Clinical Review and Evaluation

PMR Final Study Report

Application Type	sNDA: Efficacy Supplement
Application Number(s)	NDA 22087/S-009
Priority or Standard	Standard
Submit Date(s)	September 17, 2019
Received Date(s)	September 17, 2019
PDUFA Goal Date	July 17, 2020
Division/Office	Division of Dermatology and Dentistry (DDD)/ Office of Immunology and Inflammation
Review Completion Date	July 1, 2020
Established Name	calcitriol
(Proposed) Trade Name	VECTICAL (calcitriol) Ointment 3 mcg/g
Pharmacologic Class	Vitamin D analog
Code Name	None
Applicant	Galderma Laboratories, L.P.
Formulation(s)	Ointment
Dosing Regimen	Twice daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	For the topical treatment of mild to moderate plaque psoriasis in adult and pediatric patients 2 years and older

Consultant Reviews

Labeling Reviews

- Office of Surveillance and Epidemiology, Office of Medication Error Prevention and Risk Management, Division of Medication Error Prevention: Madhuri R. Patel, PharmD (Review dated May 21, 2020)
- Office of Prescription Drug Promotion: Laurie Buonaccorsi, PharmD; Prescribing Information, Review dated April 14, 2020, Patient Package Insert (PPI) (Review dated April 27, 2020)
- Division of Medical Policy Programs: Jessica Chung, Pharm D; Review PPI (Review dated April 27, 2020)
- Office of Surveillance and Epidemiology, Office of Medication Error Prevention and Risk Management, Division of Medication Error Prevention: Madhuri R. Patel, PharmD (Review dated May 21, 2020)

Other Consultations

- Division of Pediatric and Maternal Health, Pediatric División Consult Response: Leyla Sahin, M.D. (Review dated February 26, 2020)

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Glossary

25(OH)D	Vitamin D
AE	adverse event
ALT	alanine aminotransferase
BSA	body surface area
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
IDMC	Independent Data Monitoring Committee
IGA	Investigator's Global Assessment
PD	pharmacodynamic
PeRC	Pediatric Review Committee
PK	pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
PMR	postmarketing requirement
PPI	Patient Package Insert
PREA	Pediatric Research Equity Act
PTH	parathyroid hormone
SD	supporting document
SGPT	serum glutamate pyruvate transaminase
SOC	system organ class
TEAE	treatment-emergent adverse event

Note to Reader:

Trial RD.06.SRE.18102/PMR 973-1 was a pharmacokinetic/ pharmacodynamic (PK/PD) study of Vectical Ointment under maximum use conditions in 25 evaluable pediatric subjects with psoriasis aged 12 to 17. It was fulfilled on March 31, 2011 without labeling changes. See Clinical Pharmacology Review by Abimbola Adebowale dated March 3, 2011). This trial is not further reviewed in the current document.

Trial RD.06.SRE.18104 /PMR 973-2 was to conduct a PK/PD study of Vectical Ointment under maximum use conditions in pediatric subjects with psoriasis aged 2 to 12 years; the number of subjects enrolled should be sufficient to detect a 10% change in serum ionized calcium from baseline with 90% confidence or a minimum of 25 evaluable subjects, whichever is larger. This trial is reviewed in detail in Appendix 1 of the current document.

Trial RD.06.SPR. 18132 /PMR 973-3 was to conduct a vehicle-controlled study of the safety and efficacy of Vectical Ointment in pediatric subjects with psoriasis 2 to 12 years of age with a minimum of 100 evaluable subjects exposed to the active drug. This trial is reviewed in detail in Appendix 2 of the current document.

1. Executive Summary

VECTICAL® (calcitriol) Ointment is a topical product for the treatment of mild to moderate plaque psoriasis in adult and pediatric patients 2 years and older. The active ingredient, calcitriol (1α,25-dihydroxyvitamin D3), is endogenously produced and is the active hormone form of vitamin D3. The Applicant, Galderma Laboratories, L.P. submitted an efficacy supplement for Vectical Ointment that included a request for release from pediatric postmarketing requirements. The Applicant stated that, as requested by the Agency, the supplement included all data collected which is presented for evaluation. Information was also included regarding Pregnancy and Lactation Labeling Rule (PLLR) changes to the product insert.

The Applicant had four original postmarketing requirements (PMR)s to fulfill under the Pediatric Research Equity Act (PREA). One of these was fulfilled on March 31, 2011; 973-1 Conduct PK/PD study of Vectical Ointment under maximum use conditions in 25 evaluable pediatric subjects with psoriasis aged 12 to 17. Three other PMRs remained:

- 973-2 Conduct a PK/PD study of Vectical Ointment under maximum use conditions in pediatric subjects with psoriasis aged 2 to 12 years; the number of subjects enrolled should be sufficient to detect a 10% change in serum ionized calcium from baseline with 90% confidence or a minimum of 25 evaluable subjects, whichever is larger
- 973-3 Conduct a vehicle-controlled study of the safety and efficacy of Vectical Ointment in pediatric subjects with psoriasis 2 to 12 years of age with a minimum of 100 evaluable subjects exposed to active.
- 973-4 Conduct a long-term safety study of Vectical Ointment in 100 evaluable pediatric patients 2 to 17 years of age.

The Applicant stated that it had difficulty enrolling subjects to complete the studies outlined in the PMRs and two deferral extensions were granted. In 2015, the Division discussed with the Applicant the pediatric program for NDA 022087 with a goal of creating modifications and/or streamlining the program so that needed information can be collected in a reasonable amount of time. As a result, post-marketing requirements 973-2, 973-3, and 973-4 were replaced with a revised PMR:

- 973-5: Conduct a long-term safety trial, including assessment of calcium metabolism, of Vectical (calcitriol) Ointment in 100 evaluable pediatric subjects with plaque psoriasis aged 2 to 16 years and 11 months. Pharmacokinetic/Pharmacodynamic (calcium metabolism) assessment should be performed in at least 9 subjects with plaque psoriasis under maximum use conditions aged 2 to 16 years and 11 months. Due to slow study enrollment, the study was closed to enrollment in November 2017.

Safety information was obtained from the trials conducted to fulfill PMRs 973-1, 973-2, 973-3. (PMR 974-4 was rolled into PMR 973-5). These included the following:

- Trial RD.06.SRE.18102 (PMR 973-1): an open-label 8-week safety and pharmacokinetics (PK) trial conducted in 25 subjects 12 to 17 years of age
- Trial RD.06.SRE.18104 (PMR 973-2): an open-label 14-day safety and PK trial in 18 subjects 2 to 12 years of age
- Trial RD.06.SPR. 18132 (PMR 973-3): a vehicle-controlled 8-week trial in 19 subjects 2 to 12 years of age with mild to moderate plaque psoriasis
- PMR 974-4 was rolled into PMR 973-5: there is no separate clinical study report for the trial conducted to fulfill PMR 974-4.
- Trial RD.06.SPR.18131(PMR- 973-5; described above): an open-label 26-week safety and PK trial in 54 subjects 2 to 17 years of age

Data from 63 subjects aged 2 to 12 years, and 42 subjects aged 13 to 17 years showed no significant effects on indices of calcium metabolism. The systemic exposure of calcitriol in the pediatric subjects was generally comparable to the endogenous levels observed at baseline. No new safety signals were identified in subjects 2 to 17 years. Efficacy was extrapolated from adult subjects. The data in this submission is adequate to support amended labeling (Sections 1, 2, 8.1, 8.2, 8.4, 12.3).

Cases of hypercalcemia were observed in postmarketing data primarily in older adults with potential risk factors which increased exposure, who used the product for an unlabeled indication or extensive body surface area.

