3 domestic sites chosen for the magnitude of the treatment effect. The results are listed in Table 3.

Table 3: Results of DSI inspections by site

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site 011: James A Solomon, M.D. Advanced Dermatology & Cosmetic Surgery 725 W Granada Blvd, # 44 Ormond Beach, FL 32174 Ph: (386) 898- 0547, FAX: (386) 898-0551, drjsolomon@leavittmgt.com	U0267-302/ 25/	18-21 May 2010	NAI
Site 005: Kimberly Grande, M.D. The Skin Wellness Center, PC 10215 Kingston Pike #200 Knoxville, TN 37922 Ph: (865) 584-8580, FAX: (865) 694-1949	U0267-302/ 36/	2-4 Jun 2010	NAI
Site 002 Sunil Dhawan, M.D. East Bay Dermatology Medical Group, Inc. 2557 Mowry Ave., Suite 34 Fremont, CA 94538 Ph: (510) 797-4111 or (408) 957-7676	U0267-302/ 18/	12-14 July 2010	VAI

Source: Review by Roy Blay, Ph.D., Good Clinical Practice Branch II, Division of Scientific Investigations
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations

The Reviewer concludes:

> "The clinical investigator sites of Drs. Solomon, Grande, and Dhawan were inspected in support of this NDA. Although regulatory violations were noted at Dr. Dhawan's site, the findings are unlikely to impact data integrity; however, the review division may wish to consider excluding data from Subject 1292 because of the use of a protocol-prohibited medication…Otherwise, the study appears to have been conducted adequately, and the data generated by these clinical sites appear acceptable in support of the respective indication."

3.2 Compliance with Good Clinical Practices

All Final Clinical Study Reports contain the following statement:

> "This study was conducted in compliance with United States Food and Drug Administration (US FDA) and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) regulations/guidelines."

The Institutional Review Board (IRB) examines protocols and consent forms prior to the initiation of each study. The applicant reviews the credentials of the investigators.

3.3 Financial Disclosures

The financial disclosure is complete. Form 3454 is submitted for all investigators. Two investigators received total payments in excess of $25,000 from Stiefel after February 2, 1999. [redacted] (b) (6) participated as a clinical investigator in trial CAL.201. He received $26,500 as an honoraria and payment for consulting and research. [redacted] (b) (6) participated as a clinical investigator in trial U0267-301. He received $76,432.05 in 2008 and $16,500.74 in 2009 as honoraria and payment for speaking engagements.

> The applicant writes, "It is our policy that the honorariums and grants for speaking engagements and consults will not impact in any way the conduct of our studies… We manage any potential conflict of interest by focus on protocol and not on product… Strict adherence to the protocol and blinding procedures ensures the investigator will not be influenced by a specific product and also minimizes bias."

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are 2 issues that required additional discussion with the applicant during the review cycle. First, testing revealed that the clinical drug product did not consistently meet the USP<51> Antimicrobial Effectiveness Test (AET) 14-day acceptance criterion for *E. coli* and *S. aureus*. The formulation that is submitted to the Agency does not contain additional preservatives to address the testing failures. Although a 2 log reduction in these organisms is achieved at 28 days, the Division requests a formal assessment of the issue by clinical microbiology. See Section 4.2 for further discussion of this issue.

Second, three excipients (light mineral oil, white petrolatum, and isopropyl myristate) [redacted] (b) (4) See Section 6.1.10 for further discussion of this issue. Table 4 contains a list of the product components.

Table 4: Composition of calcipotriene foam

Ingredient	Function	Reference to Quality Standard [a]	Target Quantity (% w/w)
Calcipotriene	Active Ingredient	In-house	0.005
Purified Water	(b) (4)		
Propylene Glycol			
Light Mineral Oil			
Polyoxyl 20 Cetostearyl Ether			
Cetyl Alcohol			
Stearyl Alcohol			
White Petrolatum			
Isopropyl Myristate			
Dibasic Sodium Phosphate, Anhydrous			
Edetate Disodium			
dl-α-Tocopherol[b]			
Total			100%

[a] USP/NF: United States Pharmacopeia/National Formulary, current edition
[b] Vitamin E, USP

Source: NDA 22-563 Module 3, Section 3.2.P.1 Description and Composition of the Drug Product

The CMC Reviewer in consultation with the Pharmacology/Toxicology Reviewer concludes that (b) (4) the higher acceptance criteria of calcipotriene related impurities do not represent safety concerns.

(b) (4) See Section 7.7 for further discussion.

Since the NDA provides sufficient CMC information to assure the identity, strength, purity and quality of the drug product, the CMC Reviewer recommends approval of the NDA.

4.2 Clinical Microbiology

In order to assess the failure of the proposed drug product to meet USP<51> Antimicrobial Effectiveness Test (AET) specifications, an information request (IR) was submitted to the applicant on May 11, 2010 providing recommendations and requesting details concerning the following procedures:

a. Preservative effectiveness assay methods used during development and for the stability batches

b. A recommendation that the test be performed in the actual pressurized containers rather than on aliquots dispensed from the containers
c. Details of test methodologies used for microbial limits testing
d. Risk assessment or test methodologies to demonstrate that the drug product is free of the objectionable organism *B. cepacia*
e. Details of the conduct of the 8-week in-use study to include plate count data

Responses to the IR were received in the June 28, 2010 and August 6, 2010 amendments. Although the justification provided by the applicant for the lack of a preservative is not entirely convincing according to the Product Quality Microbiology Reviewer, the final product preservative effectiveness test data and data from the 8-week in-use testing study supports their rationale. The lack of preservative in this formulation is acceptable and the Product Quality Microbiology Reviewer recommends approval of the drug product from microbiology product quality standpoint.

4.3 Preclinical Pharmacology/Toxicology

There are no Pharmacology/Toxicology review issues and the product is approvable with respect to nonclinical concerns. The clinical bridge satisfies both preclinical and clinical data needs. The applicant relies on Agency findings of safety for Dovonex ointment for the single-dose toxicity, repeat-dose toxicity, genotoxicity, reproductive and developmental toxicity, carcinogenicity and photocarcinogenicity studies. The applicant conducted 14, 28 and 90-day repeat dose toxicity studies in rats; 28 and 90-day repeat dose toxicity studies in minipigs; ocular and dermal irritation studies in rabbits; and a dermal sensitization study in guinea pigs.

4.4 Clinical Pharmacology

The Pharmacology/ Toxicology reviewer describes two potential issues related to the adequacy of the clinical bridge as follows. (b) (4) The listed drug, Dovonex ointment, is indicated for adults age 18 and older and thus the applicant may not rely on safety information for the listed drug in subjects (b) (4). (b) (4)

Second, the adequacy of the clinical bridge is not confirmed for the population of subjects with BSA greater than 10%. The BSA range evaluated in the bioavailability

trial was 5-10%, while the BSA range evaluated in the in two phase 3 trials was 2-20%. Based on the data, the systemic bioavailability of calcipotriene foam is similar to Dovonex ointment in subjects with less than 10 % BSA involvement. Approximately, 14% of subjects in the Phase 3 trials have a BSA greater than 10%. Thus, an adequate clinical safety bridge is not established for subjects treated with calcipotriene foam with BSA greater than 10%. However, a reasonable assumption is that since the systemic exposure of the test and reference products is similar in the population with a BSA below 10% it is likely to be similar with a BSA above 10% assuming the same level of baseline disease severity. In addition, the mean BSA of subjects treated with calcipotriene foam in the Phase 3 trials (6.3-6.4%) is not significantly different than the mean BSA in the bioavailability trial (6.5%). Therefore, systemic exposure to calcipotriene foam is not greater than Dovonex ointment.

The Clinical Pharmacology Reviewer concludes:

> "The clinical pharmacology information submitted in NDA 22-563 is acceptable from a Clinical Pharmacology perspective to support the approval of Sorilux in the subjects with mild to moderate plaque psoriasis aged 18 years and older, provided that a mutually (acceptable) agreement is reached between the sponsor and the Agency regarding the labeling language. (b) (4)

4.4.1 Mechanism of Action

The Mechanism of Action of calcipotriene in the treatment of plaque psoriasis is not known. There is evidence that calcipotriene and natural vitamin D inhibit epidermal proliferation and inflammation and induce cell differentiation.

Refer to Section 9.2 for Agency recommendations for labeling

4.4.2 Pharmacodynamics

There is no evidence that the drug product causes a significant change in calcium metabolism as measured by albumin-adjusted serum calcium. Doses of topical calcipotriene ointment greater than 100 g per week may cause increases in the 24-hour urinary calcium concentration. No subject exposed to calcipotriene foam in Phase 2 trials has a calcium concentration above the upper limit of normal for any time point. However, screening or baseline albumin-adjusted serum calcium levels are below the

lower limit of normal in 2 subjects in each treatment group. Refer to Section 7.4.2 for further discussion of these findings.
The development program contains no assessment of the effect of the drug product on cardiac repolarization. Refer to Section 6.1.10 for further discussion of this issue.

The proposed labeling contains no Pharmacodynamic section as required by 21 CFR 201.56 (d)(1). Refer to Section 9.2 for Agency recommendations for labeling.

4.4.3 Pharmacokinetics

The pharmacokinetic study is a single-center, open label study to evaluate the bioavailability of calcipotriene foam compared to Dovonex Ointment in subjects with mild-to-moderate plaque-type psoriasis. Thirty-two subjects are enrolled with a range of body surface areas of 5 to 10% (median 6.5 to 7%). The study product is applied twice per day for two weeks. “Maximal use dosing” is defined by the applicant as 49 g/week. Both the calcipotriene foam group and the Dovonex ointment group exhibit the same baseline disease severity characteristics (38% with mild disease and 63% with moderate disease). Pharmacokinetic parameters are not calculated due to the fact that only 6/32 subjects have measureable levels of Calcipotriene. Albumin-adjusted calcium levels are measured in all subjects as a surrogate marker for calcipotriene.

Refer to Section 9.2 for Agency recommendations for labeling.

5 Sources of Clinical Data

The sources of data for this review include the trials conducted by the applicant and Agency reviews documenting findings of safety from non-clinical studies with Dovonex ointment. All trials were conducted in the United States. The applicant relies on clinical studies from the literature and the clinical bridge to findings of safety for Dovonex ointment as evidence of long-term safety.

5.1 Tables of Studies/Clinical Trials

Table 5: Phase 1 Trials

Study Number and Type	Design and Objectives	Number of Subjects	Test Products and Dosing Regimen	Duration	Subject Type
U0267-101 Cumulative irritation potential	Single-center, randomized, evaluator-blinded, vehicle controlled study of calcipotriene foam and vehicle foam to evaluate cumulative irritation potential in healthy volunteers	39 (safety analysis set)	Calcipotriene foam and vehicle foam plus positive and negative irritant controls were applied to the back every 24 hours using occlusive patches	21 Days	Healthy
U0267-102 Contact sensitizing potential	Single-center, randomized, evaluator-blinded, vehicle controlled study of calcipotriene foam and vehicle foam to evaluate contact sensitization potential in healthy volunteers	231 (safety analysis set)	Subjects received Calcipotriene foam and vehicle foam in an induction phase (3 times per week for 3 weeks) followed by a 10-14 day rest period and a single 48-hour challenge application	6 to 9 weeks	Healthy
U0267-103 Phototoxic potential	Single-center, randomized, evaluator-blinded, vehicle controlled study of calcipotriene foam and vehicle foam to evaluate phototoxic potential in healthy volunteers	40 (safety analysis set)	Subjects applied Calcipotriene foam and vehicle foam for 24 hours followed by irradiation with UVA and UVA/ UVB	5 to 9 days	Healthy
U0267-104 Photo allergic potential	Single-center, randomized, evaluator-blinded, vehicle controlled study of calcipotriene foam and vehicle foam to evaluate photoallergic potential in healthy volunteers	57 (safety analysis set)	Subjects applied Calcipotriene foam and vehicle foam for 24 hours followed by UVB irradiation; this was repeated 6 times at intervals of 72 to 96 hours. This induction phase was followed by a rest period of 10 to 17 days. The challenge period consisted of application of active and vehicle study product to naïve sites for 24 hours followed UVA and UVA/ UVB	6 to 9 weeks	Healthy

Source: NDA 22-563 Table 5, Table 6 and Table 7 are derived from Module 2, Section 2.7.6 and Section 2.7.4.

Table 6: Phase 2 Trials

Study Number and Type	Design and Objectives	Number of Subjects	Test Products and Dosing Regimen	Duration	Subject Type
CAL.201 Safety and Efficacy compared to listed drug	Multicenter, randomized, double-blind study, with active comparator (listed drug, Dovonex Ointment) and vehicle controls (vehicle foam and vehicle ointment)	101 total 36 calcipo-triene foam 36 vehicle foam 20 Dovonex Ointment 9 vehicle ointment	Calcipotriene foam; vehicle foam, Dovonex Ointment (calcipotriene 0.005%), vehicle ointment. Twice daily (morning and evening) topical application of a sufficient amount to cover all lesions (excluding the face and scalp)	8 weeks	Mild to Moderate plaque-type psoriasis
CAL.203 Systemic bioavailability compared with the listed drug	Single-center, open label study to evaluate the bioavailability of calcipotriene foam and Dovonex Ointment in subjects with mild-to-moderate plaque- type psoriasis	32 total 16 calcipo-triene foam 16 Dovonex Ointment	Calcipotriene foam; Dovonex Ointment (calcipotriene 0.005%) Twice daily (morning and evening) topical application of a sufficient amount to cover all lesions (excluding the face and scalp)	2 weeks	Mild to Moderate plaque-type psoriasis

Source: NDA 22-563 Table 5, Table 6 and Table 7 are derived from Module 2, Section 2.7.6 and Section 2.7.4.

Table 7: Phase 3 Trials

Study Number and Type	Design and Objectives	Number of Subjects	Test Products and Dosing Regimen	Duration	Subject Type
U0267-301 Safety and efficacy	Multicenter, randomized, double-blind, vehicle-controlled study of the safety and efficacy Calcipotriene foam compared to vehicle foam in subjects with plaque- type psoriasis	336 total 223 calcipo triene foam 0.005% 113 vehicle foam	Twice daily topical application of the smallest amount necessary of Calcipotriene foam or vehicle foam to cover all treatable lesions (excluding the face and scalp)	8 weeks	Mild to Moderate plaque-type psoriasis
U0267-302 Safety and efficacy	Multicenter, randomized, double-blind, vehicle-controlled study	323 total 214 calcipo-triene foam 0.005% 109 vehicle foam	Twice daily topical application of the smallest amount necessary of Calcipotriene foam or vehicle foam to cover all treatable lesions (excluding the face and scalp)	8 weeks	Mild to Moderate plaque-type psoriasis

Source: NDA 22-563 Table 5, Table 6 and Table 7 are derived from Module 2, Section 2.7.6 and Section 2.7.4.

5.2 Review Strategy

Calcipotriene foam, 0.005% is a new topical dosage form of calcipotriene for the proposed indication of the topical treatment of plaque psoriasis in patients (b) (4) It is submitted in accordance with Section 505 (b)(2) of the Federal Food Drug and Cosmetic Act.

To establish a clinical bridge to Agency findings of safety for Dovonex Ointment, Stiefel conducts two comparative trials in Phase 2 prior to the withdrawal of the listed drug. CAL. 203 is a systemic bioavailability trial and CAL. is a safety and efficacy trial. The applicant intends to use the clinical bridge to satisfy both preclinical (genotoxicity, reproductive and developmental toxicity, carcinogenicity studies, photocarcinogenicity, single-dose toxicity, and repeat-dose toxicity) and clinical informational needs.

A summary of the protocols and results is presented in Section 5.3. Safety issues associated with the Phase 2 trials are addressed in Section 7. Further analysis of the bioavailability trial is submitted in the Clinical Pharmacology Review. A list of additional non-clinical studies with calcipotriene foam is presented in Table 8: Nonclinical Studies with Calcipotriene Foam. An evaluation of these studies is submitted in the Pharmacology/ Toxicology Review.

Table 8: Nonclinical Studies with Calcipotriene Foam

Study Type	Study No.	Species	Route of Administration	Test Articles
14-day Repeat-Dose Toxicity	NPB00023	Rat	Topical dermal	Calcipotriene foam vehicle Calcipotriene foam Dovonex Ointment
28-Day Repeat-Dose Toxicity	NPB00029	Rat	Topical dermal	Calcipotriene foam vehicle Calcipotriene foam *
28-Day Repeat-Dose Toxicity	CB06-5080-P-TX	Minipig	Topical dermal	Calcipotriene foam vehicle Calcipotriene foam *
90-Day Repeat-Dose Toxicity	NPB00034	Rat	Topical dermal	Calcipotriene foam vehicle Calcipotriene foam Dovonex Ointment *
90-Day Repeat-Dose Toxicity	1236-002	Minipig	Topical dermal	Calcipotriene foam vehicle Calcipotriene foam Dovonex Ointment *
Ocular Irritation	NPB00020	Rabbit	Topical ocular	Calcipotriene foam
Dermal Irritation	NPB00021	Rabbit	Topical dermal	Calcipotriene foam
Dermal Sensitization	NPB00022	Guinea	Topical dermal	Calcipotriene foam

		Pig		

*To provide dose response information, 3 concentrations of calcipotriene foam were evaluated including the 0.005% clinical concentration and two higher concentrations, 0.015% and 0.025%
Source: NDA 22-563, Table 1 Nonclinical studies with Calcipotriene foam

Dermal safety of calcipotriene foam is evaluated with 4 Phase 1 trials in healthy subjects as summarized in Table 5. These studies include: an evaluation of cutaneous irritation potential (U0267-101), allergic contact sensitization (U0267-102), phototoxicity (U0267-103) and photoallergy (U0267-104). Refer to Section 7.1.1 for protocol summaries.

Claims of clinical efficacy are based on two identical Phase 3 trials (U0267-301 and U0267-302) to evaluate the safety and efficacy of calcipotriene foam compared to vehicle foam in subjects with mild to moderate plaque-type psoriasis. Refer to the summaries in Table 7 and reviews in Section 5.3.

5.3 Discussion of Individual Studies/Clinical Trials

Phase 2 Studies:

Protocol Number: **U0267-203** is a comparison of systemic exposure of calcipotriene foam, 0.005% versus Dovonex® Ointment, 0.005%, under maximal use conditions as measured by circulating plasma levels of calcipotriene in subjects with mild-to to moderate plaque-type psoriasis.

Study Initiation and Completion Dates: August 15, 2006 to November 2, 2006.

Investigator and Study Center: Robert Matheson, MD
Oregon Medical Research Center, P.C. 9495 SW Locust Street Portland, OR 97223

Title: A Randomized, Open-Label Study to Assess the Bioavailability of Emulsion Formulation Calcipotriene Foam, 0.005%, and Dovonex® Ointment, 0.005%, in Patients with Mild to Moderate Plaque-Type Psoriasis.

Study Population: 32 subjects are enrolled with 19 males and 13 females who range in age from 14 to 80 years old. One subject is less than age 18 and 4 subjects are greater than age 65. There are 25 Caucasians, 4 Hispanics/Latinos; 1 Asian; 1 Black, and 1 Native American/Pacific Islander.

Principle Inclusion Criteria are as follows:
1. Males or females at least 12 years of age and in good general health

2. Diagnosis of mild-to-moderate plaque-type psoriasis [Investigator's Static Global Assessment (ISGA) score of 2 or 3] involving 5% to 10% of total body surface area (BSA), excluding the face and scalp

Principle Exclusion Criteria are as follows:
1. History of hypercalcemia, vitamin D toxicity or abnormal liver function tests
2. History of renal failure, parathyroid disease, kidney stones or poorly controlled systemic disease
3. Systemic anti-psoriatic therapy or other systemic therapies known to affect psoriasis used within 4 weeks prior to enrollment or concurrently during the study
4. Topical treatments that have a known beneficial effect on psoriasis, used within the past 2 weeks prior to enrollment or concurrently during the study
5. Treatment with Fosamax, bisphosphonates, vitamin D, multivitamins containing vitamin D, or other supplements that affect calcium metabolism
6. Pregnant women, women who were breast feeding, or sexually active women of child bearing potential who were not practicing an acceptable method of birth control

Study design and plan: A single-center, open-label, randomized study of 32 subjects with mild-to-moderate plaque-type psoriasis to evaluate systemic exposure from the topical application of calcipotriene foam, 0.005% compared with Dovonex® (calcipotriene) ointment, 0.005%. Subjects are randomized 1:1 to receive calcipotriene foam or Dovonex® ointment, 0.005%. Investigators instruct subjects to apply 3.5 grams of the study product topically twice per day for 2 weeks to all lesions excluding the face and scalp. Circulating plasma levels of calcipotriene are measured on Days 1, 8 and 15.

Statistical Methods:
Descriptive statistics are used to summarize plasma concentrations and pharmacokinetic parameters by dosage group.

Safety Analysis and Results:
Adverse events and changes in albumin-adjusted calcium levels are recorded as safety assessments. The albumin- adjusted calcium levels are all within the normal range in both groups. Mean and median values for albumin adjusted serum calcium are comparable in both treatment arms. Median daily product usage is higher (6.80 g) in subjects receiving calcipotriene foam than in subjects receiving Dovonex ointment (5.55 g). There were no deaths or serious adverse events (SAEs). One subject in the calcipotriene foam group experienced an adverse event (sinus infection) classified as mild. There was one uncomplicated pregnancy. Refer to Section 7.3.4 for further discussion of the pregnancy.

Pharmacokinetics Results
The mean BSA and missed applications are comparable for both the calcipotriene foam and Dovonex ointment groups. The lower limit of detection of calcipotriene is 10 pg/ml using reversed-phase high-performance liquid chromatography and mass spectroscopy.

Pharmacokinetic parameters including Cmax, T_{max}, and AUC are not calculated since the levels of calcipotriene are below 25 pg/ml. One subject in the calcipotriene foam group and 5 in the Dovonex ointment group demonstrate detectable levels of calcipotriene. Thus, there is low systemic exposure.
Protocol Number: **U0267-201** is an evaluation of the safety and efficacy of emulsion formulation calcipotriene foam 0.005% compared to vehicle foam, Dovonex ointment 0.005%, and vehicle ointment in the treatment of mild-to-moderate plaque-type psoriasis. The estimated sample size of the pivotal Phase 3 studies is based on this study data.

Study Initiation and Completion Dates: August 4, 2006 to November 13, 2006

Table 9: Investigator and site number for study U0267-201

Investigator and Affiliation	Site Number
Ellen Frankel, MD Clinical Partners, LLC 1524 Atwood Avenue, Suite 330, Johnston, RI, 02919	001
Michael Gold, MD Tennessee Clinical Research Center 2000 Richard Jones Road, Suite 223, Nashville, TN, 37215	002
Steven Kempers, MD Minnesota Clinical Study Center 7205 University Avenue, NE, Fridley, MN, 55432	003
John Proffitt, MD Compliant Clinical Research 153 West 151st Street, Suite 100, Olathe, KS, 66061	005
Phoebe Rich, MD Oregon Dermatology and Research Center 2565 NW Lovejoy #200, Portland, OR, 97210	006
Joel Schlessinger, MD Skin Specialists, PC 2802 Oak View Mall Dr., Omaha, NE, 68144,	007
Leonard Swinyer, MD Dermatology Research Center 3920 South 1100 East, Ste 210, Salt Lake City, UT, 84124	008
Eduardo Tschen, MD Academic Dermatology Associates 1203 Coal SE, Suite B, Albuquerque, NM, 87106	009

Source: NDA 22-563, Clinical Study Report for Protocol U0267-201 Appendix 16.1.5.

Title: A Multicenter, Randomized, Double-Blind Study of the Safety and Efficacy of Emulsion Formulation Calcipotriene Foam, 0.005%, versus Vehicle Foam, Dovonex®

(calcipotriene) Ointment, 0.005%, and Vehicle Ointment in the Treatment of Mild to Moderate Plaque-type Psoriasis.

Study Population: 101 subjects are enrolled at 8 U.S. sites with 57 males and 44 females. 36 subjects apply calcipotriene foam, 36 apply vehicle foam, 20 apply Dovonex ointment and 9 apply vehicle ointment. 89 subjects range in age between 18 and 65 while 12 subjects are greater than age 65. Most are Caucasian (92/101).

Principle Inclusion criteria are as follows:
1. Males or females age 12 years or greater in good general health
2. Mild to moderate plaque type psoriasis involving 2 to 10% of total BSA (which is amended to "at least 2% treatable BSA") and ISGA scores of 2 or 3
3. Presence of a target lesion > 2 cm on the trunk or extremities with a score of 2 or 3 on a 6 point scale for erythema, scaling and plaque thickness

Principle Exclusion criteria are as follows:
1. Known allergy or other adverse reaction to calcipotriene or any component of the formulation
2. History of hypercalcemia or of vitamin D toxicity.
3. Albumin-adjusted serum calcium that is > 10% above the normal limit
4. Liver function tests outside the upper limit of normal
5. Poorly controlled systemic disease
6. Traditional or biologic systemic anti-psoriatic therapy used within 4 weeks prior to enrollment or concurrently during the study.
7. Topical treatments that have a known beneficial effect on psoriasis, including but not limited to corticosteroids, retinoids, vitamin D derivatives, tar, or anthralin used within 2 weeks prior to enrollment or concurrently during the study
8. Systemic medications for other medical conditions that are known to affect psoriasis (e.g., lithium, beta-adrenergic blockers) within the past 4 weeks prior to enrollment or concurrently during the study
9. Any investigational therapy used within the past 4 weeks.
10. Pregnant women, women who were breast feeding, or sexually active women of child bearing potential who were not practicing an acceptable method of birth control (birth control pill, patch, implant, barrier with spermicidal jelly, IUD, etc.) during the entire study

Study Design and Plan: This is a multicenter, randomized, double-blind study in which 101 subjects with mild to moderate plaque type psoriasis apply either calcipotriene foam, vehicle foam, Dovonex ointment or vehicle ointment twice per day for 8 weeks. Subjects are randomized in a 4:4:2:1 ratio of calcipotriene foam: vehicle foam: Dovonex ointment: vehicle ointment. They are instructed to apply the product to all affected areas except the face and scalp. Subjects are assessed at screening, baseline, Week 2, Week 4 and Week 8. Assessments at each visit include: Investigator's Static Global Assessment (ISGA), percentage of body surface area (BSA) affected with psoriasis,

target lesion evaluations for erythema, scaling and plaque thickness, Subject's Global Assessment (SGA), albumin adjusted serum calcium levels, drug compliance and adverse events. At baseline and Week 8, vital signs and urine pregnancy testing are performed. Albumin-adjusted serum calcium levels are collected at Week 4 and 8. Study drug containers are weighed at baseline Week 2, 4 and 8.

Protocol Amendments:

Amendment I

- primary endpoint changed to the proportion of subjects at Week 8 with an ISGA score of clear (0) or almost clear (1)
- secondary endpoint changed to the proportion of subjects with a target lesion score of 0 or 1 for erythema, scaling and plaque thickness
- subject number changed from 69 to 99
- inclusion criteria changed to include subjects with "at least 2% treatable BSA of psoriasis"
- ISGA scale was modified from a six-point scale to a five-point scale

Amendment II

- secondary endpoint changed to include the proportion of subjects who have the following at Week 8:
    - A target lesion score of 0 or 1 for erythema and at least a 2 grade improvement from baseline
    - The proportion of subjects with a target lesion score of 0 or 1 for scaling and at least a 2 grade improvement from baseline
    - The proportion of subjects with a target lesion score of 0 for plaque thickness
- antihistamine are permitted
- if the serum calcium level exceeds 10% above the upper limit of normal the subjects is instructed to discontinue the study product

Safety

Safety is assessed with adverse event reports, vital signs, concomitant medication summaries, measurements of albumin-adjusted serum calcium, urine pregnancy testing and an evaluation of compliance. Adverse events are elicited by direct questions.

Statistical Methods:

There is no formal statistical testing in trial U0267-201.

The primary efficacy analysis for both primary and secondary endpoints is conducted on an Intent-to-Treat (ITT) population with last-observation-carry-forward approach for missing values. The primary efficacy endpoint is the proportion of subjects with a score

of clear or almost clear on the Investigator's Static Global Assessment scale (ISGA) and at least a 2 grade improvement from baseline to Week 8.

The amended secondary endpoints include: a target lesion score of 0 or 1 for erythema and at least a 2 grade improvement from baseline to Week 8; the proportion of subjects with the target lesion score of 0 or 1 for scaling and at least a 2 grade improvement from baseline to Week 8.; and the proportion of subjects with a target lesion score of 0 for plaque thickness. Other assessments of efficacy include: the mean percent reduction in the BSA from baseline to Week 8 and the proportion of subjects who had a score of 0 or 1 on the SGA at Week 8.

Safety Results:
No severe AEs, deaths or SAEs occurred during this trial. Thirty one percent of enrolled subjects (31/101) reported AEs: 22% (8/36) in the calcipotriene group, 39% (14/36) in the vehicle foam group, 30% (6/20) in the Dovonex ointment group and 33% in the vehicle ointment group. AEs reported in greater than 3% of subjects include: nasopharyngitis, pharyngolaryngeal pain, upper respiratory infection, cough, and headache. Adverse events for trial U0267-201 are summarized in Table 10.

Table 10: Adverse events in trial U0267-201

	Study 201			
	Calcipotriene foam	**Vehicle foam**	**Dovonex ointment**	**Vehicle ointment**
N	**36**	**36**	**20**	**9**
All AEs	8 (22%)	14 (39%)	6 (30%)	3 (33 %)
Treatment-related AEs (Application site irritation)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Nasopharyngitis	1 (3%)	1 (3%)	1 (5%)	2 (22%)
Upper respiratory tract infection	1 (3%)	2 (6%)	1 (5%)	0 (0%)
Headache	0 (0%)	1 (3%)	2 (10%)	0 (0%)
Cough	0 (0%)	3 (8%)	0 (0%)	0 (0%)
Others [(1)]	**6 (16%)**	**6 (13%)**	**2 (10%)**	**1 (11%)**

Source: Adapted from a Biostatistical Review by Carin Kim, Ph.D.

No subject demonstrates an albumin adjusted serum calcium above the upper limit of normal at any time point.

Efficacy Results:

The percentage of subjects who achieved treatment success at Week 8 (ITT analysis set) is 17% for calcipotriene foam, 3% for vehicle foam, 35% for Dovonex Ointment and 0% for vehicle ointment. Subgroup analysis revealed no trends for race or sex.

Table 11: Success at Week 8 for the primary endpoint

	Calcipotriene foam	**Vehicle foam**	**Dovonex ointment**	**Vehicle ointment**
Number of subjects	36	36	22	9
Success N (%)	6 (17%)	1 (3%)	7 (35%)	0 (0%)

Source: NDA 22-563 U0267-201, Clinical Study Report, Section 11.4.1.1, Table 12

The percentage of subjects with success for the secondary endpoints of erythema, scaling and plaque thickness is summarized in for the ITT analysis set.

Table 12: Success at Week 8 for the secondary endpoints

	Calcipotriene foam	**Vehicle foam**	**Dovonex ointment**	**Vehicle ointment**
Number of subjects	36	36	22	9
Treatment success N (%)	5 (17%)	1 (4%)	6 (40%)	0
Erythema success N (%)	6 (17%)	2 (6%)	10 (50%)	0
Scaling success N (%)	5 (17%)	2 (7%)	9 (60%)	0
Plaque Thickness success N (%)	4 (11%)	1 (3%)	3 (15%)	0

Source: NDA 22-563 U0267-201, Clinical Study Report, Section 11.4.1.1, Table 14.2.8, Table 14.2.10, Table 14.2.12

Pivotal Phase 3 Studies:

Protocol Number: U0267-301
Study initiation and completion dates: April 24, 2008 to December 26, 2008.

Protocol Number: U0267-302
Study initiation and completion dates: April 22, 2008 to December 19, 2008.

The protocols for the 2 Phase 3 studies are identical except as noted. The methodology, inclusion/exclusion criteria and endpoints are identical.

Title: A Multicenter, Randomized, Double-Blind, Phase 3 Study of the Safety and Efficacy of Emulsion Formulation Calcipotriene Foam, 0.005%, versus Vehicle Foam in Subjects with Plaque-type Psoriasis

Objective: To evaluate the safety and efficacy of calcipotriene foam compared to vehicle foam in subjects with plaque-type psoriasis

Subject Populations: The subjects are healthy males and females age 12 years or older with mild to moderate plaque-type psoriasis involving 2-20% of body surface area (BSA)**.** In trial U0267-301**,** 336 subjects are treated with calcipotriene foam (223) or vehicle foam (113). Subjects range in age from 15 to 89 years with 86% between 18 and 64 (mean 48.7 years. In trial U0267-302, 323 are treated with calcipotriene foam (214) or vehicle foam (109). Subjects range in age from 12 to 88 years (mean 47.8 years). Group demographics were similar except that there are more Asian subjects in the calcipotriene foam cohort. See Table 16.

Protocol Amendments:
None noted.

Study Centers and Investigators:
All investigational sites are located in the United States. Trial U0267-301 is conducted in 13 centers; Trial U0267-302 is conducted in 12 centers.

Protocol Number: U0267-301

Table 13: Investigators and Study Centers for U0267-301

Investigators	Study Centers	Site Number
William Abramovits	Dermatology Treatment & Research Center 5310 Harvest Hill Rd, Suite 160 Dallas, TX 75230	001
Suzanne Bruce	Suzanne Bruce and Associates, PA, The Center for Skin Research 1900 St. James Place, #650 Houston, TX 77056	002
Zoe Draelos	Dermatology Consulting Services 2444 North Main Street High Point, NC 27262	003
Steven Kempers	Minnesota Clinical Study Center 7205 University Ave NE Fridley, MN 55432	004
Francisco A. Kerdel	Florida Academic Dermatology Centers 1400 NW 12th Ave, #4 Miami, FL 33136	005
Alexa Kimball	Clinical Unit for Research Trials in Skin, Massachusetts General Hospital 50 Staniford St, Room 240, 2ndFloor Boston, MA 02114	006
Leon Kircik	DermResearch, PLLC 1169 Eastern Parkway, #2310 Louisville, KY 40217	007
James Michael Maloney III	Creek Research, Inc. 3773 Cherry Creek North Drive, #970 Denver, CO 80209	008
Orit Markowitz	Mount Sinai School of Medicine, Dept. of Dermatology 5 East 98th Street, 5th Floor New York, NY 10029	009
Robert Matheson	Oregon Medical Research Center, P.C. 9495 SW Locust Street Portland, OR 97223	010
Stacey Smith	Therapeutics Clinical Research 9025 Balboa Ave, Suite 105 San Diego, CA 92123	011
Leonard J. Swinyer	Dermatology Research Center, Inc. 3920 South 1100 East, #210 Salt Lake City, UT 84124	012
Hector Wiltz	FMX Research, 11760 Bird Road, Suite 452 , Miami, FL 33175	013

Source: NDA 22-563: Clinical Study Report 16.1.4

Protocol Number: U0267-302

Table 14: Investigators and Study Centers for U0267-302

Investigators	Study Centers	Site Number
Steven A. Davis	Dermatology Clinical Research Center of San Antonio 7810 Louis Pasteur, Suite 200 San Antonio, TX 78229	001
Sunil Dhawan	East Bay Dermatology Medical Group, Inc. 2557 Mowry Ave., Suite 34 Fremont, CA 94538	002
Steve Feldman	Wake Forest University Health Sciences Dept. of Dermatology, Medical Center Blvd., Winston Salem, NC 27157	003
Ellen H. Frankel	Clinical Partners, LLC 1524 Atwood Ave, Suite 330 Johnston, RI 02919	004
Kimberly Grande	The Skin Wellness Center, PC 10215 Kingston Pike #200 Knoxville, TN 37922	005
David L. Kaplan	Adult & Pediatric Dermatology 4601 W. 109th Street, Suite 116 Overland Park, KS 66211-1313	006
Amy Morris	Coastal Clinical Research, Inc. 100 Memorial Hospital Drive Annex Building, #3B Mobile, AL 36608	007
Phoebe Rich	Oregon Dermatology and Research Center 2565 MW Lovejoy #200 Portland, OR 97210	008
Diya F. Mutasim (prev. Pranav Sheth)	University Dermatology Consultants, Inc. 222 Piedmont Avenue, #5300 Cincinnati, OH 45219	009
Brett Shulman	The Center for Dermatology at Lifetime Health 1850 Brighton Henrietta Townline Rd Rochester, NY 14623	010
James A Solomon	Advanced Dermatology & Cosmetic Surgery 725 W Granada Blvd, # 44 Ormond Beach, FL 32174	011
Eduardo Tschen	Academic Dermatology Associates 1203 Coal SE Albuquerque, NM 87106	012

Source: NDA 22-563: Clinical Study Report 16.1.4

Principle Inclusion Criteria are as follows:

1. Male or female subjects at least 12 years old and in good general health

2. Mild to moderate plaque-type psoriasis (ISGA score of 2 or 3 at baseline)
3. Mild to moderate plaque-type psoriasis involving 2% to 20% of total BSA (excluding the face and scalp)
4. Target lesion (>2 cm^2) on the trunk or extremities with a score of 2 or 3 on a 0 to 5 scale for each of erythema, scaling, and plaque thickness which may not be localized to the palms/soles, knees, elbows, or intertriginous areas

Principle Exclusion Criteria are as follows:
1. Previous participation in a Phase 1 or 2 calcipotriene foam study
2. Known allergy or other adverse reaction to calcipotriene, other vitamin D analogs or to any component of the study formulations
3. History of hypercalcemia or vitamin D toxicity
4. Generalized pustular or erythrodermic exfoliative psoriasis
5. Serious skin disorder or poorly controlled chronic medical condition
6. Non biologic systemic anti-psoriatic therapy or biologic therapy used within 4 weeks of enrollment
7. Topical therapies known to benefit psoriasis including corticosteroids, retinoids, vitamin D derivatives, tar, or anthralin, used within 2 weeks of enrollment. Bland moisturizer are permitted except 4 hours prior to the study visit
8. Systemic medications for other medical conditions that are known to affect psoriasis. Systemic treatments for other medical conditions are permitted including established use of inhaled/intranasal steroids (e.g., lithium, beta-adrenergic blockers) within 4 weeks of enrollment.
9. Investigational therapy used within 4 weeks of enrollment.
10. Pregnant women, breast feeding women, or sexually active women of childbearing potential who are not utilizing a medically acceptable form of birth control (e.g.. birth control pill, patch, implant, barrier with spermicidal jelly, intrauterine device [IUD].) Abstinence is considered to be a medically acceptable form of contraception.
11. Drug or alcohol abuse (drug screening not required)
12. History of any disease causing an immunocompromised state
13. Any condition placing the subject at unacceptable risk for participation in the study

Study Design and Plan: This is a multicenter, randomized, double-blind, Phase 3 study. Subjects are randomized 2:1 to the calcipotriene foam and vehicle foam groups. Investigators instruct subjects to apply the test product (calcipotriene foam, 0.005% or vehicle foam) twice daily for 8 weeks to all affected areas, all new lesions and all baseline lesions that clear with treatment. The face and scalp are excluded from treatment. Investigators instruct subjects to dispense the smallest amount that covers the treatment site.