The Applicant provided sufficient data to support risk benefit conclusions in this pediatric population that are similar to those in the adult population. This reviewer recommends an approval action for this application, NDA 22087 Supplement- 009, to revise the current indication to the topical treatment of mild to moderate plaque psoriasis in patients 2 years and older.

1.1. Benefit-Risk Assessment

Psoriasis is a common, immune-mediated skin disorder which may develop in genetically susceptible individuals. Chronic plaque psoriasis is the most common form of psoriasis in children and adults. The estimated prevalence worldwide ranges from 0 to 1.37% of children and 0.51 to 11.3% of adults. Studies of the United States population found prevalence rates of up to 4.6%. Among the estimated 7.5 million Americans affected with psoriasis, 80%t have mild to moderate disease, while 20% have moderate to severe disease affecting more than 5% of the body surface area. The onset of psoriasis may occur at any age, but often occurs in childhood. In approximately 35–50% of individuals, psoriasis develops before the age of 20. Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected individuals. At the

Patient-Focused Drug Development Meeting held at the FDA (March 17, 2016), patients discussed current challenges with variability in effectiveness, tolerability, access to treatments, and uncertainty regarding long-term effects of available treatments. Thus, the development and approval of additional safe and effective therapies for children and adults with plaque psoriasis continues to be an important goal. Current available therapies would be enhanced by approval of a (non-steroidal) product for the treatment of plaque psoriasis in the pediatric population 2 to 12 years of age.

For patients 18 years and older, the review teams based the analysis of the benefits and risks of Vectical (calcitriol) Ointment for the treatment of mild to moderate plaque psoriasis on two adequate and well-controlled 8-week clinical trials (RD.06.SRE.18053 and RD.06.SRE.18054) and an open-label trial (SRE.2663). See Clinical Review dated September 29, 2008.

Vectical (Calcitriol) Ointment, 3 mcg/g was approved by FDA on January 23, 2009 for the treatment of mild to moderate plaque psoriasis in adults 18 years and older. Submission of pediatric studies for ages 2 to 17 years was deferred because the product was ready for approval for the adult population. However, as a condition of approval, the Applicant was required to conduct additional pediatric assessments.

The current supplement (S-009) includes an abbreviated clinical study report for trial RD.06.SRE.18131., intended to fulfill PMR 973-5 (a combination of PMRs 973-2, 973-3, and 973-4). Trial RD.06.SRE.18131 was an open-label 26-week safety and PK trial in 54 subjects 2 to 17 years of age with mild to moderate psoriasis defined as Investigator's Global Assessment (IGA) score of 2 or 3 at Screening, for PK minimum of 3% body surface area (BSA) involvement. Of the 54 subjects who received calcitriol, 20 subjects (37.0%) reported 49 treatment-emergent adverse events (TEAEs). Of these, 4 subjects had 5 adverse events (AEs) related to the study drug, and 1 subject had an AE related to the study procedure. Adverse reactions were skin burning sensation (4 subjects) and skin irritation (1 subject). All AEs were mild or moderate in severity and are labeled. No subjects experienced TEAEs that were possibly related to calcium metabolism or TEAEs that led to discontinuation from the study.

Safety information was also obtained from the trials conducted to fulfill PMRs 973-1, 973-2, 973-3. (PMR 974-4 was rolled into PMR 973-5). These included the following:

- For (PMR 973-1): an open-label 8-week safety and PK trial conducted in 25 subjects 12 to 17 years of age
- For (PMR 973-2): an open-label 14-day safety and PK trial in 18 subjects 2 to 12 years of age
- For (PMR 973-3): a vehicle-controlled 8-week trial in 19 subjects 2 to 12 years of age with mild to moderate plaque psoriasis
- For (PMR- 973-5; described above): an open-label 26-week safety and PK trial in 54 subjects 2 to 17 years of age

Data from 63 subjects aged 2 to 12 years, and 42 subjects aged 13 to 17 years showed no significant effects on indices of calcium metabolism. The systemic exposure of calcitriol in the pediatric subjects was generally comparable to the endogenous levels observed at baseline. No new safety signals were identified in subjects 2 to 17 years. Efficacy was extrapolated from adult subjects.

Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and those identified during product development. No issues require further assessment with a postmarketing requirement or postmarketing commitment. A risk evaluation and mitigation strategy is not recommended.

The Applicant has provided sufficient data to fulfill the intent of the PREA (21 U.S.C. 355c) requirements, namely the assessment of the safety and tolerability of the drug in the pediatric population. Data provided are sufficient to support risk-benefit conclusions in the pediatric population that are similar to those in the adult population. This reviewer recommends an approval action for this application, NDA 22087 Supplement- 009, to revise the current indication to the topical treatment of mild to moderate plaque psoriasis in patients 2 years and older.

2. Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, immune-mediated skin disorder which may develop in genetically susceptible individuals (Mallbris et al. 2005). Chronic plaque psoriasis is the most common form of psoriasis in children and adults (Paller and Lund 2020a). Other forms of psoriasis include guttate, pustular, and erythrodermic psoriasis. The typical lesion is a sharply demarcated, erythematous plaque with micaceous scale; the plaques may be localized or widespread in distribution. Common sites of involvement are scalp, elbows, knees, and presacral region. Psoriasis, however, may occur on any cutaneous site including the palms, soles, nails, and genitalia (Shah 2013). The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, producing proinflammatory cytokines which trigger and perpetuate the inflammatory cascade.

The prevalence of psoriasis varies by geographic region. The estimated prevalence worldwide ranges from 0 to 1.37% of children and 0.51 to 11.3% of adults (Michalek et al. 2017). Studies of the United States population found prevalence rates of up to 4.6%. In Europe, the overall prevalence rate for juvenile psoriasis was found to be ~0.7%, with an increase from 0.37–0.55% in those 0 to 9 years of age to 1.01–1.37% in those 10–19 years of age (van de Kerkhof and Nestlé 2018). An estimated 7.5 million Americans are affected with psoriasis. In a large multinational survey, 73% of patients self-identified as having mild to moderate disease (which

correlated with a %BSA of ≤3) while 27% self-identified as having moderate to severe disease (Lebwohl et al. 2014).

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

The areas of involvement and presentation of psoriasis may vary with age. In infants, psoriasis often presents with symmetrical, well-demarcated, thin, erythematous plaques with minimal scale in the diaper area. In children, psoriasis commonly presents on the scalp and may involve the face (Morris et al. 2001; Mercy et al. 2013). In all age groups, psoriasis is associated with an increased risk of a variety of comorbid conditions including obesity, cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, autoimmune disorders, and psychiatric and behavioral disorders (Elmets et al. 2019).

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

2.2. Analysis of Current Treatment Options

In both children and adults, effectiveness has been demonstrated for drugs targeting immune signaling (etanercept) (Menter et al. 2019), inhibition of pro-inflammatory cytokines and chemokines (topical corticosteroids), and epidermal hyperproliferation and differentiation (vitamin D analogs). The response to both systemic and localized immunosuppression appears to be similar in all age groups (Paller and Lund 2020b).