All subjects must meet the entrance criteria and provide written informed consent. Subjects are evaluated at baseline, Week 2, Week 4 and Week 8. Concomitant medications, adverse experiences, protocol compliance and weight of study product are recorded at each visit. Assessments of ISGA, SGA and target lesion evaluations of

erythema, scaling and plaque thickness are obtained at baseline, Week 2, 4 and 8. Vital signs (temperature, blood pressure, pulse, height and weight), urine pregnancy tests, clinical photography (at selected centers at baseline and week 8 for presentation not efficacy) and the Dermatology Life Quality Index or Children's DLQI are obtained at baseline and Week 8 or early termination.

Endpoints:

Primary Efficacy Endpoint
The proportion of subjects who demonstrate:

- an ISGA score of clear (0) or almost clear (1) at Week 8 **and**
- minimum improvement in the ISGA score of 2 grades from baseline to Week 8.

In addition, all subjects are required to complete the Week 8 visit evaluation.

Key Secondary Efficacy Endpoints
The proportion of subjects who had each of the following endpoints at Week 8 was analyzed by group:

- target lesion score of 0 or 1 for erythema and at least a 2-grade improvement from baseline
- target lesion score of 0 or 1 for scaling and at least a 2-grade improvement from baseline
- target lesion score of 0 for plaque thickness
- ISGA score of 0 or 1
- primary endpoint analyzed by baseline ISGA score

Additional Efficacy Endpoints
These endpoints are analyzed by product and visit**:**

- mean percent reduction in the percent of BSA involvement with psoriasis from baseline to Week 8
- proportion of subjects who had a score of 0 or 1 on the SGA at Week 8
- change in DLQI score from baseline to Week 8 (CDLQI not performed due to small number of subjects [5] in this age group.)
- all primary and key secondary endpoints

Investigator's Static Global Assessment (ISGA)
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)

Table 15: Psoriasis grading Scale for Target Lesion

Score	Scaling	Erythema	Plaque Thickness
0	No evidence of scaling	No evidence of erythema but hyperpigmentation may be present	No elevation over normal skin
1	Minimal; occasional fine scale over less than 5% of the lesion	Faint erythema	Possible but difficult to ascertain whether there is a slight elevation above normal skin
2	Mild; fine scales predominate	Light red coloration	Slight but definite elevation, typically edges are indistinct or sloped
3	Moderate; coarse scales predominate	Moderate red coloration	Moderate elevation with rough or sloped edges
4	Marked; thick nontenacious scale predominates	Bright red coloration	Marked elevation typically with hard or sharp edges
5	Severe; very thick tenacious scale predominates	Dusky to deep red coloration	Very marked elevation typically with hard sharp edges

Source: Adapted from NDA 22-563, U0267-301 Clinical Study Report, Section 16.1.1, Appendix 2

Safety Assessments

1. Laboratory Evaluations

Urine pregnancy testing is performed in all female subjects of child-bearing potential at baseline and Week 8. Pregnant subjects are discontinued from the study but followed to term or termination of the pregnancy. Status of the mother and infant are reported for 6 months after delivery.

2. Safety Evaluations

Adverse events (AEs) are recorded at each visit after the first application of the test product using the Medical Dictionary for Regulatory Activities (MedDRA), Version 11.0. Frequencies and percentages of adverse events are classified by system organ class (SOC) and preferred term (PT). Concomitant medications are reported at each visit and coded according to the World Health Organization Drug Dictionary (WHODrug) version 2008 March 01. Categories of summarized AEs include: treatment-emergent AEs, treatment-related-AEs, AEs resulting in discontinuation and serious AEs. Reasons for withdrawal are tabulated. Vital signs are obtained at baseline and Week 8. A Post-study questionnaire is completed at Week 8/early termination to assess tolerance and preference of treatment vehicles.

Statistical Methods:
The Cochran-Mantel-Haenszel (CMH) procedure stratified by study center is used to test the superiority of calcipotriene foam over the vehicle foam. If the primary endpoint reaches significance (2 sided 0.05% significance level), then the Holm stepwise closed testing procedure is used to control multiplicity for the 4 key secondary analyses.

The primary analysis is performed on the intent-to-treat (ITT) population which includes all subjects who were randomized, received study product and were evaluated at Week 8. All missing values including those from subjects who failed to be evaluated at Week 8 are considered failures for the primary and key secondary endpoints. Additional sensitivity analyses are applied to the data analysis of the primary endpoint using a per protocol (PP) data set and an ITT data set with last response carried forward. Missing values are not imputed for the assessment of other endpoints.

The primary and key secondary efficacy analyses were performed for both ITT and PP analysis sets. In the event that any subjects are randomized but not dosed, a sensitivity analysis is run for the primary endpoint using all randomized subjects.

The per protocol (PP) data set excludes all subjects who:

- missed more than a total of 22 applications or 10 consecutive applications of study product during the 8-week treatment period
- missed efficacy evaluations at the baseline and/or week 8 visits
- used prohibited medications during the study period that were expected to interfere with the efficacy assessments of the assigned study product.
- failed to meet the eligibility criteria for the ISGA
- failed to meet the eligibility criteria for signs of psoriasis (erythema, scaling, and plaque thickness) for the target lesion
- failed to meet the eligibility criteria for percent BSA psoriasis involvement
- demonstrated other major violations that may impact the efficacy analysis

The analysis of covariance (ANCOVA) model is used to analyze percent reduction in BSA at each visit and change in DLQI and CDLQI score from baseline to Week 8 and to evaluate treatment center interaction. Summary statistics and a categorical summary are presented for both treatment duration and days on study product.

Results of the Phase 3 trials are discussed in the Review of Efficacy.

6 Review of Efficacy

Efficacy Summary

The evaluation of efficacy is based on data obtained from the two Phase 3 trials. These pivotal trials, U0267-301 and U0267-302, are identical multicenter, randomized, double-blind trials to test the superiority of calcipotriene foam, 0.005% over vehicle foam in

subjects with plaque-type psoriasis. The design of the trials is adequate to allow the evaluation of the efficacy of the study product applied twice per day for 8 weeks compared to the vehicle. The applicant powered the Phase 3 trials based on a treatment effect of 14% derived from the Phase 2 trial (Cal. 201), a dropout rate of 10% and a two-sided Type I error rate of 0.05%.

The study population does not adequately represent the intended patient population. The proposed indication for calcipotriene foam is the topical treatment of plaque psoriasis in (b) (4). However, there are only 10 subjects (2%) who were below age 18 at baseline in the Phase 3 trials.

The primary efficacy endpoint is defined as the proportion of subjects in the intent to treat (ITT) analysis set with an Investigator Static Global Assessment (ISGA) score of clear (0) or almost clear (1) at Week 8 and an improvement in the ISGA score of at least 2 grades from baseline to Week 8. Subjects without a Week 8 assessment are counted as treatment failures.

The applicant conducts 2 Phase 3 vehicle controlled trials with calcipotriene foam, 0.005%. The intent to treat analysis set includes 659 subjects. Although trial U0267-302 demonstrates the superiority of calcipotriene foam compared to vehicle foam, trial U0267-301 fails to meet the specified efficacy criteria.

The applicant proposes that the disease status at baseline influences subject response to the study product. Subjects with moderate disease at baseline (ISGA=3) who applied calcipotriene foam show a response rate that is statistically different than subjects who applied vehicle foam. However, for subjects with mild disease (ISGA=2) at baseline there is no difference in treatment response for any endpoint. In fact, subjects in trial U0267-301 with mild disease treated with vehicle foam demonstrate a higher response rate than subjects treated with calcipotriene foam. This result indicates a lack of measurable efficacy of the product in the population with mild disease.

Another factor in the analysis of treatment success in trial U0267-301 is the handling of missing data. Missing data is imputed as “failure” in the analysis by the applicant. Subjects who missed the Week 8 evaluation are considered treatment failures even if they demonstrate treatment success prior to the 8 Week evaluation. The reclassification of a single subject who is a success at Day 44 as a treatment success results in a p value less than 0.05.

The primary endpoints in both Phase 3 trials are analyzed by gender, age and race. No definitive trends are observed. Analysis of treatment effect by age and race is compromised by the limited numbers of subjects in the older age group and non-Caucasian race. Treatment success by sex is inconsistent across the 2 Phase 3 trials. In trial U0267-301 females demonstrate greater response rates whereas in trial U0267-302 males demonstrate greater response rates.

6.1 Indication

The proposed indication for this product is the topical treatment of mild to moderate plaque psoriasis in patients (b) (4).

6.1.1 Methods

The analysis of efficacy for calcipotriene foam is based on the 2 Phase 3 superiority trials (U0267-301 and U0267-302). Trials U0267-301 and U0267-302 are identical multicenter, randomized, double-blind studies comparing the safety and efficacy of calcipotriene foam, 0.005% and vehicle foam in subjects with plaque psoriasis. The protocol with inclusion and exclusion criteria is presented in Section 5.3.

Supportive efficacy data is provided by CAL. 201, the Phase 2 clinical bridge study which compares calcipotriene foam to, Dovonex Ointment, vehicle foam and vehicle ointment. The protocol with inclusion and exclusion criteria is presented in Section 5.3. The inclusion criteria for CAL. 201 are similar to U0267-301 and U0267-302 except that the baseline BSA is 2 to 10% in CAL. 201 and 2 to 20% in the Phase 3 trials. However, there are 3 subjects enrolled in trial U0267-302 with a BSA greater than 20%.

6.1.2 Demographics

In the 2 Phase 3 trials subjects ranged in age from12 to 89 years with a mean age of 48.2 years. However, there are only 10 subjects (2%) who are under age 18 at baseline. There are 90 subjects (14%) who are age 65 and above although the annual psoriasis incidence rate is the highest in the 60 to 69 age group. 3 Eighty eight percent of the subjects are white and 54% are male. Twenty one subjects (3%) are black and 119 (18%) are Hispanic or Latino. In the United Sates the prevalence of psoriasis is 1.3% in blacks 4 who comprise 12.3% of the population5. According to the 2000 Census, Hispanics/Latinos comprise 12.5% of the U.S. population. Demographic characteristics are not statistically different between the two treatment groups as presented in Table 16.

3 Neimann AL, Porter SB, and Gelfand JM. The epidemiology of psoriasis. Expert Rev. Dermatol. 2006;1:63-75.
4 Gelfand JM, Stern RS, Nijsten TN et al. The prevalence of psoriasis in African Americans: Results from a population based study. J Am Acad Dermatol 2005; 52:23-26.
5 Overview of Race and Hispanic Origin, U.S. Census Bureau, Census 2000 Brief, March 2001, p.3.

Table 16: Subject Demographics by trial (ITT Analysis Set)

	U0267-301		U0267-302	
	Calcipotriene foam	Vehicle foam	Calcipotriene foam	Vehicle foam
Age (years)				
n	223	113	214	109
Mean (SD)	48.4 (14.7)	49.2 (13.9)	47.9 (14.2)	47.5 (16.9)
Min/Max	15/89	17/83	12/81	15/88
Age group n (%)				
12<18 years	4 (2%)	1 (1%)	2 (1%)	3 (3%)
18<65 years	191 (86%)	95 (84%)	185 (86%)	88 (81%)
≥ 65 years	28 (13%)	17 (15%)	27 (13%)	18 (17%)
Sex, n (%)				
Male	132 (59%)	71 (63%)	106 (50%)	50 (46%)
Female	91 (41%)	42 (37%)	108 (50%)	59 (54%)
Race, n (%)				
White	188 (84%)	101 (89%)	194 (91%)	99 (91%)
Asian	8 (4%)	1 (1%)	10 (5%)	3 (3%)
Black	6 (3%)	6 (5%)	5 (2%)	4 (4%)
Other/Missing	21(9%)	5 (5%)	5 (2%)	3 (2%)
Ethnicity, n (%)				
Hispanic/Latino	61 (27%)	28 (25%)	16 (7%)	14 (13%)
Other	150 (67%)	77 (68%)	198 (93%)	95 (87%)

Source: Adapted from NDA 22-563 Summary Table 1.3.1, Section 14, U0267-301 Clinical Study Report; Summary Table 1.3.1, Section 14, U0267-302 Clinical Study Report

Assessment of baseline disease severity on the ISGA scale shows that 465 (71%) subjects enrolled in the Phase 3 trials have moderate disease. The mean BSA for subjects in the ITT analysis set is 6.3. Baseline values for IGSA and BSA are summarized in Table 17, Table 18, and Table 19 by trial.

Table 17: Baseline ISGA and % BSA by trial (ITT Analysis Set)

	U0267-301		U0267-302	
	Calcipotriene foam	Vehicle foam	Calcipotriene foam	Vehicle foam
n	223	113	214	109
ISGA				
Mild	73 (33%)	34 (30%)	56 (26%)	31 (28%)
Moderate	150 (67%)	79 (70%)	158 (74%)	78 (72%)
BSA				
Mean (SD)	6.4 (4.8)	5.8 (4.7)	6.3 (4.7)	6.4 (5.2)
Median	4.0	4.0	4.0	5.0
Min/Max	2.0/20.0	2.0/20.0	2.0/30.0	2.0/40.0

Source: Adapted from NDA 22-563 U0267-301, Intent to Treat Analysis Set, Table 1.4.1 Baseline Disease Characteristics; U0267-302, Intent to Treat Analysis Set, Table 1.4.1 Baseline Disease Characteristics

Table 18: % BSA at baseline in Trial U0267-301

BSA	2-10%	11-15%	16-20%	Total
ITT data set N (%)	276 (84%)	33 (10%)	21 (6%)	330
PP data set N (%)	241 (86%)	21 (8%)	17 (6%)	279

Table 18 and Table 19: Adapted from a Biostatistical Review by Carin Kim, Ph.D.

Table 19: % BSA at baseline in Trial U0267-302

BSA	2-10%	11-15%	16-20%	>20%	Total
ITT data set N (%)	275 (88%)	20 (6%)	15 (5%)	3 (1%)	330
PP data set N (%)	222 (88%)	17 (7%)	14 (6%)	0 (0%)	279

Table 18 and Table 19: Adapted from a Biostatistical Review by Carin Kim, Ph.D.

BSA= body surface area
ISGA= Investigator Static Global Assessment
SD= standard deviation
Mild= ISGA=2
Moderate= ISGA=3
ITT= intent to treat population

PP= per protocol population

6.1.3 Subject Disposition

Eight-nine percent (587/659) of enrolled subjects completed the Phase 3 trials. A smaller percentage of subjects in the calcipotriene foam groups discontinued the study medication compared with vehicle foam groups although the differences are small. The reasons for product discontinuation are summarized by trial in Table 20.

Table 20: Subject Disposition in the ITT Analysis Set

	U0267-301		U0267-302		Totals
	Calcipotriene foam N (%)	Vehicle foam N (%)	Calcipotriene foam N (%)	Vehicle foam N (%)	
N	223	113	214	109	659
Completed	204 (91%)	98 (87%)	190 (89%)	95 (87%)	587 (89%)
Discontinued	19 (9%)	15 (13%)	24 (11%)	14 (13%)	72 (11%)
Reasons for discontinuation					
Adverse event	2 (1%)	3 (3%)	7 (3%)	1 (1%)	13 (2%)
Lost to follow up	3 (1%)	3 (3%)	4 (2%)	3 (3%)	13 (2%)
Lack of efficacy	3 (1%)	1 (1%)	4 (2%)	3 (3%)	11 (2%)
Non-compliance	0 (0%)	0 (0%)	1 (<1%)	1 (1%)	2 (<1%)
Withdrawal of consent	7 (3%)	6 (5%)	8 (4%)	4 (4%)	25 (4%)
Other	4 (2%)	2 (2%)	0 (0%)	2 (2%)	8 (1%)

Source: Adapted from NDA 22-563 Summary Table 1.2, Section 14 and Summary table 1.1.2, Section 10.

In both U0267-301 and U0267-302 there are more subjects who discontinued the study product in the calcipotriene group than in the vehicle foam group. In both Phase 3 trials, the most common reason for discontinuation is withdrawal of consent. There are an equal number of subjects who experienced adverse events or are lost to follow up with a smaller number withdrawing for lack of efficacy across both trials. All subjects who discontinued trial U0267-301 and trial U0267-302 for adverse events had application site reactions or folliculitis at the application site. One subject reported a severe application site reaction in each Phase 3 trial. Both severe reactions occurred in the vehicle foam groups.

Table 21: Subject protocol deviations resulting in exclusion from the Per Protocol Analysis Set

Subject protocol deviations	U0267-301		U0267-302	
	Calcipotriene foam N (%)	Vehicle foam N (%)	Calcipotriene foam N (%)	Vehicle foam N (%)
Per Protocol Analysis Set	188 (83)	93 (80)	176 (80)	85 (77)
Number excluded from PP	39 (17)	23 (20)	44 (20)	25 (23)
Did not meet eligibility criteria at baseline	1 (<1)	2 (2)	8 (4)	5 (5)
Did not have Week 8 efficacy assessments *	26 (11)	20 (17)	27 (12)	15 (14)
Missed >22 total or >10 consecutive applications	12 (5)	5 (4)	7 (3)	6 (5)
Used a prohibited concomitant medication	3 (1)	2 (2)	2 (1)	3 (3)
Does not have treatment begin date	0	0	6 (3)	1 (1)
Improperly applied study product	1 (<1)	0	0	2 (2)
BSA not between 2-20% at baseline	0	0	2 (1)	1 (1)

Source: Adapted from NDA 22-563 Table 1.1.2 U0267-301 Clinical Study Report, Table 1.1.2 U0267-302 Clinical Study Report
* Within preset window (≥day 47 to ≤67)
Note: some subjects had more than one deviation

The most frequent protocol deviation is failure to complete the Week 8 efficacy assessment within the pre-specified window. This lack of a Week 8 assessment results in the assignment of at least one subject as a failure who had treatment success prior to this evaluation period and contributes to the failure of U0267-301 to reach statistical significance for the primary endpoint.

The pre-specified windows for each visit are summarized in Table 22.

Table 22: Pre-specified windows for visits

Visit Number	Pre-specified Range
1	Day 1
2	Day 15 ± 2
3	Day 29 ± 4
4	Day 57 ± 4

Source: Adapted from a Biostatistical Review by Carin Kim, Ph.D.

DSI inspections identified a subject enrolled in trial U0267-302 who received a prohibited medication (metroprolol). Nevertheless, trial U0267-302 demonstrates statistical significance for the primary endpoint even with the exclusion of this subject.

Table 23: Subject Disposition in the ITT Analysis Set for CAL. 201

	Calcipotriene foam	Vehicle foam	Calcipotriene ointment	Vehicle ointment
N	36	36	20	9
Completed	35 (97%)	35 (97%)	20 (100%)	9 (100%)
Discontinued	1 (3%)	1 (3%)	0 (0%)	0 (0%)
Reasons for discontinuation				
Lack of efficacy	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Withdrawal of consent	1 (3%)	0 (0%)	0 (0%)	0 (0%)

Source: Adapted from NDA 22-563 Table 14.1.2, Section 14.1 Clinical Study Report CAL. 201

There are 41 protocol deviations in CAL. 201 occurring in 29% (29/101) of subjects. They are categorized in Table 24.

Table 24: Categories of protocol deviations for CAL. 201

Subject protocol deviations	N (%)
Out of window visits	24 (24%)
Excess missed doses	3 (3%)
Prohibited medications	2 (2%)
Did not meet inclusion criteria	2 (2%)
Missing assessments	2 (2%)
Un-necessary pregnancy test	1 (1%)
Unscheduled visit at Week 6	1 (1%)
Randomized at screening visit	1 (1%)
Lost lab sample; replacement out of window	1 (1%)

Source: Adapted from NDA 22-563 U0267-201, Clinical Study Report, Section 10.2

The pattern of protocol deviations for CAL. 201 is similar to trials U0267-301 and U0267-302. The most common type of protocol deviation in CAL. 201 is out-of-window visits. The majority of the visits outside of the pre-specified range are at Week 8.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint is defined as the percentage of subjects in the intent to treat (ITT) analysis set with treatment success. Treatment success is characterized as an Investigator Static Global Assessment (ISGA) score of clear (0) or almost clear (1) at Week 8 and an improvement in the ISGA score of at least 2 grades from baseline to Week 8. Subjects with mild disease at baseline must achieve treatment success by becoming "clear" in contrast to subjects with moderate disease at baseline who may achieve treatment success by becoming "clear" or "almost clear". This composite endpoint is consistent with Division recommendations for capturing drug effectiveness in the treatment of plaque psoriasis. Subjects who missed the Week 8 evaluation are considered treatment failures.

Trial U0267-301 does not meet the specified efficacy criteria and does not replicate the findings of trial U0267-302. Examination of the data from the ITT analysis set from U0267-302 demonstrates that 58 subjects (27%) in the calcipotriene foam group and 17 subjects (16%) in the vehicle foam group achieve treatment success. This difference is statistically significant. However, examination of the data from U0267-301 demonstrates that 31 subjects (14%) in the calcipotriene foam group and 8 subjects (7%) in the vehicle foam group achieve treatment success. Although the calcipotriene foam group achieves greater efficacy than vehicle foam group in trial U0267-301 the difference is not statistically significant.

The results of trials U0267-301 and U0267-302 are summarized in Table 25.

Table 25: Subjects with treatment success at Week 8 by trial (ITT analysis Set)

	U0267-301		U0267-302	
Treatment	Calcipotriene foam	Vehicle foam	Calcipotriene foam	Vehicle foam
N	223	113	214	109
Treatment Success N (%)	31 (14%)	8 (7%)	58 (27%)	17 (16%)
P- value	0.058		0.016	

P-value was derived from the Cochran-Mantel-Haenszel test stratified by pooled center
Source: Modified from NDA 22-563 Summary Tables 2.1.1, Section 14, Study U0267-301 and Study U0267-302, Module 5, Section 5.3.5.1

The applicant proposes that the disease status at baseline influences subject response to the study product. In both Phase 3 trials subjects with moderate disease at baseline (ISGA=3) who applied calcipotriene foam demonstrate greater treatment success than subjects who applied vehicle foam. However, in trial U0267-301 subjects with mild disease (ISGA=2) at baseline demonstrate greater treatment success with vehicle foam than calcipotriene foam. This result may reflect the impact of the emollient properties of

the vehicle, difficulty in achieving a score of “clear” or the lack of measurable efficacy of calcipotriene foam in the population with mild disease.

The evaluation of the primary endpoint by baseline Investigator’s Global Assessment score is summarized by trial in Table 26 and Table 27,

Table 26: Subjects Achieving Treatment Success by Baseline ISGA Score

U0267-301		
ISGA Score at baseline	**Calcipotriene foam**	**Vehicle foam**
N	223	113
2- Mild n (%)	2/73 (3%)	3/34 (9%)
3-Moderate n (%)	29/150 (19%)	5/79 (6%)
p-value	0.058	

Source: NDA 22-563 Summary Table 2.3.1, Section 14, Study U0267-301, Module 5, Section 5.3.5.1

Table 27: Subjects Achieving Treatment Success by Baseline ISGA Score

U0267-302		
ISGA Score at baseline	**Calcipotriene foam**	**Vehicle foam**
N	214	109
2- Mild n (%)	8/56 (14%)	4/31 (13%)
3-Moderate n (%)	50/158 (32%)	13/78 (17%)
p-value	0.016	

Source: NDA 22-563 Summary Table 2.3.1, Section 14, Study U0267-302, Module 5, Section 5.3.5.1
ISGA =Investigator’s Static Global Assessment
ITT= Intent to Treat

Supportive data from CAL. 201 is summarized in Table 28 and presented by baseline disease severity in Table 29.

Table 28: CAL. 201: Primary Endpoint: Subjects with Treatment Success at Week 8 (ITT analysis Set)

	Calcipotriene foam	Vehicle foam	Dovonex ointment	Vehicle ointment
N	36	36	20	9
Success N (%)	6/36 (17%)	1/36 (3%)	7/20 (35%)	0/9 (0%)

Source: Modified from NDA 22-563 Summary Table 14.2.3, Section 14, Study CAL. 201, Module 5, Section 5.3.5.1

Table 29: CAL. 201: Subjects with treatment success at Week 8 by baseline disease severity (ITT analysis set)

	Calcipotriene foam	Vehicle foam	Dovonex ointment	Vehicle ointment
N	36	36	20	9
Mild N (%)	1/14 (7%)	0/14 (0%)	1/7 (14%)	0/2 (0%)
Moderate N (%)	5/22 (23%)	1/22 (5%)	6/13 (46%)	0/7 (0%)

Source: Modified from NDA 22-563 Summary Table 14.2.6, Section 14, Study CAL. 201, Module 5, Section 5.3.5.1

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoints assessed at Week 8 are:

- target lesion score of 0 or 1 for erythema and at least a 2-grade improvement from baseline
- target lesion score of 0 or 1 for scaling and at least a 2-grade improvement from baseline
- target lesion score of 0 for plaque thickness
- proportion of subjects who have an ISGA score of 0 or 1
- primary endpoint by baseline ISGA score

The secondary endpoints are included in Table 30. The calcipotriene foam group demonstrates significantly greater efficacy than vehicle foam group for all endpoints. As discussed in Section 6.1.5, there is no greater treatment response with calcipotriene foam compared with vehicle foam for any endpoint in the subjects with mild disease at baseline. All differences are significant among subjects with moderate disease at baseline.

Table 30: Analysis of key secondary endpoints by trial and baseline ISGA

	ISGA grade at baseline	Calcipotriene foam N (%)		Vehicle foam N (%)	
		301	302	301	302
1. Erythema	Mild Moderate	10 (14%) 31(21%)	16 (29%) 51 (32%)	6 (18%) 5 (6%)	8 (26%) 14 (18%)
2. Scaling	Mild Moderate	11 (15%) 37 (25%)	17 (30%) 55 (35%)	4 (12%) 8 (10%)	8 (26%) 12 (15%)
3. Plaque thickness	Mild Moderate	9 (12%) 21 (14%)	18 (32%) 24 (15%)	4 (12%) 1 (1%)	7 (23%) 5 (6%)
4. ISGA	Mild Moderate	22 (30%) 29 (19%)	28 (50%) 50 (32%)	9 (26%) 5 (6%)	14 (48%) 13 (17%)

Source: NDA 22-563 Summary Table 2.9.1 and Table 2.9.2, Section 10
The *P*-value was derived from a Cochran-Mantel-Haenszel test stratified by study.
301=U0267-301

302=U0267-302

Table 31: Treatment success by secondary endpoints in trial U0267-301

Trial U0267-301			
	Calcipotriene foam	Vehicle foam	p-value
1. Erythema	41 (18%)	11 (10%)	0.03
2. Scaling	48 (22%)	12 (11%)	0.01
3. Plaque thickness	30 (13%)	5 (4%)	<0.01
4. ISGA	51 (23%)	14 (12%)	0.02

Source: Adapted from a Biostatistical Review by Carin Kim, Ph.D.

Table 32: Treatment success by secondary endpoints in trial U0267-302

Trial U0267-302			
	Calcipotriene foam	Vehicle foam	p-value
1. Erythema	67 (31%)	22 (20%)	0.03
2. Scaling	72 (34%)	20 (18%)	<0.01
3. Plaque thickness	42 (20%)	12 (11%)	0.05
4. ISGA	78 (36%)	27 (25%)	0.03

Source: Adapted from a Biostatistical Review by Carin Kim, Ph.D.

1. Subjects with target lesion scores of 0 or 1 for erythema and at least a 2 grade improvement at Week 8
2. Subjects with target lesion scores of 0 or 1 for scaling and at least a 2 grade improvement at Week 8
3. Subjects with target lesion scores of 0 for plaque thickness at Week 8
4. Subjects who have an ISGA score of 0 or 1 at Week 8

6.1.6 Other Endpoints

Additional efficacy endpoints analyzed without multiplicity adjustments include:

- mean percent reduction in the percent of BSA involvement at each visit and the change in DLQI or CDLQI score from baseline to week 8 (or end of treatment) are analyzed using analysis of covariance (ANCOVA). If the treatment-study interaction is not significant at the 0.1 level, this interaction is to be excluded in the ANCOVA model.
- proportion of subjects who had a SGA score of 0 or 1 at each visit is tested using the Cochran-Mantel-Haenszel (CMH) procedure stratified by study. All primary and key secondary endpoints at each visit are tested using the CMH procedure stratified by study.

These endpoints are tabulated for the ITT analysis set.

Table 33: Mean percent reduction in the percent of BSA involvement of psoriasis from baseline to Week 8.

	U0267-301		U0267-302	
	Calcipotriene foam	Vehicle foam	Calcipotriene foam	Vehicle foam
N	201	96	188	95
Mean (SD)	-1.3 (3.3)	-0.5 (2.8)	-1.9 (3.0)	-1.2 (2.6)

Source: NDA 22-563 Summary Table 2.5.1, Section 14
BSA= body surface area

Table 34: The proportion of subjects who had a score of 0 or 1 on the ISGA at Week 8.

	U0267-301		U0267-302	
	Calcipotriene Foam	Vehicle Foam	Calcipotriene Foam	Vehicle Foam
N	223	113	214	109
Week 8	37 (16.6%)	12 (10.6%)	47 (22.0%)	20 (18.3%)

Source: Summary Table 2.6.1, Section 14
SGA= Subject's Global Assessment

• The change in DLQI score from baseline to week 8. (The CDLQI was not performed due to the small number of subjects [n = 5] in this age group.)

6.1.7 Subpopulations

The primary endpoint is evaluated by age, gender and race. Age is dichotomized as 12-49 years and >49 years. Race is dichotomized as Caucasian or non-Caucasian. Analysis of treatment effect by age and race is compromised by the limited numbers of subjects in the older age group and non-Caucasian race. Treatment success by sex is inconsistent across the 2 Phase 3 trials. In trial U0267-301 females demonstrate greater response rates whereas in trial U0267-302 males demonstrate greater response rates.

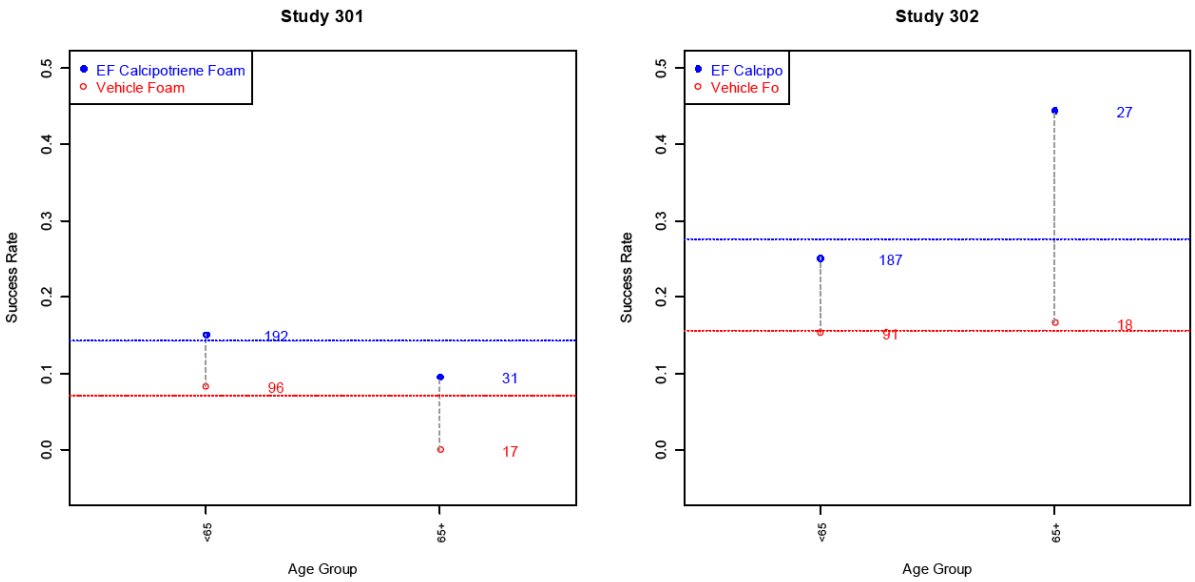

Figure 1: Treatment success by age

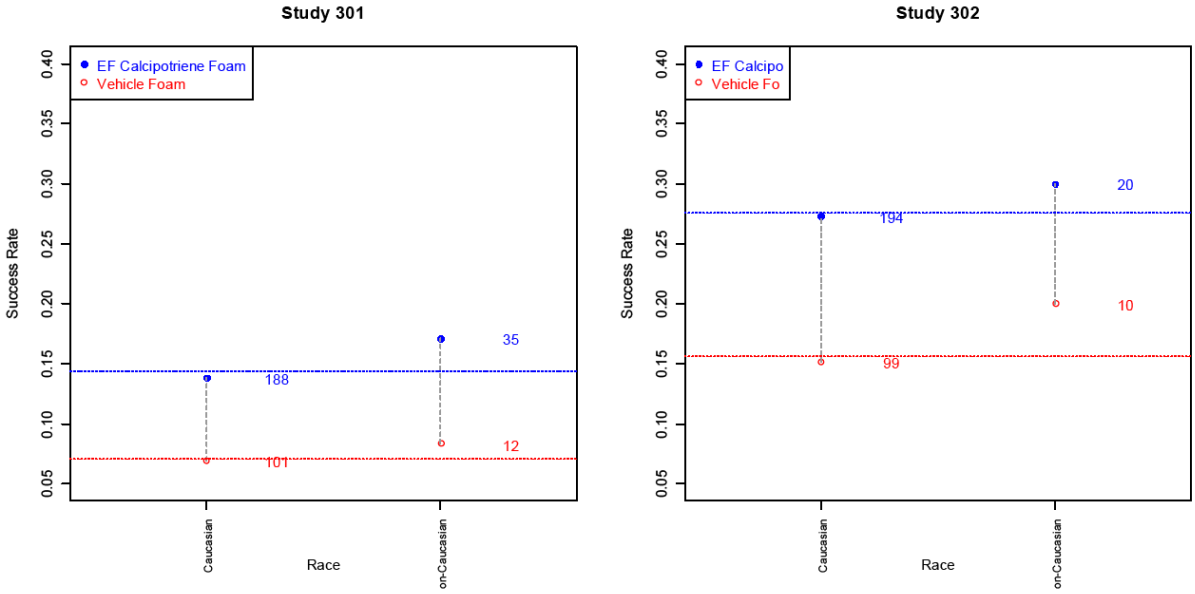

Figure 2: Treatment success by race

Source: Adapted from a Biostatistical Review by Carin Kim, Ph.D.

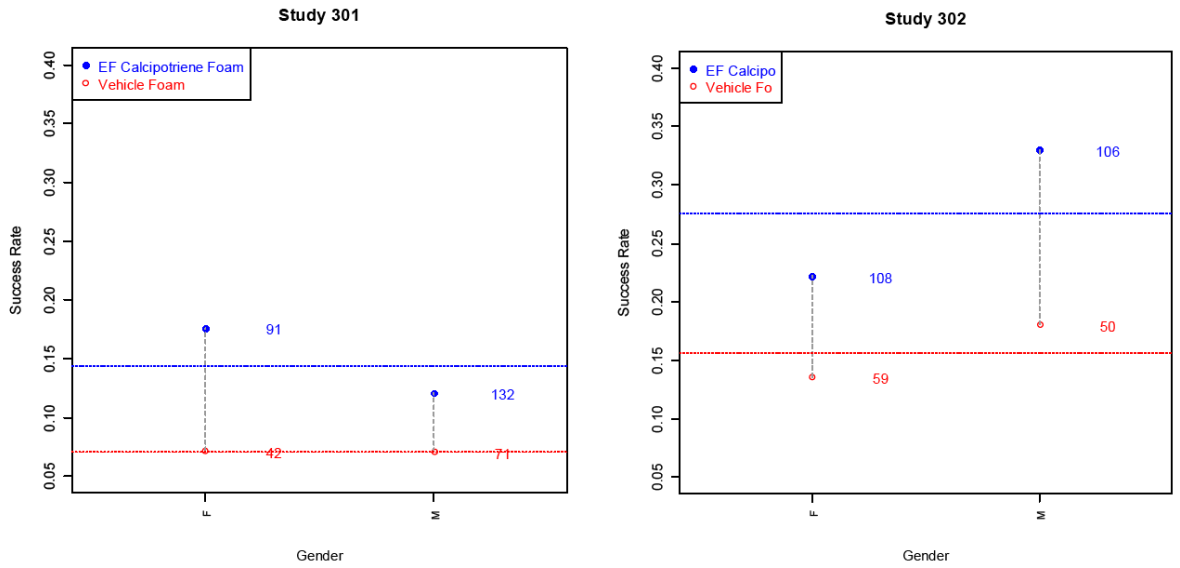

Figure 3: Treatment success by gender

Source: Adapted from a Biostatistical Review by Carin Kim, Ph.D.

In addition, the primary endpoint is analyzed by target lesion location, erythema score, and plaque thickness. Since subgroup analyses by lesional characteristics are not considered for labeling these results are not presented. Refer to Section 6.1.4. for analysis of the primary endpoint by percent BSA at baseline.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No dose ranging studies are conducted with calcipotriene foam, 0.005% in humans. The rational is that the effective dose is well established for the moiety since calcipotriene has been marketed for greater than15 years. Refer to section 7.2.2.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The issues of persistence of efficacy and tolerance are not addressed in this 505 (b)(2) application. The applicant does not conduct any long term studies with the drug product in which these issues could be assessed.

6.1.10 Additional Efficacy Issues/Analyses

1. The applicant identifies the physiochemical function of light mineral oil, white petrolatum, and isopropyl myristate in the formulation as (b) (4) In response to an information request dated 2010-05-3, Stiefel acknowledges that light mineral oil, white petrolatum, and isopropyl myristate (b) (4)

(b) (4)
The applicant states that the excipients serve the following specific physiochemical functions in the formulation:

- light Mineral Oil- (b) (4)
- white Petrolatum- (b) (4)
- isopropyl Myristate - (b) (4)

These physiochemical functions are consistent with those identified for other previously approved foam products marketed by Stiefel. (b) (4)

2. Photographs are obtained during Phase 3 trials at some study sites for publication or presentation purposes only. These are not included as part of the efficacy assessment.

3. Efficacy by site
For sites with fewer than 12 subjects, the data is pooled. This strategy is utilized with 2 sites in trial U0267-301. The Statistical Reviewer applied further sensitivity analyses to Site 10 in trial U0267-301 which demonstrates the greatest treatment effect. As anticipated, efficacy results did not reach statistical significance with the exclusion of Site 10 (p-value=0.1516). When the site with the greatest treatment effect in trial U0267-302 is excluded (Site 02) the efficacy results reached statistical significance (p-value 0.034). Thus, the efficacy results are not driven by site since they remained the same with the exclusion of the sites with the greatest treatment effect in each trial.