Examples of products available for the topical treatment of plaque psoriasis include those listed below:

Table 1: Products Available for the Topical Treatment of Plaque Psoriasis

Product Class	Example
Corticosteroid	Clobetasol foam
Synthetic vitamin D3 derivative	Calcipotriene cream
Synthetic vitamin D3 derivative/ corticosteroid combination product	Calcipotriene and betamethasone dipropionate ointment
Retinoid	Tazarotene cream

Table 2: Product Class for the Topical Treatment of Plaque Psoriasis

Example Product/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Info	Important Safety and Tolerability Issues
Product Class: Corticosteroid				
Olux E (clobetasol propionate) Foam/2007	CSRD* (one trial was done in mild to moderate plaque-type psoriasis)	Apply a thin layer twice daily. Treatment should be limited to 2 consecutive weeks and patients should not use greater than 50 grams per week	Randomized trial, subjects 12 yrs and older with mild to moderate plaque psoriasis, 253 subjects treated with Olux-E Foam & 123 subjects treated with vehicle foam, 41/253 (16%) treated with Olux-E Foam versus 5/123 (4%) treated with vehicle foam achieved treatment success, defined as Investigator's Static Global Assessment score of clear (0) or almost clear (1) with at least 2 grades of improvement from baseline, scores of none or faint/minimal (0 or1) for erythema & scaling and a score of (0) for plaque thickness.	Use in pediatric patients under 12 years of age not recommended because of numerically high rates of hypothalamic-pituitary-adrenal axis suppression

Example Product/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Info	Important Safety and Tolerability Issues
Product Class: Synthetic vitamin D3 derivative				
Dovonex (Calcipotriene cream)**/ 1996	Plaque psoriasis	Apply thin layer twice daily	Adequate and well-controlled trials have demonstrated improvement usually beginning after 2 weeks of therapy. This improvement continued with approx. 50% of patients showing at least marked improvement in the signs and symptoms of psoriasis after 8 weeks of therapy, but only approx. 4% showed complete clearing.	Reversible elevation of serum calcium has occurred.
Product Class: Synthetic vitamin D3 derivative/corticosteroid combination product				
Taclonex (Calcipotriene and betamethasone dipropionate) Ointment/2006	Plaque psoriasis in patients 12 years of age and older	Use once daily for up to 4 weeks	1603 subjects, mild to very severe plaque psoriasis, trunk & limbs, treated once daily for 4 weeks. Subjects randomized to 1 of 4 treatment arms; Taclonex ointment, calcipotriene hydrate 50 mcg/g in the same vehicle; betamethasone dipropionate 0.64 mg/g in the same vehicle and vehicle alone. Treatment effect was 48%, 16.5%, 23.3% and 7.6%, respectively. Efficacy assessed as proportion of subjects with absent or very mild disease according to Investigator's Global Assessment of disease severity at end of treatment (4 weeks)	Hypercalcemia and hypercalciuria and HPA axis suppression have been observed Patients ages 12 to 17 years of age should not use more than 60 g per week. Treatment of more than 30% body surface area not recommended.

Example Product/Year Approved	Relevant Indication	Dosage & Admin	Efficacy Info	Important Safety and Tolerability Issues
Product Class: Retinoid				
Tazorac (tazarotene cream)***0.05%, 0.1%/2000	Plaque psoriasis	Apply thin film once daily	Improvements in plaque elevation, scaling and erythema were generally significantly greater with tazarotene 0.05% and 0.1% than with vehicle. The number of patients with none. Minimal or mild overall disease was significantly greater with tazarotene 0.05% and 0.15 vs. vehicle	Retinoids may cause fetal harm when administered to a pregnant woman.

*Indication: "treatment (or relief) of inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses (CSRD), which includes the psoriasis indication.
**Safety and effectiveness (of Dovonex Cream 0.005%) in pediatric patients have not been specifically established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk than adults of systemic adverse effects when treated with topical medication. (Current labeling Dovonex: Pediatric Use Section)
***The safety and efficacy of tazarotene cream have not been established in patients with psoriasis under the age of 18 (Current labeling tazorac: Pediatric Use Section)

2.3. Patient Experience Data

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

3. Regulatory Background

Background: Original NDA Submission (associated IND 62151)
PREA Postmarketing Requirements:

Vectical (calcitriol) Ointment, 3 mcg/g was approved on January 23, 2009 for the topical treatment of mild to moderate plaque psoriasis in adults 18 years and older. The submission of pediatric studies for ages 2 to 17 years for this application was deferred because the product was ready for approval for the adult population. The deferred pediatric studies included the following:

1. 973-1
Conduct PK/PD study of Vectical Ointment under maximum use conditions in 25 evaluable pediatric subjects with psoriasis aged 12 to 17 years.

Study Start: June 2006
Final Report Submission: March 2010

The Applicant has fulfilled PMR #1 as stated in correspondence (Fulfillment of Postmarketing Requirement) dated March 31, 2011 (under NDA 22087).

2. 973-2
Conduct a PK/PD study of Vectical Ointment under maximum use conditions in pediatric subjects with psoriasis aged 2 to 12 years; the number of subjects enrolled should be sufficient to detect a 10% change in serum ionized calcium from baseline with 90% confidence or a minimum of 25 evaluable subjects, whichever is larger.

Protocol submission: April 2009
Study start: July 2009
Final Report Submission: March 2012

3. 973-3
Conduct a vehicle-controlled study of the safety and efficacy of Vectical Ointment in pediatric subjects with psoriasis 2 to 12 years of age with a minimum of 100 evaluable subjects exposed to the active drug.

Protocol Submission: April 2009
Study Start: July 2009
Final Report Submission: July 2011

4. 973-4
Conduct a long-term safety study of Vectical Ointment in 100 evaluable pediatric patients 2 to 17 years of age.

Protocol Submission: April 2009
Study Start: October 2009
Final Report Submission: January 2012

Pediatric Written Request:
On September 3, 2009 (supporting document 62 to the IND) the Applicant requested that the Agency issue a Written Request for the pediatric studies. Supporting document 62 contained three protocols for the study of Vectical Ointment in pediatric subjects aged 2 to 17 years designed to address postmarketing requirements attached to product approval (NDA 22087).

On October 10, 2010, the Agency issued a Pediatric Written Request. Reference was made to the September 3, 2009 Proposed Pediatric Study Request submitted to NDA 22087 for Vectical (calcitriol) Ointment, 3 mcg/g.

In a submission dated April 7, 2011(supporting document (SD) #42 to NDA 22087) the Applicant stated that they were declining the Pediatric Written Request due to the type and complexity of the studies necessary to demonstrate safety and efficacy in the pediatric population.

Deferral Extension Request January 8, 2013:
The Applicant requested a deferral extension for the three outstanding postmarketing requirement pediatric studies associated with Vectical (final reports originally due March 2012, July 2011, and January 2012). In a letter dated July 9, 2013, the Applicant was informed that the Agency agreed to extend the Final Report Submission dates for the outstanding PREA PMRs. The extensions were granted because of factors beyond the Applicant's control and good faith efforts to complete the trials.

Second Deferral Extension Request May 28, 2015:
On May 28, 2015 (Supporting Document #321 to NDA 22087) the Applicant submitted a request for another deferral extension for study 973-2 (Galderma Protocol number RD.06.SPR.18104), a PK/PD study of Vectical Ointment under maximum use conditions in pediatric subjects and psoriasis aged 2 to 12 years. The Applicant stated that there had been difficulties in enrolling subjects in the study.

The Applicant proposed May 31, 2018 as the new date for final report submission.

In the July 8, 2015 meeting, the Pediatric Review Committee (PeRC) agreed to grant a deferral extension until November 30, 2015. However, the PeRC recommended that the Division and the Applicant have a meeting to discuss the pediatric program for NDA 022087 with a goal of making modifications and/or streamlining the program so that needed information can be collected in a reasonable time-frame.