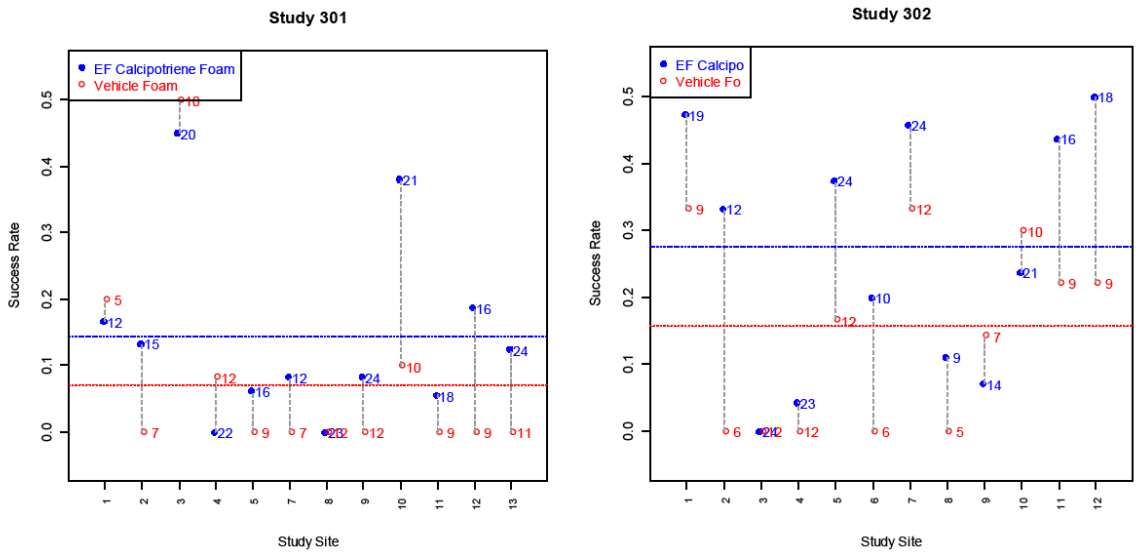

Figure 4: Efficacy by site

Source: Adapted from a Biostatistical Review by Carin Kim, Ph.D.

7 Review of Safety

Safety Summary

There are 3 trials that form the basis of the safety evaluation for the to-be marketed-formulation of calcipotriene foam: the Phase 2 clinical bridge study comparing calcipotriene foam to the listed drug (Cal. 201) and the 2 Phase 3 trials (U0267-301 and U0267-302). See Section 5.3 for protocol summaries. Supportive safety data is provided by the 4 Phase 1 dermal safety studies (U0267-101, U0267-102, U0267-103 and U0267-104) and the Phase 2 bioavailability study.

The integrated summary of safety analysis set contains all subjects who are randomized and receive study product in the Phase 3 trials or are randomized and receive calcipotriene foam or vehicle foam in the Phase 2 trial CAL. 201. There are 731 subjects in the pooled safety data set with 657 subjects (90%) completing the trial and 74 subjects (10%) discontinuing the trial prematurely.

In the Integrated Safety Analysis Set, 79 subjects (17%) in the calcipotriene group and 55 subjects (21%) in the vehicle foam group experienced at least 1 AE. The most common AEs are application site irritation and nasopharyngitis reported by 2% of subjects in each group. There are no deaths among subjects in the development program. However, there are 3 subjects who experienced non-fatal serious adverse events. These events include unilateral deafness and acute intestinal obstruction in 2 subjects treated with vehicle foam and atrial fibrillation with congestive heart failure in a subject treated with calcipotriene foam. A relationship between these events and the study product is unlikely.

In addition, Severe AEs are reported by 4 subjects (1%) receiving calcipotriene foam and 4 subjects (2%) receiving vehicle foam. These included dental caries, drug hypersensitivity, musculoskeletal pain and migraine in subjects applying calcipotriene foam and deafness, abdominal distension, abdominal pain, constipation, Crohn's disease, intestinal obstruction, nausea and application site erythema, irritation, pain and vesicles in subjects applying the vehicle foam. There are no treatment- related severe AEs in the calcipotriene foam group and 2 treatment-related severe AEs in the vehicle group.

Adverse events are summarized in Table 35.

Table 35: Summary of Adverse Events (Integrated Safety Analysis Set)

	Calcipotriene Foam (N = 473) n (%)	**Vehicle Foam (N = 258) n (%)**
Subjects reporting any AE	79 (17)	55 (21)
Subjects reporting any SAE	1 (<1)	2 (1)
Subjects who died	0	0
Subjects reporting any treatment-related AE[a]	22 (5)	16 (6)
Subjects reporting any severe AE	4 (1)	4 (2)
Subjects reporting any severe treatment-related AE	0	2 (1)
Subjects reporting any AE leading to discontinuation	9 (2)	4 (2)

Source: Summary Table 3.1, Table 3.3, Table 3.4, Table 3.5, Table 3.6, Table 3.8, Section 13; CSRs CAL.201, U0267-301 and U0267-302, Module 5, Section 5.3.5.1

Stiefel did not conduct any long term studies with calcipotriene foam. The applicant intends to rely on Agency findings of long term safety of Dovonex ointment from NDA 20-273 with support from findings of long term safety of calcipotriene from the literature. In a review of the literature, Scott et al.6 conclude that the adverse event profile in long term studies in adults is similar to short term studies in adults. This conclusion is based on 5 long term studies ranging from 24 to 52 weeks with a dose of 50 μg/g twice per day. Rare adverse events included: hypercalcemia, hypercalciuria, contact dermatitis, pustular psoriasis, photosensitivity and headache.

Adverse events result in premature discontinuation from the trial in 2% of subjects in both the calcipotriene group and the vehicle group. Application site reactions with bleeding, erythema, exfoliation, irritation, edema, pain, pruritus, swelling and vesiculation account for all AEs except for one report of folliculitis.

Dermal safety is assessed during 4 provocative Phase 1 studies: U0267-101, U0267-102, U0267-103, and U0267-104. One subject experienced contact sensitization and there is no difference in photoallergic or phototoxic potential among active, vehicle or blank patches. The mean irritation scores for calcipotriene foam and vehicle foam were similar and significantly below the positive control (sodium lauryl sulfate).

Subgroup analysis does not reveal any difference in the incidence of AE based on age, sex or race. The treatment groups are similar in the frequency and type of AEs and no specific safety concerns emerge from this evaluation.

6 Scott LJ, Dunn CJ, Goa KL. Calcipotriol Ointment. A Review of its Use in the Management of Psoriasis. Am J Clin Dermatol. 2001; 2(2):95-120.

Calcium homeostasis is a particular concern with all vitamin D analogs. It is assessed in this development program during the two Phase 2 trials by measuring the albumin-adjusted total serum calcium levels. Although none of the subjects develop albumin-adjusted total serum calcium levels above the normal range, this method of evaluating fluctuations in calcium is not sufficiently sensitive to assure patient safety. In addition, baseline values are below the lower limit of normal in a number of subjects. However, calcium homeostasis was carefully assessed for the listed drug (calcipotriene ointment) in a trial which was recommended by the Agency. In this trial, investigators evaluated total serum calcium, 24 hour urine calcium, 24 hour urine hydroxyproline, PTH, fractionated alkaline phosphatase, and bone densitometry. There was no evidence of abnormal calcium metabolism. In addition, there were no unexplained, consistent, abnormal laboratory findings in a 52-week long-term safety study which included serum calcium levels.

7.1 Methods Studies/Clinical Trials Used to Evaluate Safety

The focus of the safety review includes the safety data base from trials CAL. 201, U0267-301 and U0267-302. These studies are listed in Table 36 and summarized in Section 5.3.

Table 36: Clinical studies included in the Integrated Safety Analysis

Trial Number	Study Phase, Design, and Type of Control	Safety Endpoints	Number of Subjects in ITT Analysis Set
CAL. 201	Phase 2, multicenter, randomized, double-blind study, with active comparator (Dovonex Ointment) and placebo controls (vehicle foam and vehicle ointment)a	Adverse events, albumin-adjusted serum calcium levels, urine pregnancy test, vital signs, concomitant medications	101 total 36 calcipotriene foam 36 vehicle foam 20 Dovonex Ointment 9 vehicle ointment
U0267-301	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	Adverse events, urine pregnancy test, vital signs, concomitant medications	336 total 223 calcipotriene foam 113 vehicle foam
U0267-302	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	Adverse events, urine pregnancy test, vital signs, concomitant medications	323 total 214 calcipotriene foam 109 vehicle foam

Source: Modified from NDA 22-563, Table 1, Module 5, Integrated Summary of Safety

Supportive safety data is provided in the 4 dermal safety studies and trial CAL. 203 as well as Agency findings of safety for the listed drug, Dovonex ointment. Safety data for calcipotriene ointment is presented in NDA 22-563, Module 2, Section 2.7.4 in multiple tables. Table 6 and Table 8 in the NDA submission list adverse events in adults treated with calcipotriene ointment for up to 8 weeks. Table 9 in the NDA submission lists adverse events from the literature in children treated with calcipotriene ointment as young as age 2 from 3 foreign studies.

Dermal Safety Studies:
The Phase 1 dermal safety studies conducted with calcipotriene foam consist of provocative studies of cumulative irritancy, sensitization, phototoxicity and photoallergy. Results of ultraviolet and visible spectroscopy on calcipotriene foam demonstrate minimal absorbance (0.14 absorbance units at 290 nm) but indicate the need for phototoxicity and photoallergenicity studies.

The inclusion/exclusion criteria are similar for all the dermal safety studies. The study populations are healthy subjects ranging in age from 18 to 65. Fitzpatrick skin types I, II, III is specified in the protocols for all studies and Fitzpatrick skin type IV is permitted in the irritancy and sensitization studies. Sexually active females of childbearing potential participating in the studies agree to use a medically acceptable form of contraception. Use of corticosteroids, immunosuppressive, anti-inflammatory medications and calcium supplements is restricted. Subjects with a history of hypercalcemia or evidence of vitamin D toxicity are excluded. The phototoxicity and photoallergenicity studies exclude subjects with cancer including skin cancer, severely photo damaged skin, immunocompromised status, a history of severe reactions to sunlight and photosensitizing medications.

The Test Site Evaluation Scales are identical across all studies except that the Study of Cumulative Irritancy includes assessments of edema, papule formation and vesiculation in addition to the Erythema Scale. All scales adequately capture the findings.

Protocol Number: **U0267-101**
Study Initiation and Completion Dates: September 16, 2008 – October 20, 2008.

Study center: Eric Erlbaum, MD, Hill Top Research, Inc. 3225 North 75th Street Scottsdale, Arizona 85251 USA

Title: A Single-Center, Evaluator-Blinded, Randomized, Placebo-Controlled, Phase 1 Clinical Trial Evaluating the Cumulative Irritation Potential of Topically Applied EF Calcipotriene Foam, 0.005% in Healthy Volunteers

Objective: to evaluate the irritation potential of calcipotriene foam and vehicle foam in 39 healthy volunteers

Study Plan: This is a single-center, evaluator-blinded, placebo-controlled study to evaluate the potential of calcipotriene Foam, 0.005% and vehicle foam to induce cutaneous irritation using a 21-day cumulative irritation assay in 39 healthy adult volunteers. Two hundred micoliters of calcipotriene foam, 0.005% and vehicle foam are applied to the backs of all subjects under occlusive patches every 24 hours for 3 weeks. The positive control (200 micro liter of 0.1% sodium lauryl sulfate) and negative control (200 micro liter of distilled water) are applied on separate occlusive patches. Irritation is evaluated after every patch removal using an eight point scale.

Patches are removed from a site if the investigator noted a score of 3 or greater on the 8-point integer scale or significant superficial skin reactions. The following scales are used to grade test site responses:

Table 37: Inflammatory Skin Responses Scale

Score	Definition
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Moderate erythema, readily visible; or minimal edema or minimal papular response
3	Strong erythema, or erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Source: NDA 22-563, U0267-101, Clinical Study Report, Section 16.1.1., Appendix 1

Table 38: Superficial Skin Responses Scale

Score	Definition
A	Slight glazed appearance
B	Marked glazing
C	Glazing with peeling and cracking
D	Glazing with fissures
E	Film of dried serous exudate covering all or portion of the patch site
F	Small petechial erosions and/or scabs

Source: NDA 22-563, U0267-101, Clinical Study Report, Section 16.1.1., Appendix 1

Table 39: Notations Replacing Scores

Notation	Definition
X	Subject absent
PD	Patch dislodged
NA	Patch not applied
NP	No patch due to limiting irritation

Source: NDA 22-563, U0267-101, Clinical Study Report, Section 16.1.1., Appendix 1

Endpoints:
The co-primary endpoints are as follows:

- mean cumulative irritation score and the total cumulative irritation score calculated for each product.

Statistical Methods:
Descriptive statistics are used to summarize safety results. All randomized subjects who received the test product are included in the safety assessment. The Per-Protocol data set is used for analysis of the primary endpoint with last observation carried forward (LOCF) for missing data.

Results:
Twelve subjects report at least 1 AE. The most common AEs are application site pruritus in 4 subjects, nasopharyngitis in 2 subjects, contact dermatitis in 2 subjects and pruritus in 2 subjects. The mean converted and mean total converted cumulative irritation scores for the positive control (0.1% SLS) are significantly greater than calcipotriene foam. In addition, the mean converted and total converted cumulative irritation scores for calcipotriene foam are significantly greater than the negative control in 2 way ANOVA analyses.

Protocol Number: **U0267-102**
Study initiation and completion dates: September 20, 2008 to January 31, 2009

Study center: Eric Erlbaum**,** MD, Hill Top Research, Inc., 3225 North 75th Street, Scottsdale, Arizona 85251, USA

Title: A Single-Center, Evaluator-Blinded, Randomized, Placebo-Controlled, Phase 1 Clinical Trial Evaluating the Potential of Topically Applied EF Calcipotriene Foam, 0.005% to Induce Contact Sensitization in Healthy Volunteers Upon Exposure to Repeated Skin Patch Applications

Objective: to evaluate the sensitization potential of calcipotriene foam and vehicle foam in 231 healthy volunteers

Study Plan: This is a single-center, evaluator-blinded, randomized, placebo-controlled study to evaluate the potential for the cutaneous sensitization of calcipotriene foam and vehicle foam in 231 healthy volunteers. The study is conducted in 4 phases: an induction phase, rest period, a challenge phase and potentially a rechallenge phase. During the induction phase 200 μl of calcipotriene foam and 200 μl of vehicle foam are applied under occlusive patches to the backs of 231 subjects 3 times per week for 3 weeks. Inflammatory responses are assessed when the patches are replaced. A 10 to 14 day rest period follows the induction phase. During the challenge phase 200 μl of

calcipotriene foam and 200 μl of vehicle foam are applied under occlusive patches to naïve sites to the backs of all subjects for 48 hours. Inflammatory responses are recorded after removal of the patches at 24, 48 and 72 hours. If contact sensitization is suspected from the results of the challenge phase then the subjects are rechallenged after a 2 week rest period.

The following scales are used to grade contact sensitization:

Table 40: Erythema Grading Scale

Response	Symbol
No visible reaction	0
Slight, confluent, or patchy erythema	+
Mild erythema (pink)	1
Moderate erythema (definite redness)	2
Strong erythema (very intense redness)	3

Source: NDA 22-563, U0267-102, Clinical Study Report, Section 16.1.1., Appendix 1

Table 41: Local Skin Reaction Grading Scale

Response	Notation
Edema-swelling, spongy feeling when palpated	E
Papule-red, solid, pinpoint elevation	P
Vesicle-small elevation containing fluid	V
Bulla reaction-fluid-filled lesion (blister)	B
Spreading-evidence of the reaction beyond the Webril pad area	S
Weeping-result of a vesicular or bulla reaction-serous exudate	W
Induration-solid, elevated hardened, thickened skin	I
Residual reaction to earlier application after absence	*
Response occurs on ≤ 25% of test site	-

Source: NDA 22-563, U0267-102, Clinical Study Report, Section 16.1.1., Appendix 1

Table 42: Superficial Effects Grading Scale

Response	Notation
Glazing	g
Peeling	y
Scab, dried film of serous exudate of vesicular or bulla reaction	c
Hyperpigmentation (reddish-brown discoloration of test site)	d
Hypopigmentation (loss of visible pigmentation at the test site)	h
Fissuring (grooves in the superficial layers of the skin	F
Additional comments	@

Source: NDA 22-563, U0267-102, Clinical Study Report, Section 16.1.1., Appendix 1

Table 43: Other Effects Grading Scale

Notation	Definition
X	Subject absent
PD	Patch dislodged
NA	Patch not applied
NP	No patch due to limiting irritation
NC	No 9th grade in induction

Source: NDA 22-563, U0267-102, Clinical Study Report, Section 16.1.1., Appendix 1

Endpoints:
The primary endpoint is the investigator evaluation of patch test sites for inflammatory responses (erythema and local skin reactions) or superficial effects which are graded according to the contact sensitization scales. Effects must occur on at least 25% of the test site to be significant.

Statistical Methods:
All randomized subjects who received the test product are included in the safety assessment. The Per Protocol (PP) data set is used to evaluate the primary endpoint (contact sensitization). Subjects in the PP data set must complete the induction and challenge phases and present for follow up 24 hours after patch removal.

Results:
At the onset of the study 90% of the patches containing calcipotriene foam or vehicle foam are graded as 0; at the 9th patch replacement approximately 50% of the patches containing calcipotriene foam or vehicle foam are graded as 0. One subject experienced contact sensitization in the PP data set.

Protocol Number: **U0267-103**
Study initiation and completion dates: September 27, 2008 to October 5, 2008.

Study center: John V. Murray, MD
Hill Top Research, 6699 13th Avenue North, St. Petersburg, FL 33710

Title: A Single-Center, Evaluator-Blinded, Randomized, Placebo-Controlled, Phase 1 Clinical Trial Evaluating the Phototoxic Potential of Topically Applied EF Calcipotriene Foam, 0.005% in Healthy Volunteers

Objective: to evaluate the phototoxic potential of calcipotriene foam and vehicle foam in 39 healthy volunteers

Study Plan:
This is a single-center, evaluator-blinded, randomized, placebo controlled, Phase 1 study to assess the phototoxic potential of calcipotriene foam. Thirty nine healthy

volunteers have 2 sets of three patches containing Calcipotriene Foam, 0.005%, vehicle foam or no product applied to their backs. One set of patches is removed after 24 hours and the site is irradiated with 16 joules/ cm^2 of ultraviolet A light (UVA) and 0.75 minimal erythema dose (MED) of UVA/UVB. The second set of patches is removed and serves as a non-irradiated control. All sites are examined at 1, 24, 48 and 72 hours after patch removal for inflammation and local reactions. Refer to trial U0267-102 for the grading scales used in trial U0267-103.

Endpoints:
The primary safety endpoint is the inflammatory response (erythema and local skin reactions) or superficial effects comprising ≥ 25% of the test site.

Statistical Methods:
Descriptive statistics are used to provide safety results from photopatch testing. The per protocol (PP) data set is used for analysis of the primary endpoint with last observation carried forward (LOCF) for missing data.

Results:
There are no differences in phototoxic potential among active, vehicle or blank patches as measure by inflammatory responses or superficial effects after irradiation. At least 92% of subjects experienced no local skin reactions and at least 95% of subjects experienced no superficial effects throughout the study.

Protocol Number: **U0267-104**
Study initiation and completion dates: October 13, 2008 to November 24, 2008.

Study center: John V. Murray, MD
Hill Top Research, 6699 13th Avenue North, St. Petersburg, FL 33710

Title: A Single-Center, Evaluator-Blinded, Randomized, Placebo-Controlled, Phase 1 Clinical Trial Evaluating the Photoallergic Potential of Topically Applied EF Calcipotriene Foam, 0.005% in Healthy Volunteers

Objective: to assess the photoallergic potential of calcipotriene foam and vehicle foam in 57 healthy volunteers

Study Plan:
This is a single-center, evaluator-blinded, randomized, placebo-controlled phase 1 study to evaluate the photoallergic potential of calcipotriene foam and vehicle foam in 57 subjects. There were 4 phases after screening: induction, rest, challenge and rechallenge (if indicated by the results of the challenge).The minimal erythema dose (MED) for each subject is determined during the screening period. There are 2 patches in each set (calcipotriene foam and vehicle foam). Each set is applied for 24 hours and then removed. The test sites are assessed, irradiated with twice the MED of UVB and

then reassessed at 48 hours. This procedure is conducted at 3 to 4 day intervals for a total of 6 induction phases. Each of the six sets is applied to the same site unless there is evidence of a severe inflammatory reaction. After a 10 to 17 day rest period, 2 sets of 3 patches (calcipotriene foam, vehicle foam and no product) are applied to naïve sites for 24 hours. One set is removed and irradiated with 16 joules/cm^2 of UVA and 0.75 MED of UVB/UVA. The second set is removed and served as non-irradiated controls. All sites are evaluated at 1, 24, 48 and 72 hours after irradiation. If a positive response is observed a rechallenge is conducted. Refer to trial U0267-103 for the grading scales used in trial U0267-104.

Endpoints: The primary safety endpoint is the inflammatory response (erythema and local skin reactions) or superficial effects comprising ≥ 25% of the test site.

Statistical Methods:
Descriptive statistics are used to provide safety results from photopatch testing. All randomized subjects who received the test product are included in the safety assessment. The Per Protocol data set is used for analysis of the primary endpoint with last observation carried forward (LOCF) for missing data.

Results:
During the challenge phase, irradiation of calcipotriene and vehicle patches produced erythema scores graded as none to mild erythema in 96% of subjects at 72 hours. There are no differences in photoallergic potential among active, vehicle or blank patches as measured by inflammatory responses or superficial effects after irradiation. One subject withdrew due to abdominal pain that resolved in 2 days with treatment.

7.1.2 Categorization of Adverse Events

Safety assessments include adverse event records, concomitant medication summaries, study termination narratives, visual grading of patch tests and urine pregnancy testing. A subject reporting multiple episodes of the same event is counted once at the level of highest severity.

All adverse events are classified on the basis of the MedDRA terminology (Version 11.0) by organ class and preferred term. The following categories of AEs are summarized: treatment-emergent AEs, treatment-related AEs, AEs leading to discontinuation and serious AEs (SAEs). Treatment-emergent AEs are defined as events occurring during study treatment and 30 days after completion of study treatment. The following tables of treatment-related AEs are provided in the NDA: incidence of AEs, incidence of severe AEs, incidence of severe related AEs, incidence of SAEs, incidence of serious treatment–related AEs and the incidence of AEs leading to study discontinuation. The classification of verbatim terms with preferred terms in Phase 2 and Phase 3 studies appears to be acceptable. Safety data, demographic data and exposure data are presented with descriptive statistics

The Phase 2 and Phase 3 trials are discussed in Section 5.3.

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

The integrated safety analysis includes data from all subjects who received study product in the 2 pivotal trials (U0267-301 and U0267-302) and from all subjects who received calcipotriene foam or vehicle foam in the Phase 2 study (CAL. 201). The rationale for excluding data from the other studies is that subjects in these trials are exposed to smaller amounts of the study drug or apply the product for a shorter duration of time.

7.2 Adequacy of Safety Assessments

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

There are 731 subjects in the integrated safety analysis set. Table 44, Table 45 and Table 46 summarize subject exposure.

Table 44: Number of Applications (Integrated Safety Analysis Set)

	Calcipotriene foam N = 473	**Vehicle foam N = 258**
Number of Applications		
n	460	251
Mean (SD)	107 (20.4)	105 (22.8)
Median	112	111
Min, max	5, 161	6, 224

Source: Adapted from NDA 22-563 Tables 5, Module 5, Integrated Summary of Safety.

Table 45: Total Amount of Study Product Used (Integrated Safety Analysis Set)

	Calcipotriene foam N = 473	**Vehicle foam N = 258**
Amount of study product used (g)		
n	413	227
Mean (SD)	191.5 (126.73)	185.9 (117.31)
Median	173.1	162.5
Min, max	3.5, 684.4	6.0, 689.9

Source: Adapted from NDA 22-563 Tables 6, Module 5, Integrated Summary of Safety.

Table 46: Daily Study Product Use (Integrated Safety Analysis Set)

	Calcipotriene foam N = 473	**Vehicle foam N = 258**
Daily study product used (g)		
n	408	223
Mean (SD)	3.6 (2.3)	3.5 (2.1)
Median	3.1	3.2
Min, max	0.1, 12.2	0.2, 13.6

Source: Adapted from NDA 22-563 Tables 7, Module 5, Integrated Summary of Safety.

Subjects treated with calcipotriene foam experienced greater exposure to the test product than subjects treated with vehicle foam. Eighty nine percent of subjects are treated with calcipotriene foam for 52 days or more; 86% of subjects are treated with vehicle foam for 52 days or more. The mean total exposure and daily exposure are greater for calcipotriene foam than vehicle foam. One explanation is that subjects who observe an improvement are more likely to remain compliant.

In addition, subjects in the calcipotriene group are at greater risk for dose related AEs since their exposure is greater. However, tables of adverse events versus total dose indicate a minimal increase in AEs with exposures greater than 100 g. This is demonstrated by Figure 5 which plots albumin-adjusted serum calcium by total product used.

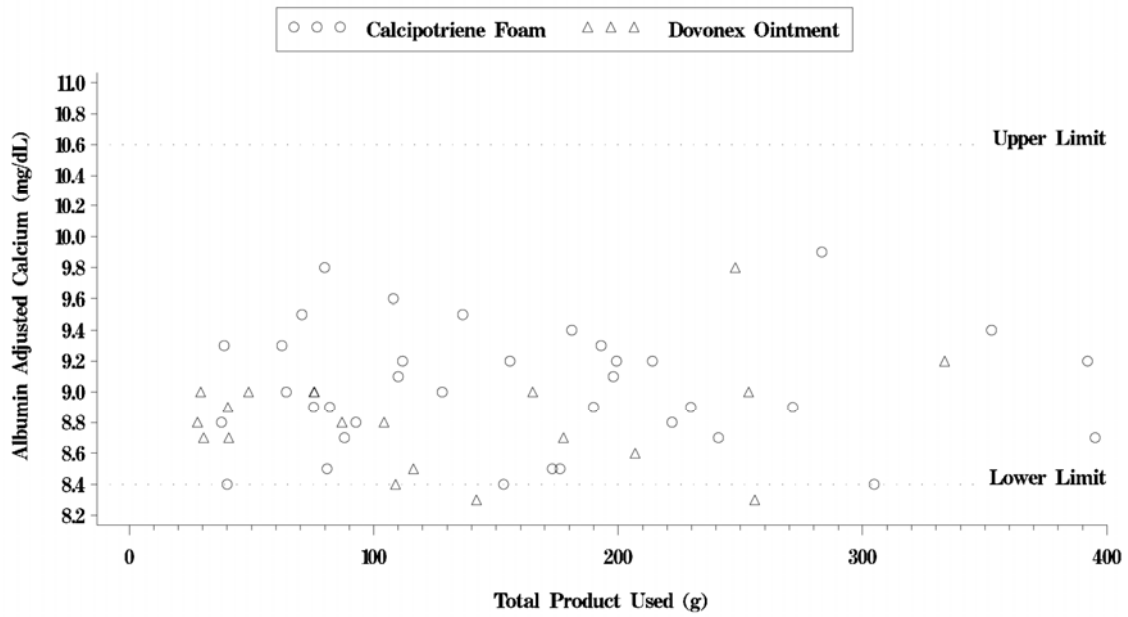

Figure 5: Albumin-adjusted calcium at Week 8 by treatment and total product used (ITT analysis set)

Source: Amendment to NDA 22-563 dated May 17, 2010, Figures for CAL. 201 and 203

The study is completed (+/- 4 days) by 89% (419) of subjects in the calcipotriene group and 86% (222) in the vehicle group.

The demographic profile for subjects in the safety data set is comparable to the demographic profile for subjects in the Phase 3 trials. The age range for subjects in the integrated safety analysis set is 12 to 89 with 85% (622) of subjects in the 18 to <65 interval. Only 1% of subjects in the integrated safety data set are less than age 18 at baseline and 14% of subjects are age 65 and above. The subjects are 55% (400) male and 89% (648) Caucasian. Demographic measures are similar in both the control group and the treatment group.

However, the study population does not reflect the demographics of the United States population. According to the Census Bureau the United States population is categorized as 75.1% Caucasian, 12.3% Black and 12.5% Hispanic. 7. The prevalence of psoriasis in the United States is 2.5% among Caucasians and 1.3% among African Americans. 8 According to Neiman and others the overall incidence rate is highest among individuals aged 60 to 69 and greater for men than women.9 Thus, there are insufficient numbers of non-Caucasian and elderly subjects and subjects between the ages 12 and 17.

7 Overview of Race and Hispanic Origin, U.S. Census bureau, Census 2000 Brief, March 2001, p.3
8 Gelfand JM et al. The prevalence of psoriasis in African Americans: Results from a population-based study. J Am Acad Dermatol 2005;52:23-26.
9 Neimann AL et al. the epidemiology of psoriasis. Expert Rev. Dermatol. 2006;1:63-75.

Table 47: Subject Demographics (Integrated Safety Analysis Set)

	Calcipotriene foam N = 473	**Vehicle foam N = 258**	**Total N = 731**
Age (years)			
Mean (SD)	48.2 (14.5)	48.2 (15.3)	48.2 (14.8)
Median	48	48	48
Min, Max	12, 89	15, 88	12, 89
Age Category (years), n (%)			
<18	6 (1)	4 (2)	10 (1)
18 to <65	408 (86)	214 (83)	622 (85)
≥65	59 (12)	40 (16)	99 (14)
Sex, n (%)			
Male	257 (54)	143 (55)	400 (55)
Female	216 (46)	115 (45)	331 (45)
Race, n (%)			
American Indian or Alaska Native	1 (<1)	0	1 (<1)
Asian	18 (4)	4 (2)	22 (3)
Black	11 (2)	10 (4)	21 (3)
Multiracial	17 (4)	7 (3)	24 (3)
Native Hawaiian or Other Pacific Islander	2 (<1)	1 (<1)	3 (<1)
White	414 (88)	234 (91)	648 (89)
Missing	10 (2)	2 (1)	12 (2)
Ethnicity, n (%)			
Hispanic or Latino	81 (17)	44 (17)	125 (17)
Not Hispanic or Latino	380 (80)	206 (80)	586 (80)
Missing	12 (3)	8 (3)	20 (3)

Source: Modified from NDA 22-563 Summary Table 1.3.3, Section 13

7.2.2 Explorations for Dose Response

No dose ranging studies were performed in humans for calcipotriene foam since the moiety has been marketed in the United States at the same concentration in different formulations since 1993 (NDA 20-273). However, dose response information is obtained in two 28-Day Repeat-Dose Toxicity studies and two 90-Day Repeat-Dose Toxicity studies in the rat and minipig. Refer to Section 5.2.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing is performed for this 505 (b) (2) application.

7.2.4 Routine Clinical Testing

The scheduled laboratory assessments obtained during the pivotal trials (U0267-301 and U0267-302) include urine pregnancy tests collected at baseline and at Week 8. Subjects who are found to be pregnant are discontinued from the trial and followed to term or early termination. Partners of subjects who become pregnant are followed to term or early termination. Infants are followed for 6 months after delivery.

The scheduled laboratory assessments obtained during CAL. 201 include albumin-adjusted serum calcium levels in addition to urine pregnancy tests. Refer to Section 7.4.2.

7.2.5 Metabolic, Clearance, and Interaction Workup

This 505 (b)(2) application does not contain an evaluation of potential drug interactions. Clinically meaningful drug interactions are not expected with the limited systemic exposure demonstrated in bioavailability studies. Section 4.4.3. addresses pharmacokinetics and drug metabolism. The following statement in Section 12.3 of labeling provides information about the metabolism and clearance of calcipotriene:

> Absorbed calcipotriene is known to be converted to inactive metabolites within 24 hours of application. (b) (4) [redacted] (b) (4) metabolism [redacted] (b) (4) occurs via a similar pathway to the natural hormone. [redacted]

Refer to Section 9.2 for Agency recommendations for labeling.

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

Hypercalcemia is a rare but consistent adverse event observed with vitamin D analogs. Based on the literature and the Summary Basis of Approval for Dovonex Ointment the applicant concludes that 100 grams per week (recommended dose for 20% BSA) is not associated with albumin-adjusted serum calcium elevations. The studies which inform this conclusion for Dovonex Ointment are described in 7.4.5. During the calcipotriene foam development program measurements of albumin-adjusted serum calcium are obtained in studies U0267-201 (CAL. 201) and U0267-203 (CAL. 203). Refer to Section 7.4.2 and 7.4.5.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported during the course of the trials included in the integrated safety analysis set.

7.3.2 Nonfatal Serious Adverse Events

One subject (<1%) experienced a Serious Adverse Event (SAE) in the calcipotriene foam group and 2 subjects (<1%) experienced 1 or more SAEs in the vehicle foam group. Summaries and narratives are provided in Table 48 and paragraphs to follow.

Table 48: Summary of Serious Adverse Events (Integrated Safety Analysis Set)

SYSTEM ORGAN CLASS Preferred Term	Calcipotriene Foam (N = 473) n (%)	Vehicle Foam (N = 258) n (%)
Subjects reporting any SAE	1 (<1)	2 (1)
CARDIAC DISORDERS	1 (<1)	0
Atrial fibrillation	1 (<1)	0
Cardiac failure congestive	1 (<1)	0
EAR AND LABYRINTH DISORDERS	0	1 (<1)
Deafness unilateral	0	1 (<1)
GASTROINTESTINAL DISORDERS	0	1 (<1)
Intestinal obstruction	0	1 (<1)

Source: NDA 22-563 Summary Table 3.6, Section 13

The following narratives describe the serious adverse events that occurred during the development program.

Subject ID: (b) (6)/004-1046 (atrial fibrillation/congestive heart failure), calcipotriene foam group

A 60-year-old Caucasian male subject (004-1046) is hospitalized for mild atrial fibrillation and moderate congestive heart failure approximately 5 weeks after the last application of calcipotriene foam for plaque-type psoriasis in trial U0267-301. His past medical history is remarkable for hypertension, heart palpitations, ruptured disc, multiple thoracic spine compression fractures, laminectomy, back pain, restless leg syndrome, morbid obesity (weight 195 kg, BMI of 53), and sleep apnea. Concomitant medications include verapamil, lisinopril, amitriptyline, tramadol, aspirin, acetaminophen, ibuprofen,

melatonin, valerian, and gabapentin. The subject completed the study as per protocol and the event of atrial fibrillation resolved on August 12, 2008.

The investigator assesses the events of atrial fibrillation and congestive heart failure as serious due to the hospitalization and possibly related to study product since both are new diagnoses after initiating the study medication. However, the applicant assesses both conditions as unrelated to study product, based on the normal electrolyte profile (including calcium) and significant co-morbid conditions such as morbid obesity, obstructive sleep apnea and hypertension leading to diastolic dysfunction.

Subject ID: (b) (6)/006-1151 (acute intestinal obstruction), vehicle foam group
A 59-year-old white male subject with plaque-type psoriasis is hospitalized for acute intestinal obstruction while enrolled in trial U0267-301 after 18 days of treatment with vehicle foam. His past medical history is remarkable for Crohn's disease (1964), partial colectomy(1991), hyperlipidemia (2000) and osteopenia (2006). Concomitant medications include Flagyl (metronidazole) and Colestid (colestipol). A small bowel follow-through revealed a high-grade segmental stenosis of the bowel in the region of the ileorectal anastomosis resulting in a partial mechanical obstruction. The bowel obstruction gradually resolved. On October 28, 2008, the acute bowel obstruction is considered resolved with the sequelae of an ongoing stricture. The subject resumed the study product on November 2, 2008. However, he is terminated from the study on November 10, 2008 due to his need for prohibited medications and additional procedures to treat the event.

The investigator and the applicant assess the event as unrelated to the study product.

Subject: (b) (6)/003-1114 (deafness unilateral), vehicle foam group
A 60-year-old white female subject with plaque-type psoriasis receiving vehicle foam experiences significant disability due to hearing loss in the right ear while enrolled in trial U0267-302. Her past medical history is remarkable for of psoriasis, hypothyroidism, and seasonal allergies. Concomitant medications include Synthroid (levothyroxine) and Allegra (fexofenadine). At the week 4 study visit, the subject reports that she had a spinning sensation, hearing loss, nausea and vomiting. She is diagnosed with a viral inner ear infection by her primary care physician (PCP) and prescribed prednisone, meclizine, and promethazine. On June 26, 2008, the subject is withdrawn from the study due to treatment with prednisone. The 70% hearing loss is confirmed by an ear, nose and throat (ENT) physician. The subject notes gradual improvement without return to baseline.

The investigator and applicant assess the event of hearing loss in the right ear as not related to the study product.

7.3.3 Dropouts and/or Discontinuations

Table 49 summarizes the disposition of study subjects including the reasons for product discontinuation. Nine subjects (2%) in the calcipotriene foam group and 4 subjects (2%) in the vehicle group discontinued the trials due to adverse events. Application site reactions are the most common AEs to cause subjects to leave the trials (12/13) as presented in Table 49.

Table 49: Reasons for Study Product Discontinuation (ITT Analysis Set)

	Calcipotriene foam n (%)	**Vehicle foam n (%)**	**Total n (%)**
N	473	258	731
Completed	429 (91%)	228 (88%)	657 (90%)
Discontinued	44 (9%)	30 (13%)	74 (10%)
Reasons for discontinuation			
Adverse event	9 (2%)	4 (2%)	13 (2%)
Lost to follow-up	7 (1%)	6 (2%)	13 (2%)
Lack of efficacy	7 (1%)	5 (2%)	12 (2%)
Non-compliance with study treatment	1 (<1%)	1 (<1%)	2 (<1%)
Withdrawal of consent	16 (3%)	10 (4%)	26 (4%)
Other	4 (1%)	4 (2%)	8 (1%)

Source: Modified from NDA 22-563 Summary Table 1.2.1, Section 10

Table 50: Summary of Adverse Events Leading to Discontinuation (Integrated Safety Data Set)

SYSTEM ORGAN CLASS **Preferred Term**	**Calcipotriene Foam (N = 473) n (%)**	**Vehicle Foam (N = 258) n (%)**
Subjects reporting any AE leading to discontinuation	9 (2)	4 (2)
GASTROINTESTINAL DISORDERS	0	1 (<1)
Small intestinal stenosis	0	1 (<1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (2)	3 (1)
Application site bleeding	1 (<1)	0
Application site erythema	6 (1)	2 (1)
Application site exfoliation	1 (<1)	0
Application site irritation	5 (1)	1 (<1)
Application site oedema	0	1 (<1)
Application site pain	0	1 (<1)
Application site pruritus	6 (1)	2 (1)
Application site swelling	1 (<1)	0
Application site vesicles	0	1 (<1)
INFECTIONS AND INFESTATIONS	1 (<1)	0
Application site folliculitis	1 (<1)	0

Source: NDA 22-563 Summary Table 3.8, Section 13

7.3.4 Significant Adverse Events

Severe AEs are reported by 4 subjects (1%) receiving calcipotriene foam and 4 subjects (2%) receiving vehicle. There are no treatment- related Severe AEs in the calcipotriene foam group and 2 treatment-related Severe AEs in the vehicle group consisting of application site reactions. The severe adverse events are summarized in Table 51.