T-con with Applicant July 31, 2015:
The Division discussed with the Applicant the pediatric program for NDA 022087 with a goal of making modifications and/or streamlining the program so that needed information can be collected in a reasonable time-frame. The Applicant agreed to submit a proposal to amend the ongoing pediatric clinical program that would address the critical elements of the postmarketing requirements.

Applicant's Proposal to Amend Pediatric Clinical Program (September 2, 2015):
On September 2, 2015 (Supporting Document #322) the Applicant submitted a revised program of clinical studies to meet PMRs 2, 3 and 4 for consideration by the Division.

The Applicant proposed to amend the long-term safety study (Study 18131 – PMR #4) in order to evaluate the calcitriol plasma levels in approximately 9 patients mainly in the age range of 2 to 6 years old. A limited sampling strategy was to be employed which, according to the Applicant, was supported by the available pharmacokinetics data collected in studies 18102 and 18104 and would facilitate recruitment and consent of pediatric subjects.

PeRC Meeting October 14, 2015:
The Division presented the plan to replace post-marketing requirements 973-2, 973-3, and 973-4 with the revised PMR and the PeRC concurred.

Release from Postmarketing Requirement/New Postmarketing Requirement November 20, 2015:
In a letter dated November 20, 2015, the Agency stated that the Applicant is released from PMRs 973-2, 973-3, and 973-4 because they will be replaced by a new PMR, under the PREA that combines all age cohorts into a single study. These requirements have been revised in the new requirement described below:

> "We are deferring submission of your pediatric study for ages 2 to 16 years and 11 months for this application because this product is approved for use in adults and the pediatric study has not been completed.
>
> Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. This required study is listed below.
>
> > 973-5
> > Conduct a long-term safety trial, including assessment of calcium metabolism, of Vectical®(calcitriol) Ointment in 100 evaluable pediatric subjects with plaque psoriasis aged 2 to 16 years and 11 months. Pharmacokinetic/Pharmacodynamic (calcium metabolism) assessment should be performed in at least 9 subjects with plaque psoriasis under maximum use conditions aged 2 to 6 years and 11 months old.

Final Protocol Submission: 12/2015
Study Completion: 08/2017
Final Report Submission: 12/2017"

Submission of September 27, 2017 (SD #341):
In the submission of September 27, 2017, the Applicant proposed "to close the ongoing pediatric study program since they believe that the critical elements of the Post-Marketing Requirements have been addressed. Sufficient data have been gathered and no additional activities are necessary from a clinical standpoint, or feasible from a prevalence and recruitment standpoint."

Teleconference November 8, 2017 with Applicant:
From t-con minutes (Document Archiving, Reporting and Regulatory Tracking System (DARRTS) November 8, 2017):
"The Agency conveyed to the Applicant that at this point, another request for Deferral Extension can be pursued or an Efficacy Supplement can be submitted. The Applicant sounded interested in pursuing submission of an Efficacy Supplement, which would need to be inclusive of all data, proposed labeling (if applicable) and an explanation/justification of enrollment efforts and challenges faced."

Action items:
The Applicant was to consider their options and pursue one of the outlined regulatory paths (likely the submission of an Efficacy Supplement to the NDA).

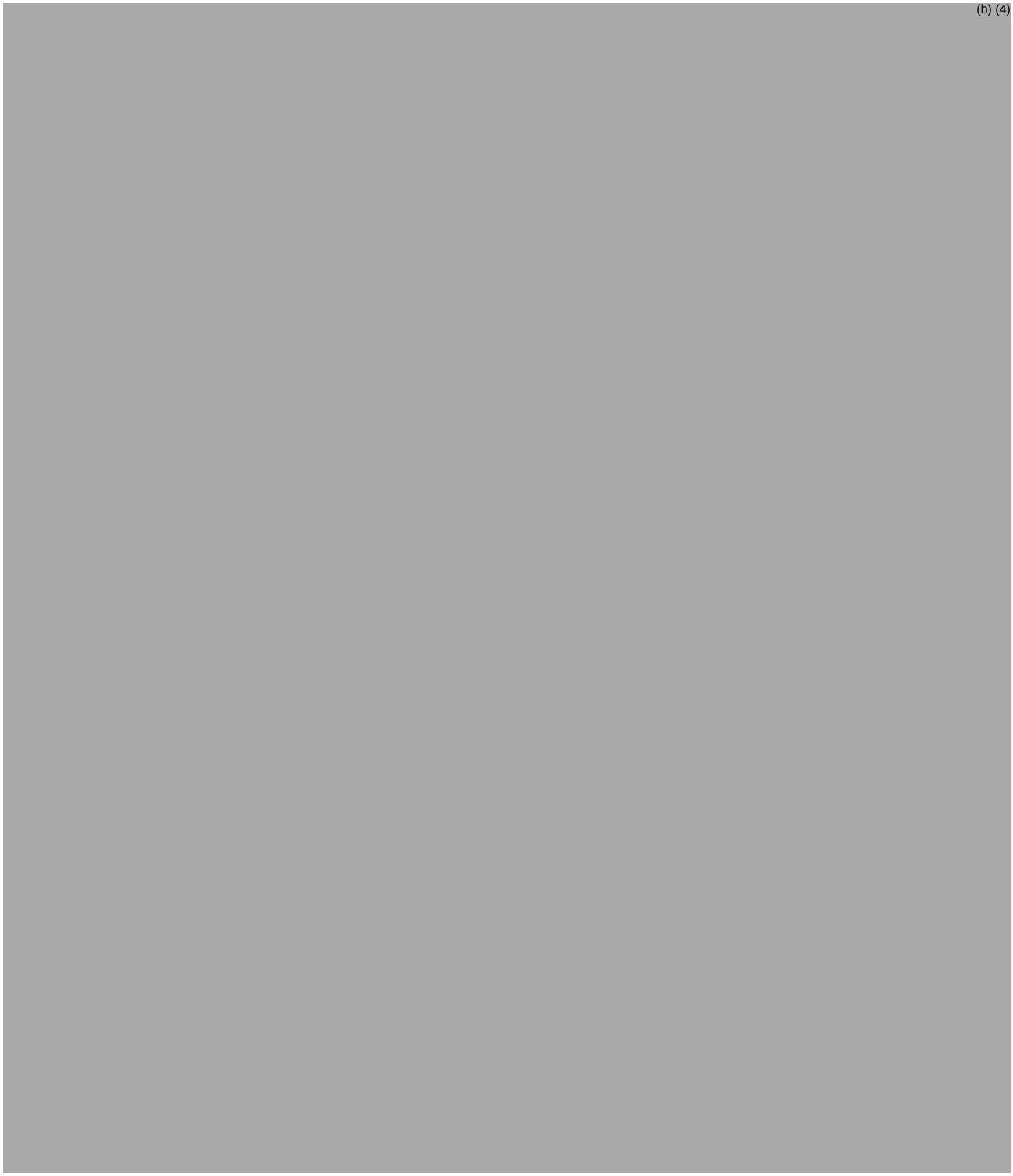
Submission of January 29, 2018 (SD #344):
On January 10, 2018, the Applicant was sent a notification letter of non-compliance with PREA. The Agency stated that it had determined that the Applicant had failed to meet the (PMR of the PREA for NDA 22087 because the Applicant had not yet submitted the pediatric assessment for PMR 973-5, which was deferred until December 31, 2017. The Applicant, in this submission, requested an additional deferral extension request for the pediatric supplement.

PeRC Meeting February 21, 2018:
The Division of Dermatology and Dental Products recommended approval of the Deferral Extension Request and the PeRC concurred. The PeRC also stated that the Applicant should be requested to submit their studies, if possible, before the proposed December 2018 deadline.