Table 51: Summary of Severe Adverse Events (Integrated Safety Analysis Set)

SYSTEM ORGAN CLASS Preferred Term	Calcipotriene Foam (N = 473) n (%)	Vehicle Foam (N = 258) n (%)
Subjects reporting any severe AE	4 (1)	4 (2)
EAR AND LABYRINTH DISORDERS	0	1 (<1)
Deafness unilateral	0	1 (<1)
GASTROINTESTINAL DISORDERS	1 (<1)	1 (<1)
Abdominal distension	0	1 (<1)
Abdominal pain	0	1 (<1)
Constipation	0	1 (<1)
Crohn's disease	0	1 (<1)
Dental caries	1 (<1)	0
Intestinal obstruction	0	1 (<1)
Nausea	0	1 (<1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	2 (1)
Application site erythema	0	1 (<1)[a]
Application site irritation	0	1 (<1)[a]
Application site pain	0	1 (<1)[a]
Application site vesicles	0	1 (<1)[a]
IMMUNE SYSTEM DISORDERS	1 (<1)	0
Drug hypersensitivity[b]	1 (<1)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (<1)	0
Musculoskeletal pain	1 (<1)	0
NERVOUS SYSTEM DISORDERS	1 (<1)	0
Migraine	1 (<1)	0

Source: NDA 22-563 Summary Table 3.4, Section 13

The following narratives describe the 2 pregnancies that occurred during the development program.

Subject ID: (b) (6)/010-1093 (pregnancy), vehicle foam group
A 28-year-old Caucasian female subject (010-1093) becomes pregnant while enrolled in trial U0267-301 after exposure to vehicle foam between May 22, 2008 and June 22, 2008. The vehicle foam is discontinued and she is withdrawn from the study. Her pregnancy is uncomplicated and the subject delivered a normal infant. Additional information is requested from the subject.

The investigator and the applicant assess the pregnancy as not related to the study product.

Subject ID: 3006 (pregnancy), Calcipotriene foam group
A 33-year-old Caucasian female subject (3006) becomes pregnant while enrolled in trial U0267-203 after exposure to calcipotriene foam between August 23, 2006 and September 6, 2006. Urine pregnancy test was negative when she attended the Day 1 Visit but is found to be positive after she completed the last application of the study product. The subject delivered a normal infant at 34 weeks gestation on (b) (6). Information concerning that status of the infant and mother at the 6 month follow up visit is not included. Since this event occurred during trial U0267-203 it is not included in the Integrated Safety Data Set.

The investigator and the applicant assess the pregnancy as not related to the study product.

7.3.5 Submission Specific Primary Safety Concerns

The most common treatment related adverse events are associated with application site reactions. The most significant potential adverse event is hypercalcemia which is a class effect. Refer to Section 7.4.2.

Table 52: Summary of Treatment-Related Adverse Events (Integrated Safety Analysis Set)

SYSTEM ORGAN CLASS **Preferred Term**	**Calcipotriene Foam (N = 473) n (%)**	**Vehicle Foam (N = 258) n (%)**
Subjects reporting any treatment-related AE	22 (5)	16 (6)
CARDIAC DISORDERS	1 (<1)	0
Atrial fibrillation	1 (<1)	0
Cardiac failure congestive	1 (<1)	0
GASTROINTESTINAL DISORDERS	1 (<1)	0
Diarrhoea	1 (<1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	18 (4)	10 (4)
Application site bleeding	2 (<1)	0
Application site erythema	9 (2)	2 (1)
Application site excoriation	0	1 (<1)
Application site exfoliation	1 (<1)	0
Application site irritation	9 (2)	4 (2)
Application site oedema	0	2 (1)
Application site pain	2 (<1)	1 (<1)
Application site pruritus	7 (1)	6 (2)
Application site rash	2 (<1)	0
Application site reaction	1 (<1)	0
Application site swelling	1 (<1)	0
Application site vesicles	0	1 (<1)
Oedema peripheral	1 (<1)	0
		Continued

SYSTEM ORGAN CLASS Preferred Term	Calcipotriene Foam (N = 473) n (%)	Vehicle Foam (N = 258) n (%)
INFECTIONS AND INFESTATIONS	1 (<1)	1 (<1)
Application site folliculitis	1 (<1)	0
Pharyngitis	0	1 (<1)
Upper respiratory tract infection	0	1 (<1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (<1)
Excoriation	0	1 (<1)
NERVOUS SYSTEM DISORDERS	0	2 (1)
Dizziness	0	1 (<1)
Headache	0	1 (<1)
RENAL AND URINARY DISORDERS	1 (<1)	0
Urine odour abnormal	1 (<1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (1)	2 (1)
Dermatitis contact	1 (<1)	0
Erythema	1 (<1)	0
Pruritus generalised	1 (<1)	1 (<1)
Rash	1 (<1)	0
Skin chapped	0	1 (<1)

Source: NDA 22-563, Summary Table 3.3, Section 13

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events are elicited by open-ended questioning. Prior to the administration of any study product, subjects are instructed to report “any physical changes or new symptoms they notice during the course of the study” or any “problems with the study drug.”

Most of the treatment-related adverse events (AEs) involve application site reactions. Approximately 4% percent of subjects in both the calcipotriene foam and vehicle foam groups experience application site bleeding, erythema, excoriation, exfoliation, irritation, edema, pain, irritation, pruritus, rash, swelling, vesicles or a cutaneous reaction.

Table 53 summarizes the AEs by preferred term in descending order of frequency that are reported by at least 2% of the subjects exposed to each study product.

Table 53: Summary of Most Frequent Events Experienced by Preferred Term (Integrated Safety Analysis Set)

Preferred Term	Calcipotriene Foam (N = 473) n (%)	Vehicle Foam (N = 258) n (%)
Application site irritation	9 (2)	4 (2)
Application site pruritus	7 (1)	6 (2)
Nasopharyngitis	8 (2)	4 (2)
Application site erythema	9 (2)	2 (1)
Headache	4 (1)	4 (2)
Upper respiratory tract infection	3 (1)	5 (2)
Cough	2 (<1)	5 (2)
Pharyngolaryngeal pain	1 (<1)	4 (2)

Source: NDA 22-563 Summary Table 3.1, Section 13

7.4.2 Laboratory Findings

Calcium homeostasis is assessed with albumin-adjusted total serum calcium levels in the two Phase 2 trials. This measurement accounts for the binding of calcium to varying levels of serum albumin. Albumin-adjusted serum calcium levels are evaluated at screening, Week 4 and Week 8 in study CAL. 201 and at screening, baseline, Day 8 and Day 15 in study Cal. 203. Among the 101 subjects with mild to moderate psoriasis enrolled in study CAL. 201, 36 received calcipotriene foam and 18 received Dovonex ointment. All 32 subjects enrolled in study CAL. 203 received calcipotriene foam. None of the subjects treated with calcipotriene foam or ointment developed albumin-adjusted serum calcium levels above the normal range. However, some subjects have screening or baseline levels below the normal range.

There is one positive pregnancy test during the course of trial CAL. 203 and one positive pregnancy test during the course of trial U0267-301. Refer to Section 7.3.4 for a narrative of each case.

7.4.3 Vital Signs

Vital signs are recorded for all subjects in Cal. 201 and the Phase 3 trials at baseline and Week 8. There are no clinically significant changes from baseline values except as noted below:

<u>Study U0267-302</u>
• Subject 009-1171 (calcipotriene foam group): pyrexia on day 30, mild intensity and unrelated to study product

• Subject 010-1190 (calcipotriene foam group): hypertension reported as an ongoing problem on day 57, moderate intensity and unrelated to study product
• Subject 012-1061 (calcipotriene foam group): hypertension reported as ongoing on day 51, moderate intensity and unrelated to study product

7.4.4 Electrocardiograms (ECGs)

No electrocardiograms are obtained during CAL.201 or the pivotal trials. In response to an Information Request letter dated 2010-05-3, Stiefel requests a waiver to conduct a thorough QT/QTc study and includes their rationale for the request. The applicant acknowledges the recommendation of the International Conference on Harmonization (ICH) *Guidance for Industry – E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* to consider the need to assess the cardiac repolarization effect of a new drug or an approved drug, when a new dose or route of administration is being developed that results in significantly higher exposure (i.e., Cmax or AUC) or if the drug or members of its chemical or pharmacological class have been associated with QT/QTc interval prolongation, Torsade de pointes, or sudden cardiac death during postmarketing surveillance. They assert:

- Systemic bioavailability of calcipotriene from topically applied calcipotriene foam is very low, and in most instances is below the level of quantification and certainly no higher than the bioavailability reported for the listed drug (Dovonex ointment).
- A search of the relevant literature for the period 01 Jan 1980 to 01 May 2010 did not reveal any relevant association of calcipotriene and vitamin D analogs with QT/QTc interval prolongation or related events.

Pharmacokinetic studies indicate a maximal systemic exposure of 6.6 nM.

An examination of the AERS database by the Office of Surveillance and Epidemiology reveals 3 cases associated with pro-arrhythmic adverse events. These cases contain multiple confounding variables or are not sufficiently well documented to support a causal relationship between cardiac arrhythmias and calcipotriene. A search of the literature does not identify any additional reports of cardiac arrhythmias associated with exposure to the moiety. Thus, the Division of Pharmacovigilance recommends no further assessment of cardiac repolarization at this time and no enhancements to labeling.

Thus, the Division accepts the request for a waiver to submit data from a thorough QT/QTc study on the basis of low systemic exposure and no evidence of a relevant safety signal for the moiety.

7.4.5 Special Safety Studies/Clinical Trials

No special studies are conducted in this development program.

In contrast to the current development program for calcipotriene foam, the development program for Dovonex ointment contained a rigorous assessment of calcium homeostasis. Investigators collected measurements of total serum calcium, 24 hour urine calcium, 24 hour urine hydroxyproline, parathyroid hormone, fractionated alkaline phosphatase and bone densitometry at multiple time points in 78 subjects with mild to moderate plaque psoriasis (5-20% BSA). Subjects were treated with calcipotriene ointment or vehicle twice daily for eight weeks. There were no clinically significant changes in total serum calcium, 24 hour urine calcium, 24 hour urine hydroxyproline or bone densitometry indicating abnormal calcium metabolism. Six subjects demonstrated elevated fractionated alkaline phosphatase and two subjects who were treated with vehicle show elevated parathyroid hormone.

In addition, investigators conducted a 52 week trial with Dovonex 0.005% ointment in 397 patients with mild to moderate psoriasis vulgaris to evaluate long term safety and calcium homeostasis. Blood chemistry, hematology and urine samples were collected at multiple time points throughout the study. Serum calcium levels ranged from 8.5 to 10.6. However, only one patient demonstrated consistently elevated calcium levels throughout the study but the baseline level of serum calcium was10.5.

7.4.6 Immunogenicity

The applicant includes a study by Suzuki et al 10 investigating the antigenicity of calcipotriol which concludes that calcipotriol does not induce the production of IgE antibodies in mice or IgG1 antibodies in guinea pigs.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No dose ranging studies are conducted in this development program. All the trials included in the safety database evaluate the safety and efficacy of the same concentration of calcipotriene foam.

The applicant submits some data concerning the dose dependency of adverse events in the response to an Information Request dated 2010-05-11 which includes graphic

10 Suzuki, T et al. An antigenicity study of calcipotriol (MC903). J Toxicolog Sci. 1996: 21(supp II): 457-463.

presentations of baseline BSA versus serum calcium increase, drug exposure versus serum calcium increase and drug exposure versus overall adverse events. For subjects who apply greater than 100 grams, the table indicates a slight trend to greater numbers of application site reactions and other adverse events. The Clinical Pharmacology Reviewer concludes that the graphs visualizing the calcium changes per BSA or total drug exposure demonstrate no evidence of differential effects on calcium metabolism by calcipotriene foam versus Dovonex ointment. No subject, regardless of amount of exposure to the study product, exhibits an elevated albumin-adjusted serum calcium level. This is consistent with the finding of no significant difference in pharmacokinetics between the calcipotriene foam and Dovonex ointment in Cal. 203 since most of plasma levels are below the level of quantization.

7.5.2 Time Dependency for Adverse Events

In general, investigators compare clinical and laboratory assessments of systemic effects at baseline and end-of-treatment. Although some trials include interval assessments, the trials are not designed to evaluate time dependency for adverse events.

7.5.3 Drug-Demographic Interactions

There are no special dosing recommendations indicated by subgroup analyses. Subgroup analysis of adverse events is conducted by sex, age and race. There is no difference in the incidence of AEs between males and females who received calcipotriene foam. Application site irritation (3% vs. 0%) and application site pruritus (4% vs. 1%) are greater in females than males in the vehicle foam treatment group. There are no clinically meaningful differences in the incidence of AEs by age group. However, adverse events in subjects less than 18 years old are not included in the NDA summary table of AEs by age since there are only 10 subjects in this age group in the Integrated Summary of Safety analysis set. The one 14-year-old subject in Cal. 203 exposed to calcipotriene foam reports no adverse events. No AE is reported by more than 1 subject in this age group which is summarized in Table 54.

Table 54: Incidence of treatment emergent adverse events for subjects <18

System Organ Class Preferred Term	Calcipotriene foam	Vehicle foam
N	6	4
Subjects Reporting Any Adverse Event, n (%)	1 (17)	1(25)
Infections and Infestations0	1 (17)	1(25)
Infected insect bites	1 (17)	0
Nasopharyngitis	0	1(25)
Injury, Poisoning and Procedural Complications	0	1(25)
Limb injury	0	1(25)
Skin Laceration	0	1(25)
Respiratory, thoracic and Mediastinal Disorders	0	1(25)
Cough	0	1(25)

Source: NDA 22-563 Summary Table 3.11.1, Module 5, Integrated Summary of Safety

The incidence of AEs in white and non-white subjects does not differ in any clinically meaningful way.

7.5.4 Drug-Disease Interactions

No formal analyses are conducted on calcipotriene foam for drug-disease interactions.

7.5.5 Drug-Drug Interactions

The applicant did not conduct drug interaction studies with calcipotriene foam or its active ingredient. The applicant proposes that since systemic exposure is low after cutaneous application of the product then clinically meaningful pharmacodynamic interactions are not anticipated. They state “There have been no indications that calcipotriene foam poses any risks related to interactions with other drugs.”

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The clinical development program does not include studies of human carcinogenicity. Safety signals for human carcinogenicity are not evident for this pharmacologic class of drugs. However, the results of non-clinical studies with calcipotriene are reported in labeling in Section 13.1. One study suggests that calcipotriene may enhance the effect of UVR to induce skin tumors. Refer to the Appendix for labeling information.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well controlled studies of the safety of calcipotriene foam in nursing mothers and pregnant women. The applicant recommends avoiding the use of this product in these populations. The two subjects who became pregnant while enrolled in trials in this development program delivered normal healthy infants. Narratives are included in Section 7.3.4.

7.6.3 Pediatrics and Assessment of Effects on Growth

The pivotal trials are not designed to evaluate the effect of calcipotriene foam on growth and development in the pediatric population. The applicant cites 3 small studies to support the safety and efficacy of calcipotriene in the pediatric population ages 0 to 12. These studies (Oranje AP, 1997; Darley CR, 1996; Park SB, 1999) 11;12;13 are conducted with calcipotriene ointment and "do not provide definitive evidence of safety and effectiveness in children aged 0 to 12 years, but suggest that the product is safe, well tolerated and efficacious in this population." According to product labeling calcipotriene ointment, cream and solution are indicated for adults.

(b) (4) This request was submitted to IND 71-198 and includes their rationale with supportive data from the literature.

(b) (4) the following sections of the Pediatric Research Equity Act of 2007:

- Section 505(b)(a)(4)(B)(i): necessary studies are impossible or highly impracticable
- Section 505(b)(a)(4)(B)(iii):the drug or biological product-(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and (II) is not likely to be used by a substantial number of pediatric patients in that age group

However, data from a population –based study in the United Kingdom by Gelfand et al 14 provides an estimate of the prevalence of psoriasis in patients ages 9 and below as

11 Oranje AP et al. Topical calcipotriol in childhood psoriasis. J Am Acad Dermatol 1997; 36(1):203-8.
12 Darley CR et al. Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris. Br J Derm 1996; 135:390-393.
13 Park SB et al. A pilot study to assess the safety and efficacy of topical calcipotriol treatment in childhood psoriasis. Ped Derm 1999: 16(4);321-325.
14 Gelfand JM et al. Prevalence and Treatment of Psoriasis in the United Kingdom: A Population-Based Study. Arch Dermatol 2005;141:1537-41.

55.02 per 10,000. According to the United States Census data from 2000 15, there are 40 million individuals aged 9 and below. Thus, the estimated prevalence of psoriasis among patients in this age group in the United States is 220,000. This exceeds the number defined by the Agency as "a substantial number of patients with a condition for which the drug is indicated, and for which pediatric studies would be required" even without the inclusion of patients aged 10 and 11. In addition, approved treatment options for children with psoriasis are limited to corticosteroids that are labeled for use in the pediatric age group. Children treated chronically with topical corticosteroids are at risk for adverse events such as HPA axis suppression and atrophy at the application site. Therefore, a treatment option indicated for mild to moderate psoriasis in children greater than age 2 represents a meaningful benefit over existing therapies.

(b) (4) However, the reviewer from the Pediatric and Maternal Health team recommends a partial waiver for studies in pediatric patients younger than 2 years of age. Less than 2% of patients with psoriasis are less than 2 years of age. In view of the prevalence, calcipotriene foam may not be used in a substantial number of patients and the studies would not be feasible in this age group. Therefore, the studies could not be required under PREA. This partial pediatric waiver is consistent with recent waivers granted for similar psoriasis products.

In addition, the data are not sufficient to support labeling in pediatric patients age 12 to 16 since only 6 subjects in this age group received treatment with calcipotriene foam and 4 subjects received treatment with vehicle foam in Phase 3 trials. The pharmacokinetic study includes 1 patient less than 18 years old at baseline. The reviewer from the Pediatric and Maternal Health team recommends that the applicant conduct a pharmacokinetic and efficacy study in the 2 to 11 year age group and a smaller pharmacokinetic study in the 12 to 17 year age group. Efficacy in subjects age 12 to 17 may be extrapolated from the efficacy in adults since the pathophysiology and disease progression are similar in adults and children. A more rigorous assessment of calcium homeostasis may be included in the safety evaluation for these studies.

In response to comments by the Agency, the applicant submitted a Pediatric Plan, a (b) (4) Partial Pediatric Waiver for subjects less than 2 years of age and a deferral for studies required under PREA for subjects age 2 to 11. The rationale for the (b) (4) Partial Pediatric Waiver is that the necessary studies are impossible or highly impracticable.

The PeRC Meeting was convened on July 21, 2010 and the following studies were recommended and accepted to fulfill PREA requirements:

15 U.S. Census Bureau. DP-1. Profile of General Demographic Characteristics:2000

1. PK/PD trial of calcipotriene foam under maximal use conditions in 20 evaluable pediatric subjects with plaque psoriasis age 12 to 16 years.

2. PK/PD trial of calcipotriene foam under maximal use conditions in 25 evaluable pediatric subjects with plaque psoriasis age 2 to 11 years.

3. Vehicle-controlled trial of the safety and efficacy of calcipotriene foam in 100 evaluable pediatric subjects with plaque psoriasis age 2 to 12 years.

Refer to Section 9.2 for Agency recommendations for labeling.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant includes the statement: (b) (4) However, overdose potential does exist since hypercalcemia is reported with increased frequency with weekly exposures to calcipotriene greater than 100 grams.

The applicant conducted no trials to assess the potential for withdrawal or rebound.

Refer to Section 9.2 for Agency recommendations for labeling.

7.7 Additional Submissions / Safety Issues

Stiefel did not conduct any long term studies with calcipotriene foam. The applicant intends to rely on Agency findings of long term safety of Dovonex Ointment from NDA 20-273 with support from findings of long term safety of calcipotriene from the literature. In a review of the literature, Scott et al.[16] conclude that the adverse event profile in long term studies is similar to short term studies in adults. This conclusion is based on 5 long term studies ranging from 24 to 52 weeks with a dose of 50 μg/g twice per day. Rare adverse events included: hypercalcemia, hypercalciuria, contact dermatitis, pustular psoriasis, photosensitivity and headache.

A 52 week study to assess long term safety and efficacy of calcipotriene 0.005% ointment in 397 patients with mild to moderate psoriasis vulgaris (5-20% BSA) showed no consistent, unexplained abnormal laboratory results attributed to the study product. There were 142 adverse events (AEs) in 120 subjects which were considered to be secondary to the calcipotriol ointment. All AEs were described as non-serious and the most common AEs were lesional irritation, worsening psoriasis and dermatitis. See Section 7.2.5.

16 Scott LJ, Dunn CJ, Goa KL. Calcipotriol Ointment. A Review of its Use in the Management of Psoriasis. Am J Clin Dermatol. 2001; 2(2):95-120.

Another issue related to the safe use of this product is the container fill size. The proposed container size is 60 grams. (b) (4) In an Information Request dated 2010-05-11 the applicant was asked to provide graphs that plot baseline BSA and amount of drug exposure versus serum calcium increase and drug exposure versus overall adverse events. The Clinical Pharmacology Reviewer concludes that the graphs visualizing the calcium changes per BSA or total drug use demonstrate no evidence of differential effects on calcium metabolism by calcipotriene foam versus Dovonex ointment. This is consistent with no significant differences in the pharmacokinetics between the two drugs since most of plasma data are below the level of quantitation. (b) (4)

8 Postmarket Experience

Calcipotriene foam, 0.005% has not been marketed in this or any other jurisdiction. The risk management plan includes updated spontaneous reporting and quarterly post-marketing periodic reports unless a safety signal is identified.

9 Appendices

9.1 Literature Review/References

The literature references are included within the review document.

9.2 Labeling Recommendations

The applicant submitted draft labeling as part of the New Drug Application on December 18, 2009. Within the eCTD document, labeling is included in Word and SPL formats. Initial recommendations are provided by the Regulatory Project Manger in an IR letter dated 2010-3-22.

Additional recommendations to proposed labeling include the following:
HIGHLIGHTS:

- Remove the contact information for the Stiefel website since it is not available for examination, may contain promotional information and does not allow patient reports to be assessed by a health care professional
- Remove language in CONTRAINDICATIONS section about evidence of Vitamin D toxicity but include “Do not use in patients with known hypercalcemia”
- Remove [redacted] (b) (4) from WARNINGS AND PRECAUTIONS since there is no documented evidence of anaphylaxis
- Clarify ADVERSE REACTIONS “Adverse events reported in greater than 1% of subjects and in a higher rate in subjects treated with SORILUX Foam compared to vehicle were limited to erythema. (6.1)”

FULL PRESCRIBING INFORMATION

- Modify INDICATIONS AND USAGE [redacted] (b) (4) : “SORILUX is [redacted] (b) (4) for the topical treatment of plaque psoriasis in patients aged 18 and older”
- Remove language in CONTRAINDICATIONS section about evidence of Vitamin D toxicity and include “SORILUX should not be used by patients with known hypercalcemia”
- Delete [redacted] (b) (4) from DOSAGE AND ADMINISTRATION since this information is for health care providers and add “For topical use only”
- Remove [redacted] (b) (4) from WARNINGS AND PRECAUTIONS since there is no documented evidence of anaphylaxis. Consider language about ultraviolet light exposure since the risk is documented in non-clinical studies.

- Amplify and clarify Section 6.1 concerning Clinical Trials Experience since the CFR 201.57 (7)(i) mandates inclusion of a description of the number of subjects, and the nature and extent of the exposure to allow interpretation of the findings
- Add section 7 DRUG INTERACTIONS
- Remove warnings about container puncture and storage at high temperatures from Section 5.1 since it is repeated in STORAGE AND HANDLING
- Reorganize statements in Section 8.1 Pregnancy to place the most important information first and delete (b) (4)
- Replace Section 8.5 Geriatric Use since an insufficient number of subjects > age 65 are included in the Phase 3 trials to assess a difference in response from younger patients
- Modify Section 10 to state "Topically applied calcipotriene can be absorbed in sufficient amounts to produce systemic effects. Elevated serum calcium has been observed with use of topical calcipotriene"
- Include a Section 12.2 Pharmacodynamics. The Clinical Pharmacology reviewer modifies Section 12 to be non-promotional
- Clarify and amplify Section 14 Clinical Studies since CFR 201.57 (15) mandates inclusion of a description of the study design, populations, endpoints and results
- Remove (b) (4)
- (b) (4)

Patient Package Insert

- Include photographs if figures are included to illustrate the steps in applying SORILUX
- Add the word "Foam" after SORILUX

Changes to labeling recommended by reviewers from other disciplines are as follows:

<u>Pharmacology/ Toxicology</u>

- Concurs with acceptability of the pharmacologic class designation and deletion of (b) (4) from Section 8.1

<u>Clinical Pharmacology</u>

- Change the INDICATIONS AND USAGE section: "SORILUX is (b) (4) indicated for the topical treatment of plaque psoriasis in patients aged <u>18</u> and older."
- Add Section 7 DRUG INTERACTIONS "No drug interaction studies were conducted with SORILUX
- Replace the Clinical Pharmacology Section 12 with the follow text:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Calcipotriene is a synthetic vitamin D3 (b) (4) that has a similar receptor binding affinity as natural vitamin D3. However, the exact mechanism of the action contributing to the clinical efficacy in the treatment of psoriasis is unknown.

12.2 Pharmacodynamics

(b) (4)

12.3 Pharmacokinetics

The systemic absorption of calcipotriene in psoriatic patients was evaluated at steady state following application of SORILUX or calcipotriene ointment. In the SORILUX treatment group, (b) (4) showed calcipotriene plasma concentrations below the limit of quantitation (10 pg/ml), while in the calcipotriene ointment treated group, 5 among 16 subjects had measurable calcipotriene plasma concentrations at various time points. All measurable plasma calcipotriene concentrations were below 25 pg/ml.

The systemic disposition of calcipotriene is expected to be similar to that of the naturally occurring vitamin (b) (4) Absorbed calcipotriene is known to be converted to inactive metabolites within 24 hours of application and the metabolism occurs via a similar pathway to the natural hormone.

Chemistry (CMC)

- Clarify the product description in Section 3 DOSAGE FORMS AND STRENGTHS “0.005% foam”
- Modify Section 11 DESCRIPTION: add (b) (4)
- Modify the Section 16.1 HOW SUPPLIED: add “(calcipotriene) Foam, 0.005%”
- Revise the units of measure on the primary and secondary container/closure labels to use “mcg” for micrograms rather than abbreviation "µg.” Provide colored mock-ups with indicated changes.
- (b) (4)

Division of Medication Error Prevention and Analysis (DMEPA)

- Revise the container label and carton labeling so that the dosage form and active ingredient are on the same line.

- Add the statement 'For topical use only' on the principal display panel of the container labels and carton labeling as per 21 CFR 201.100(b)(3)
- Modify the manufacture's tradedress for this product since it is nearly identical to the tradedress for Veltin
- Include in the patient package insert "Avoid excessive exposure of the treated areas to natural or artificial sunlight"
- Include photographs rather than drawings with the instructions for applying the product and illustrating the instructions to "break the tiny plastic piece at the base of the can's rim by gently pushing back (away from the piece) on the nozzle."
- Revise the units of measure to use 'mcg' for micrograms throughout the labels and labeling.
- Revise (b) (4) to read "Apply a thin layer to affected areas twice daily, (b) (4) to help minimize the risk of inappropriate application
- Delete the (b) (4) that appears on the container label and carton labeling
- Requested revisions to the carton and container were discussed with the applicant during a teleconference on August 31, 2010. The applicant agrees to provide a response by September 10, 2010.

<u>Division of Risk Management (DRISK)</u>
The Reviewer provided the following comments and revisions are included in the final label which is attached**.**

- Do not use all capital letters in patient information except for product names.
- Include patient friendly language
- Revise statements about hypercalcemia to be consistent with the PI
- Remove the statement (b) (4) since it is removed from the PI
- Delete information (b) (4) because this information was deleted from section 2 of the PI
- Develop consistent statements in the PI and PPI telling patients to notify their physician if their skin does not improve
- Add an instruction for what patients should do about a missed dose
- Develop the Patient Counseling Information in Section 17 to address information to be conveyed to the patient by the healthcare provider
- Use actual pictures as figures to show the steps for applying Sorilux foam. Each figure should be labeled, placed adjacent to the relevant text, and referenced in the text. All parts should be labeled.
- Clarify how to dispense the foam and add an instruction here about how to dispense the foam, such as "press on the nozzle"
- Add Section 17 telling patients what to do if contact occurs with the eyes, (b) (4) This important information is not currently in the PI and must first be added before it may be included in the PPI

- Delete information [redacted] (b) (4) since this statement is not present in the PI. The applicant should clarify this information and address in Section 17 of the PI, if appropriate.
- For consistency with other patient labeling [redacted] (b) (4)
- Add to patient labeling "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088
- [redacted] (b) (4)
- Applicant should include a website address if available. We recommend conveying the toll-free number as all numbers and not mixed numbers and letters.

Division of Drug Marketing, Advertising, and Communications (DDMAC)

5. WARNINGS AND PRECAUTIONS;
- Eliminate the promotional advantage of the absence of a warning concerning hypercalcemia
- Clarify the warning about natural or artificial sunlight
- [redacted] (b) (4)

6.1 Clinical Trials Experience
- Omit the phrase [redacted] (b) (4)
- [redacted] (b) (4)

10 Overdosage
- Revise language to show whether the risk is related to normal use versus excessive use. If DDDP's intent is to communicate that this is a risk of normal usage, we recommend that you consider putting this in the Warnings/Precautions section of the label.

12.3 Pharmacokinetics
- Modify this language since it sounds promotional
- Identify the number of subjects who were studied
- Reconsider the inclusion of comparator data in this section since it could be promotional
- Clarify the statements that "absorbed calcipotriene is converted to inactive metabolites" [redacted] (b) (4)

14 CLINICAL STUDIES

- Define the criteria that constitute “mild” and “moderate” or to identify the scale used to classify subjects as “mild” or “moderate”
- Identify the grading system
- Omit the phrase that drug has been studied in (b) (4)

PATIENT INFORMATION

Recommend that PPI be formatted in the current preferred formatting

- Revise indication statement to be consistent with the indication stated in the PI, using consumer-friendly language
- Reconsider the description of psoriasis
- Revise the statement that (b) (4) in consumer-friendly language
- Remove (b) (4) since it is not included in the Contraindications section of the PI
- Delete (b) (4) since it has been deleted in the PI.
- Include “Avoid excessive exposure of the treated areas to either natural or artificial sunlight, including tanning booths and sun lamps
- Include risk of elevated serum calcium since it is included in the Overdosage section of the PI

Labeling is under review. Draft labeling is appended.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was convened in response to issues in this application.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MELINDA L MCCORD
09/08/2010

JILL A LINDSTROM
09/17/2010

MEMORANDUM TO FILE

Date: 2010-03-16
To: NDA 22563, SD 3 and SD 4
From: Melinda McCord, MD
RE: NDA 22-563, Sorilux (calcipotriene) Foam, 0.005%
1. Information Request-Response to 74 Day letter
2. Information Request-Response to Project Manager Inquiry March 8, 2010 to locate form FDA-3542a

Background:
Stiefel Laboratories, Inc. submitted NDA 22-563 for review on December 18, 2009. The 74 Day letter dated March 1, 2010 informed the sponsor that the application is sufficiently complete to permit a substantive review with a user fee goal date of October 21, 2010. The sponsor is informed that the Agency identified two potential review issues.

> **Clinical Pharmacology**
> 1. The study population in the pharmacokinetics study does not sufficiently represent the age group of 12-18 years. The adequacy of data will be a review issue and may have an impact on the target patient population of your proposed product.
>
> **Biostatistics**
> 2. The site information included in Section 16.1.4 for Studies 301 and 302 is inadequate as it does not include the site number as provided in your SAS transport files.

The sponsor is asked to submit the following information:

> **CMC**
> 1. A copy of Master Batch Record for review and a representative sample for dosage form evaluation.
>
> **Biostatistics**
> 2. A revised Section 16.1.4 for studies 301 and 302 to include the site numbers along with investigator name and address. The site numbers provided in Section 16.1.4 should correspond to those provided in your electronic data sets (i.e. SAS transport files).

Sponsor Response:
In a letter dated March 11, 2010, the sponsor provided a copy of the current master batch record proposed for manufacturing process validation and a revised Section 16.1.4 for studies 301 and 302 to include the site numbers along with investigator name and address. The site numbers provided in Section 16.1.4 correspond to the site numbers in the SAS transport files that were included with the original submission.

Study Centers and Investigators:
All investigational sites are located in the United States. Study U0267-301 utilizes 13 centers; U0267-302, utilizes 12 centers

Protocol Number: U0267-301

Table 1: Investigators and Study Centers for U0267-301

Investigators	Study Centers	Site
William Abramovits	Dermatology Treatment & Research Center 5310 Harvest Hill Rd, Suite 160 Dallas, TX 75230	001
Suzanne Bruce	Suzanne Bruce and Associates, PA, The Center for Skin Research 1900 St. James Place, #650 Houston, TX 77056	002
Zoe Draelos	Dermatology Consulting Services 2444 North Main Street High Point, NC 27262-7833	003
Steven Kempers	Minnesota Clinical Study Center 7205 University Ave NE Fridley, MN 55432	004
Francisco A. Kerdel	Florida Academic Dermatology Centers 1400 NW 12th Ave, #4 Miami, FL 33136	005
Alexa Kimball	Clinical Unit for Research Trials in Skin, Massachusetts General Hospital 50 Staniford St, Room 240, 2ndFloor Boston, MA 02114	006
Leon Kircik	DermResearch, PLLC 1169 Eastern Parkway, #2310 Louisville, KY 40217	007
James Michael Maloney III	Creek Research, Inc. 3773 Cherry Cherry Creek North Drive, #970 Denver, CO 80209	008
Orit Markowitz	Mount Sinai School of Medicine, Dept. of Dermatology 5 East 98th Street, 5th Floor New York,	009

	NY 10029	
Robert Matheson	Oregon Medical Research Center, P.C. 9495 SW Locust Street Portland, OR 97223	010
Stacey Smith	Therapeutics Clinical Research 9025 Balboa Ave, Suite 105 San Diego, CA 92123	011
Leonard J. Swinyer	Dermatology Research Center, Inc. 3920 South 1100 East, #210 Salt Lake City, UT 84124	012
Hector Wiltz	FXM Research 11760 Bird Road, Suite 452 Miami, FL 33175	013

Source: NDA 22-563: Clinical Study Report 16.1.4

Protocol Number: U0267-302

Table 2: Investigators and Study Centers for U0267-302

Investigators	Study Centers	Site
Steven A. Davis	Dermatology Clinical Research Center of San Antonio 7810 Louis Pasteur, Suite 200 San Antonio, TX 78229	001
Sunil Dhawan	East Bay Dermatology Medical Group, Inc. 2557 Mowry Ave., Suite 34 Fremont, CA 94538	002
Steve Feldman	Wake Forest University Health Sciences Dept. of Dermatology, Medical Center Blvd. Winston Salem, NC 27157	003
Ellen H. Frankel	Clinical Partners, LLC 1524 Atwood Ave, Suite 330 Johnston, RI 02919	004
Kimberly Grande	The Skin Wellness Center, PC 10215 Kingston Pike #200 Knoxville, TN 37922	005
David L. Kaplan	Adult & Pediatric Dermatology 4601 W. 109th Street, Suite 116 Overland	006

	Park, KS 66211-1313	
Amy Morris	Coastal Clinical Research, Inc. 100 Memorial Hospital Drive Annex Building, #3B Mobile, AL 36608	007
Phoebe Rich	Oregon Dermatology and Research Center 2565 MW Lovejoy #200 Portland, OR 97210	008
Diya F. Mutasim (prev. Pranav Sheth)	University Dermatology Consultants, Inc. 222 Piedmont Avenue, #5300 Cincinnati, OH 45219	009
Brett Shulman	The Center for Dermatology at Lifetime Health 1850 Brighton Henrietta Townline Rd Rochester, NY 14623	010
James A Solomon	Advanced Dermatology & Cosmetic Surgery 725 W Granada Blvd, # 44 Ormond Beach, FL 32174	011
Eduardo Tschen	Academic Dermatology Associates 1203 Coal SE Albuquerque, NM 87106	012

Source: NDA 22-563: Clinical Study Report 16.1.4

In a letter dated March 11, 2009, the sponsor responded to the request for form FDA-3542a which provides patent information.

Recommended comments to be incorporated into a regulatory letter for conveyance to sponsor in addition to concurrence with the commitment described above:
No comments need to be conveyed to the sponsor.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22563	ORIG-1	STIEFEL LABORATORIES INC	CALCIPOTRIEN FOAM 0.005%

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/s/

MELINDA L MCCORD
03/16/2010

JILL A LINDSTROM
03/24/2010

DDDP CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY	X			
1. Identify the general format that has been used for this application, e.g. electronic CTD.	X	eCTD		
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5. Are all documents submitted in English, or are English translations provided when necessary?	X			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57, current divisional and Center policies, and the design of the development package?	X			Carton, container and draft labeling referencing other formulations (RLD) Section 1.14
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e*, Module 2 summaries)?	X			
9. Has the applicant submitted the integrated summary of safety (ISS)?	X			Section 5.3.5.3 Section 2.5
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Section 5.3.5.3 Section 2.5
11. Has the applicant submitted a benefit-risk analysis for the product?	X			Section 2.5
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)(2) RLD: Dovonex Ointment			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e*., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:		X		No dose ranging studies with calcipotriene foam
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1 (Section 5.3.5.3) U0267-301	X			343 subjects and 330 subjects randomized 2:1 calcipotriene:vehicle

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

Indication: mild to moderate plaque-type psoriasis affecting 2-20% BSA Pivotal Study #2 (Section 5.3.5.3) U0267-302 Indication: mild to moderate plaque-type psoriasis affecting 2-20% BSA				U0267-301 may not reach statistical significance in primary endpoint (more mild disease subjects who responded to the vehicle)
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Primary efficacy endpoint is the proportion of subjects who had an ISGA score of clear or almost clear (0 or 1) at week 8 and a minimum improvement in the ISGA score of 2 grades from baseline to week 8 (treatment success; missing week 8 evaluations were counted as treatment failures)
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	No foreign sites.
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			TQT not addressed.
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?		X		
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	X			
OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?		X		No dose ranging study but 15 year history of use of the moiety. Potential impact of product on QT/QTc not discussed at the meetings. However, no cardiac safety signal with the

				moiety and low systemic exposure.
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (*e.g.*, labeling comprehension)?			X	
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Partial Pediatric Waiver (b) (4) (Rationale: No meaningful benefit since less severe and studies impractical due to low prevalence).
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
27. Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
29. Are all datasets to support the critical safety analyses available and complete?	X			
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	X			
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			CRFs include those lost to follow up. No deaths in development program.
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			CRFs included for early terminations, discontinuations due to adverse events, and serious adverse events.
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			Forms 3454 for all investigators included. (b) (6) total payments from Stielfel $26,500 (consulting, research and honoraria); (b) (6) $76,432.05 (2008), $16,500.74

				(2009) (honoraria, speaking).
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Each study contains a statement affirming GCP. IRB supervision and consent documented.
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	X			

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

The effect of the product on cardiac repolarization has not been adequately addressed. Data from a thorough QT/QTc study or a rationale for why such a study is not needed is not included your application.

Reviewing Medical Officer

Clinical Team Leader

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22563	ORIG-1	STIEFEL LABORATORIES INC	CALCIPOTRIEN FOAM 0.005%

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/s/

MELINDA L MCCORD
02/03/2010

JILL A LINDSTROM
02/05/2010