Letter dated March 3, 2018:
For PMR 973-5: Conduct a long-term safety trial, including assessment of calcium metabolism, of Vectical (calcitriol) Ointment in 100 evaluable pediatric subjects with plaque psoriasis aged 2 to 16 years and 11 months. Pharmacokinetic/Pharmacodynamic (calcium metabolism) assessment should be performed in at least 9 subjects with plaque psoriasis under maximum use conditions aged 2 to 6 years and 11 months. Final report submission December 2018 (deferral extension date).

The Agency acknowledged the Applicant's proposed revised milestones and agreed with the Applicant's deferral extension request for this PREA PMR because of good faith efforts to complete trials and potential recruitment challenges.

(b) (4)



(b) (4)

Supplement S-009 Prior Approval: (Current Submission)
On September 17, 2019 (SD #362), the Applicant submitted an efficacy supplement for Vectical Ointment that included a request for release from pediatric postmarketing requirements. The Applicant stated that, as requested by the Agency, the supplement included all data collected which is presented for evaluation. Data were also included regarding the PLLR addition to the product insert.

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

4.1. Office of Scientific Investigations

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

4.2. Product Quality

The Applicant determined that the formulation of Vectical Ointment which was approved for use in adult population was acceptable for use in the target pediatric populations. Therefore, the Applicant submitted no new product quality data. For the analysis of the chemistry, manufacturing, and controls information which supported the original approval and assured the identity, strength, purity and quality of the drug product refer to the chemistry, manufacturing, and controls review by Jane L. Chang, Ph.D. dated October 9, 2008.

The Office of Product Quality Reviewer, Joel S. Hathaway, Ph.D., analyzed the request for categorical exclusion from the requirement to conduct an environmental assessment (EA).

The Applicant claims a categorical exclusion from the environmental assessment requirements in compliance with categorical exclusion criteria 21 CFR Part 25.31 (b), applicable for action on a supplement to an NDA resulting in an increase in use, but where the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 part per billion.

The product Quality Reviewer states that: “As the Applicant has certified that the expanded patient population will not increase the exposure of the drug substance to the environment

above the 1ppb threshold, the request for Categorical Exclusion from the requirement for a revised EA is acceptable."

The Applicant proposed no changes to the chemistry, manufacturing, and controls related sections of the Prescribing Information, Patient Information, or carton and container labeling. Dr. Hathaway concluded that this supplement is recommended for approval. See review by Joel S. Hathaway, Ph.D., dated March 2, 2020.

5. Pharmacology Toxicology

The Applicant submitted no new pharmacology/toxicology data in this pediatric efficacy supplement. The Pharmacology/Toxicology team conducted a comprehensive review of the nonclinical data which was submitted to support the original approval of Vectical Ointment. For an analysis and discussion of the nonclinical data, refer to the review by Norman A. See, Ph.D. dated July 2, 2008.

During the review of NDA 222087 S-009, the Pharmacology/Toxicology Reviewer provided comments regarding the relevant subsections of labeling, Sections 8 Use in Specific Populations and 13 Nonclinical Toxicology (review by Norman A. See, Ph.D. dated March 2, 2020.)

6. Clinical Pharmacology

See Clinical Pharmacology Review by Cindy (Liping) Pan, Ph.D. and dated 3/234/2020.
At the time of original approval, there were four PREA PMRs. Two of these PMRs addressed obtaining PK/PD information in pediatric subjects. These two PMRs were:

#1 Conduct PK/PD study of Vectical Ointment under maximum use conditions in 25 evaluable pediatric subjects with psoriasis aged 12 to 17 years.
#2 Conduct a PK/PD study of Vectical Ointment under maximum use conditions in pediatric subjects with psoriasis aged 2 to 12 years; the number of subjects enrolled should be sufficient to detect a 10% change in serum ionized calcium from baseline with 90% confidence or minimum of 25 evaluable subjects, whichever is larger.

PMR #1 was reviewed earlier by Dr. Abimbola Adebowale and was considered fulfilled without labeling revisions during the review cycle (see Clinical Pharmacology Review dated March 3, 2011).

On November 20, 2015, the Agency released the Applicant from PMRs #2, 3, 4 and generated a new PMR #5 below:

#5 Conduct a long-term safety trial, including assessment of calcium metabolism, of Vectical (calcitriol) Ointment in 100 evaluable pediatric subjects with plaque psoriasis aged 2 to 16 years and 11 months. Pharmacokinetic/Pharmacodynamic (calcium metabolism) assessment should be performed in at least 9 subjects with plaque psoriasis under maximum use conditions aged 2 to 6 years and 11 months old.

In the current supplemental New Drug Application (sNDA), the Applicant submitted final abbreviated study reports to fulfill PMRs #2 and 5.

Based on the data in the current supplement, The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology has concluded that the Applicant has fulfilled the PMR #2 and PMR #5 from a Clinical Pharmacology's perspective.

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

6.1. Pharmacokinetics

For ages 12 to 17 years (PMR 973-1) Maximal Use PK:
In trial RD.06.SRE.18102, 25 subjects aged 12 to 17 years applied a twice daily dose of calcitriol ointment 3 mcg/g for 8 weeks to a body surface area of 10% to 35%. The mean daily dose was 10.43 g/day.

For ages 2 to 12 years (PMR 973-2) Maximal Use PK:
In trial RD.06.SRE.18104, 17 subjects aged 2 to 12 years applied a twice daily dose of calcitriol ointment 3 mcg/g for 14 days to a body surface area of 3% to 18%. The mean daily dose was 17.09 g/day.

In both the trials, the systemic concentrations of calcitriol post treatment were relatively flat and were generally comparable to the endogenous levels observed at baseline. As stated in the clinical pharmacology review, PK parameters could not be reliably estimated.

Additional single female subject age 4 (PMR 973 -5):
In trial RD.06.SPR.18131, PK samples were collected from one subject (b) (6) aged 4, who received the topical treatment of calcitriol 3 mcg/g BID for 26 weeks to 5% BSA.

In this subject, there was no clear evidence of any increase in systemic absorption of calcitriol post-treatment.

6.2. Pharmacodynamics

For trial RD.06.SRE.18102 (ages 12 to 17 years) and trial RD.06.SRE.18104 (ages 2 to 12 years), there was no correlation between elevations in calcitriol levels and the pharmacodynamic parameters of serum albumin adjusted calcium, serum phosphorus, urinary calcium, and urinary phosphorus.

For trial RD.06.SPR.18131, including single PK subject (age 4), (Clinical reviewer comment: serum pharmacodynamic parameters in this subject were within normal limits for the duration of this trial. Urine pharmacodynamic parameters for this subject included 24-hour calcium and 24-hour creatinine which were low at Screening and remained so for the duration of the trial. The urine calcium/creatinine ratio was normal at Screening and remained so for the duration of the trial. These findings are assessed as not being clinically significant in view of normal serum PD (pharmacodynamic) parameters and the presence of a normal urine calcium/creatinine ratio.)

7. Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Under the (PREA (21 U.S.C. 355c), all applications for new active ingredients (which include new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

From the original approval letter dated January 23, 2009: “We are waiving the pediatric study requirements for ages 0 months to 2 years because necessary studies are impossible or impracticable. This is because there are too few children with the condition to study.

We are deferring submission of your pediatric studies for ages 2 to 17 years for this application, because this product is ready for approval for use in adults and the pediatric studies have not been completed.”

At the time of approval of NDA 22087 it was stated that (see NDA review, Sept 29, 2008 NDA Patricia Brown, MD):

- The Applicant should conduct a PK/PD study under maximum use conditions to assess systemic exposure in children. The Applicant should evaluate the effect of their product on calcium in all subjects.
- The Applicant should conduct a vehicle-controlled trial (or trials) in pediatric subjects with plaque psoriasis, to understand the efficacy and broad safety profile which would include local and systemic safety. The Applicant should evaluate the effect of their product on calcium in all subjects.
- The Applicant should conduct a long-term safety study in children. An open-label study may be acceptable.

As noted in the regulatory history, the Applicant had four original PMRs to fulfill. One of these was fulfilled March 31, 2011:

- 973-1

Conduct PK/PD study of Vectical Ointment under maximum use conditions in 25 evaluable pediatric subjects with psoriasis aged 12 to 17 years.

Three other PMRs remained:

1. 973-2

Conduct a PK/PD study of Vectical Ointment under maximum use conditions in pediatric subjects with psoriasis aged 2 to 12 years; the number of subjects enrolled should be sufficient to detect a 10% change in serum ionized calcium from baseline with 90% confidence or a minimum of 25 evaluable subjects, whichever is larger.

2. 973-3

Conduct a vehicle-controlled study of the safety and efficacy of Vectical Ointment in pediatric subjects with psoriasis 2 to 12 years of age with a minimum of 100 evaluable subjects exposed to active.

3. 973-4

Conduct a long-term safety study of Vectical Ointment in 100 evaluable pediatric patients 2 to 17 years of age.

The Applicant stated that they had difficulty enrolling subjects to complete the studies outlined in the PMRs and two deferral extensions were granted. In 2015, the Division discussed with the Applicant the pediatric program for NDA 022087 with a goal of creating modifications and/or streamlining the program so that needed information can be collected in a reasonable amount of time. As a result, post-marketing requirements 973-2, 973-3, and 973-4 were replaced with a with a revised PMR:

973-5

Conduct a long-term safety trial, including assessment of calcium metabolism, of Vectical (calcitriol) Ointment in 100 evaluable pediatric subjects with plaque psoriasis aged 2 to 16 years

and 11 months. Pharmacokinetic/Pharmacodynamic (calcium metabolism) assessment should be performed in at least 9 subjects with plaque psoriasis under maximum use conditions aged 2 to 6 years and 11 months old.

In the submission of September 27, 2017, the Applicant proposed "to close the ongoing pediatric study program since they believe that the critical elements of the Post-Marketing Requirements have been addressed. Sufficient data have been gathered and no additional activities are necessary from a clinical standpoint, or feasible from a prevalence and recruitment standpoint."

In a teleconference November 8, 2017 with Applicant, "The Agency conveyed to the Applicant that at this point, another request for Deferral Extension can be pursued or an Efficacy Supplement can be submitted. The Applicant sounded interested in pursuing submission of an Efficacy Supplement, which would need to be inclusive of all data, proposed labeling (if applicable) and an explanation/justification of enrollment efforts and challenges faced."

The current submission includes an efficacy supplement, wherein all data collected is presented for evaluation~~, as requested by the Agency~~. The Applicant referenced the teleconference with the FDA on November 8, 2017 requesting a release from post-marketing requirements.

•To address PMR 973-5 and support the use of Vectical (calcitriol) Ointment 3mcg/g in younger pediatric patients with mild to moderate plaque psoriasis, the Applicant conducted a trial (RD.06.SRE.18131) entitled, "*A multicenter open-label uncontrolled study of the long-term safety and efficacy of calcitriol 3 mcg/g ointment applied twice daily for 26 weeks in pediatric subjects (2 to 16 years and 11 months of age) with mild to moderate plaque psoriasis*." The final study design (Version 3, December 2, 2015) is summarized below:

Table 3: Clinical Trial RD.06.SRE.18131

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Subjects	Study Population	No. of Centers and Countries
Studies to Support Safety							
RD.06.SRE.18131	Multicenter, open-label. Uncontrolled, long-term safety and efficacy, PK/PD	Twice daily for 26 weeks	% of subjects with IGA clear or almost clear. change from baseline in pruritus, change from baseline in %BSA Safety: serum albumin-adjusted calcium, urine calcium: creatinine ratio, phosphorus, PTH PK: plasma conc calcitriol, PD: serum calcium, phosphorous, albumin, PTH PD (urine) urine calcium & creatinine 24-hour urine	26 weeks, 4 weeks	54 enrolled	Pediatric, ages 2 to 16 years 11 months, mild to moderate plaque psoriasis IGA 2 or 3 at Screening, for PK minimum of 3% BSA involved	Approx. 30 sites planned, US, Canada, Europe

Abbreviations: PK = pharmacokinetic, PD = pharmacodynamic, PTH = parathyroid hormone, BSA = body surface area, IGA = Investigator's Global Assessment
Source: Reviewer's Table

7.1.2. Review Strategy for Clinical Trial RD.06.SRE.18131/ PMR 973-5

The focus of this review was the local and systemic safety of Vectical (calcitriol) Ointment which included the PK and PD findings.

As the pathophysiology of plaque psoriasis and response to treatment are similar in the adult and pediatric populations (Paller and Lund 2020a) (Paller and Lund 2020b), efficacy in the population ages 2 to 16 years was extrapolated from data in the adult population.

Data Sources
The sources of data used for the evaluation of the efficacy and safety of Vectical (calcitriol) Ointment for the proposed indication included a final abbreviated clinical study report for Clinical Trial RD.06.SRE.18131 submitted by the Applicant, and literature references.

This application was submitted in electronic common technical document (eCTD) format and entirely electronic. The electronic submission including the protocol, clinical study reports, are located in the following network path: \\CDSESUB1\evsprod\NDA022087\022087.enx

Data and Analysis Quality
In general, the data submitted by the Applicant to support the safety of Vectical (calcitriol) Ointment for the indication topical treatment of mild to moderate plaque psoriasis in adult and pediatric patients appeared adequate.

7.2. Review of Relevant Trial

7.2.1. Study Design and Endpoints

Clinical Trial RD.06.SRE.18131

Objectives:
Conduct a long-term safety trial, including assessment of calcium metabolism, of Vectical(calcitriol) Ointment in 100 evaluable pediatric subjects with plaque psoriasis aged 2 to 16 years and 11 months. Pharmacokinetic/Pharmacodynamic (calcium metabolism) assessment should be performed in at least 9 subjects with plaque psoriasis under maximum use conditions aged 2 to 6 years and 11 months old.

Study Population
The original intent of the study was to screen approximately 167 subjects in order to enroll a target of 100 subjects. Pharmacokinetic investigations were to be conducted on a subset of approximately 9 enrolled subjects, aged 2 to 6 years and 11 months (inclusive at Screening) and with a minimum 3% BSA involvement. Due to slow study enrollment the study was closed to enrollment in November 2017. At the time of study closure, 54 subjects were enrolled and had

received study drug. At that time, 41 subjects had completed the study (including 1 PK subject). An Independent Data Monitoring Committee (IDMC) was established to monitor this trial on an ongoing basis.

The key entry criteria that defined the study population for the final version of the protocol are as follows:

Key Inclusion Criteria

- Male or female 2 to 16 years and 11 months of age (Version R03)
- Specific for PK: Pediatric subjects 2 to 6 years and 11 months of age (inclusive at Screening) and with a minimum 3% BSA involvement
- Clinical diagnosis of stable mild to moderate plaque type psoriasis
- Subjects with an IGA score of 2 or 3 at Screening and Baseline
- Female of non-childbearing potential (pre-menarcheal).
- Female of childbearing potential with a negative urine pregnancy test at visit(s) Screening (Day -14) and Baseline (Day 0).
- Female of childbearing potential who:
    - has been strictly abstinent 1 month prior to baseline and agrees to continue for the duration of the clinical trial,
    - And/or agrees to use a highly effective and approved contraceptive method(s) during the study and for at least 1 month after the last study drug application. A highly effective method of contraception is defined as:
        - combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month prior to baseline

Key Exclusion Criteria:

- Subjects with guttate psoriasis, pustular psoriasis, erythrodermic psoriasis or active infection (i.e., an infection associated with fever, swollen lymph nodes, and/or signs of localized inflammation of tissue and/or joints). *Note: allergic or vasomotor rhinitis is not exclusionary.*
- The subject has hypercalcemia (serum albumin-adjusted calcium above the upper normal range) at Screening.
- The subject has urinary calcium: creatinine ratio above the upper normal range at Screening.
- The subject has history or signs and symptoms of urolithiasis.
- Subjects with known or suspected disorders of calcium metabolism.
- Subjects with liver dysfunction, defined as laboratory aspartate aminotransferase or alanine aminotransferase >2x upper limit of normal or Total bilirubin >1.5x upper limit of normal
- Subjects with creatinine clearance <85mL/min per 1.73 m2 at Screening
- Subjects with underlying systemic or other dermatological conditions that require the use of systemic supplements of calcium or vitamin D. (Subjects taking oral calcium and

- vitamin D for prophylactic purposes must be on a stable dose for at least 4 weeks prior to Screening and are not to exceed the Recommended Daily Allowance for calcium (1,300 mg for subjects aged 12-16 years and 11 months and 1,000 mg for subjects less than 12 years) or Vitamin D (600 IU).
- The Subject has Vitamin D deficiency (25(OH)D <20 ng/mL) at Screening (Note: Subjects with 25(OH)D <20 ng/mL at Screening may undergo re-screening after at least 4 weeks of Vitamin D deficiency treatment to determine eligibility.).
- The Subject has secondary hyperparathyroidism or parathyroid hormone (PTH) above Upper Limit of Normal at Screening.

Study Design

This was an open-label, uncontrolled, multicenter long-term safety and efficacy study in pediatric subjects (age 2 to 16 years and 11 months) with mild to moderate plaque psoriasis who received calcitriol 3 mcg/g ointment, without occlusion, for a period of up to 26 weeks. This study, along with 3 others (PK studies RD.06.SRE.18102 (PMR 973-1: fulfilled) and RD.06.SRE.18104 (PMR 973-2), and efficacy and safety study RD.06.SRE.18132 PMR 973-3)), were conducted to fulfill four original post-marketing commitments. This study was PMR 973-5 which was developed by modifying an earlier version of RD.06.SPR.18131 (PMR 973-4) to become the current version (Version 3, December 2, 2015) RD.06.SRE.18131 (PMR 973-5).

Application of study drug was to be done by either the subject's parent/legal guardian or by the subject him/herself. A thin film of study drug was to be applied as needed to cover all involved areas twice daily (morning and evening), without exceeding a maximum of 0.5 g/kg of body weight or 28 g daily (whichever was the lower). If the subject experienced complete clearing of psoriasis per physician assessment (i.e., IGA score of 0), the subject was to discontinue the study drug but continue to follow the visit schedule through the Week 26 visit. Treatment with study drug was to be resumed if the IGA score was >0 and <4. Study participation for each subject was approximately 32 weeks, including and up to 2-week screening period, 26 weeks of treatment, and 4 weeks of follow-up.

Subjects were evaluated at Screening, Baseline, and Weeks 4, 12, and 26, and at follow-up Week 30, as described in the Schedule of Assessments Table 6 below

Concomitant Medications

No other topical treatments, other than the test materials, were permitted on the treated areas. However, emollients on healthy skin areas were permitted during the course of the study. Moisturizing Cream and Skin Cleanser (provided by the Applicant) were to be used as needed, on non-treated areas of the skin. Subjects were permitted to use medicated shampoos that do not contain corticosteroids or vitamin D derivatives to treat scalp psoriasis. Tar products could be used on the face and scalp areas. Sunscreen was to be used as needed on non-treated areas of the skin.

Subjects taking oral calcium and vitamin D for prophylactic purposes were to be on a stable dose for at least 4 weeks prior to Screening and were not to exceed the Recommended Daily Allowance for calcium (1,300 mg for subjects aged 12-16 years and 11 months and 1,000 mg for subjects less than 12 years) or Vitamin D (600 IU). Subjects were to remain on the same dose throughout the course of the study.

Prohibited Products

Prohibited products also included Drugs that may cause alterations in serum or urine calcium levels: The Applicant provided a list in an Appendix to the protocol (RD.06.SPR.18131 V03 - 02 Dec 2015 eUS)

Table 4: Prohibited Products

Topical treatment(s) or Procedures:	
• Corticosteroids or topical immunomodulators	2 weeks
• Tar (on areas to be treated with study drug)	2 weeks
• Vitamin D derivatives	2 weeks
• Vitamin A derivatives	2 weeks
• Intralesional steroid injections	4 weeks
Systemic treatment(s):	
• Homeopathic or herbal preparations	1 weeks
• Calcium containing products	2 weeks
• Immunomodulators and biologics known to affect psoriasis	4 weeks
• Corticosteroids or ACTH analogs	4 weeks
• Phototherapy/PUVA therapy	4 weeks
• Laser therapy	4 weeks

Objectives and Related Endpoints

The primary objective of the study was to evaluate the safety of up to 26 weeks of treatment with calcitriol 3 mcg/g ointment when used twice daily, without occlusion, to treat pediatric subjects (2 to 16 years and 11 months, Version R03) with plaque psoriasis.

As a secondary objective, calcitriol plasma levels were assessed at several time points throughout the study duration in a subset of children 2 to 6 years and 11 months old with a minimum of 3% BSA involvement.

The efficacy objective was to evaluate the long-term efficacy of up to 26 weeks of treatment with calcitriol 3 mcg/g ointment when used twice daily, without occlusion, to treat pediatric subjects (2 to 16 years and 11 months, Version R03) with mild to moderate plaque psoriasis.

Investigators

A total of 16 study sites enrolled subjects for this trial and were located in Belgium (1), Canada (2), Germany (3), Italy (2), and the United States (8).

Table 5: Study Sites and Enrollment

Site Number	Principal Investigator	Location	Subjects Enrolled (N)
5447	Pr. Sofie De Schepper	Gent, Belgium	2
8026	Dr. Charles Lynde	Ontario, Canada	3
8442	Dr. Danielle Marcoux	Montreal, Canada	8
5434	Pr. Stefan Beissert	Dresden, Germany	1
5543	Dr. Petra Staubach	Mainz, Germany	1
5604	Pr. Ulrike Blume-Peytavi	Berlin, Germany	2
5894	Pr. Andrea Perserico	Padova, Italy	3
5895	Dr. Sergio Di Nuzzo	Parma, Italy	2
8133	Dr. Angela Moore	Arlington, TX, USA	18
8142	Dr. Scott Fretzin	Indianapolis, IN, USA	1
8355	Dr. Cheryl Hull	Rogers, AR, USA	3
8412	Dr. Holly Kanavy	Bronx, NY, USA	2
8436	Dr. Stephen Shidler	Carmel, IN, USA	4
8437		USA	1
8438	Dr. Martin Kay	Burbank, CA, USA	2
8447	Dr. sandy Johnson	Fort Smith, AR, USA	1

Source: Compilation by reviewer from table 14.1.1.2 RD.06.SPR.18131, and SDN 365, NDA 22087.

Table 6: Schedule of Assessments Trial RD.06.SRE.18131

	Clinical Trial Assessments					
	Screening Period	Treatment Period[a]				Follow-up Period
	Screening (Day -14)[b] Visit 1	Baseline[c] (Week 0) Visit 2	Week 4[d] Visit 3	Week 12[d] Visit 4	Week 26 / ET[d,e] Visit 5	Week 30[d] Visit 6
Informed Consent / Assent Form /HIPAA/PIPEDA	X					
Demographics	X					
Medical history	X					
Previous therapies/procedures[f]	X					
Physical examination and Vital signs[g]	X	X		X	X	
Inclusion/Exclusion criteria	X	X[h]				
Urine pregnancy test (postmenarcheal)	X	X	X	X	X	X
Record % BSA involved	X	X	X	X	X	X
Routine blood chemistry and hematology	X		X	X	X	X[i]
Urinalysis	X		X	X	X	X
Pharmacodynamic serum[j]	X	X[k]	X	X	X	X[i]
Pharmacokinetic blood sampling[l]	X	X	X	X	X	X
Pharmacodynamic urine[m]	X			X[n]	X[n]	X[i]
25(OH)D & 1,25 $(OH)_2$ D	X			X	X	X[i]
Investigator's Global Assessment	X	X	X	X	X	X
Pruritus	X	X	X	X	X	X
Drug application		Twice a day from Baseline to Week 26, Visit 5[o]				
Study drug dispensing (D) and accountability (A)[p]		D	D/A	D/A	A	
AE information collection[q,r]	X	X	X	X	X	X
Concomitant therapies/Procedures[f]	X	X	X	X	X	X
Moisturizer and cleanser dispensed[s]		X	X	X	X	
Exit Form[e]						X

Abbreviations: A = accountability; AE = adverse event; BSA = body surface area; D = dispensing; ET = early termination; IDMC = Independent Data Monitoring Committee; PCP = Primary Care Physician; PD = pharmacodynamics; PK = pharmacokinetic; PTH = parathyroid hormone

Note: Unscheduled visit was to occur when necessary and exceptionally, because of either an AE that needed a specific treatment, AE that led to withdrawal from the study, laboratory result(s) that warranted further testing, or other reason.

Note: An ongoing dialogue between the subject, parent/legal guardian, and Investigators that focused on all aspects of the study was encouraged. Any new information that arose in relation to the study and that might have affected the willingness of the subject and/or parent/legal guardian was to be discussed. This brief discussion was to be documented during each study visit.

a) There were no visits at Week 8 and Week 20, after the protocol amendment.

b) Subjects could re-screen once, with written approval from the Applicant prior to re-entry into the study.

c) Visit window of ±5 days

d) Visit window of ±3 days

e) Or at any time in case of early termination

f) Any therapy or medication other than study ointment was to be noted on the Drugs/Therapies Form. Subjects who required a wash-out period of a prohibited therapy for >2 weeks, were to be screen failed and could be re-screened once after completion of the washout period.

g) Physical examination included weight and review of systems: skin, cardiovascular, respiratory, abdomen, head and neck, musculoskeletal, neurological, lymph nodes and psychological. Height was evaluated at Screening only. Vital signs included blood pressure and pulse rate.

h) Reconfirmed that subject continued to meet inclusion/exclusion criteria.

i) Laboratory testing (full panel) was completed at Week 30 for subjects in the PK group. For all other subjects, laboratory testing at Week 30 was completed at the Investigator's discretion.

j) PD Serum (non-fasting): calcium, phosphorus, albumin (in order to calculate the serum albumin-adjusted calcium) and PTH.
k) Serum PD was assessed at Baseline only for subjects 2 to 6 years and 11 months of age for whom PK analysis was conducted, in order to assess PK/PD relationships at Baseline for these subjects.
l) For subjects in the PK group, a single blood sample at Screening and Baseline was to be taken, then a single pre-dose blood sample was to be taken at Weeks 4, 12, 26, and 30, to assess the calcitriol plasma concentration. The volume of each blood sample was to be 5 mL. A total volume of 30 mL was to be collected during the study for PK assessment.
m) PD Urine: Urine calcium and creatinine on 24-hour urine collection, whenever possible, or a urine sample after fasting for 4 hours in order to calculate urine calcium: creatinine ratio. Subjects who were toilet-trained were to be actively encouraged to complete a 24-hour urine collection. A urine collection container/material was given to the subject/subject's parent/legal guardian with the instruction to start collecting urine as of that visit and to bring the container back after the 24-hour/4-hour collection.
n) The visit before: Container was to be distributed and instructions provided for 24-hour urine collection to be started 1 day prior to Week 12 and Week 26/ET visits. The study site was to contact the parent/legal guardian 48 hours prior to the visit to remind them to start the urine collection.
o) At Baseline, the study nurse was to show the subject's parents how to apply the drug.
p) Total amount of study drug applied to involved skin was not to exceed 0.5 g/kg of body weight or 28 g per day (whichever was the lower). First application was to be made under the supervision of the Investigator or designee. Daily administration was to be recorded on the dosing calendar. Dosing calendar was to be checked at each visit after Baseline.
q) Events that occurred after the Informed Consent Form and Assent Form (when applicable) had been signed, were to be recorded as Adverse Events in the eCRF
r) Subjects with suspected kidney stones were to temporarily discontinue study drug and were to be referred to their PCP for care in tandem with Applicant consultation of the IDMC.
s) Cetaphil® Moisturizing Cream and Cetaphil® Gentle Skin Cleanser or equivalents were to be provided by the Applicant.
Source: Clinical Study Report for RD.06.SRE.18131, section 9.1, pages 12, 13

Safety Assessments

Safety parameters were evaluated and recorded over the course of the study and included AEs, laboratory parameters (hematology, blood chemistry [nonfasting], and urinalysis), physical examination (including weight), and vital signs (blood pressure and pulse rate).

In addition, an IDMC was established to monitor laboratory results for PTH, calcium, phosphorus, albumin, and creatinine levels on an ongoing basis as defined in the IDMC Charter. The IDMC was to inform the Applicant and recommend actions to be taken, if safety signals were observed.

Pharmacokinetic Assessments

For subjects in the PK subset (approximately 9 subjects), the calcitriol plasma concentration was to be assessed by a single blood sample at Screening and Baseline, followed by a single pre-dose blood sample (Ct) at Weeks 4, 12, and 26. A blood sample drawn at the Week 30 visit was to allow determination of the calcitriol plasma concentration 1 month after the last drug product application. The volume of each blood sample was to be 5 mL, with a total volume of 30 mL collected during the study for PK assessment.

Study drug was not to be applied on the areas used for blood sampling, as defined at Screening by the Investigator. In addition, the blood sampling had to occur 12 hours (±1 hour) after the last product application. At the Weeks 4, 12, and 26 visits, study drug applications were to be performed on site after the PK pre-dose blood sampling was obtained.

Pharmacodynamic Assessments

Serum PD were to be assessed during the Baseline visit only for subjects 2 to 6 years and 11 months of age, for whom PK analysis was conducted; the purpose was to assess PK/PD relationships at Baseline for these subjects.

For the PD variables, the effects of Vectical Ointment on calcium and phosphorus homeostasis were assessed.

The following PD variables were evaluated:

- Serum (nonfasting): calcium, phosphorus, albumin (in order to calculate the albumin-adjusted calcium), and intact PTH. Pharmacodynamic serum was assessed at Screening, Baseline, and Weeks 4, 12, 26, and 30.

- Urine: calcium and creatinine; a 24-hour urine collection whenever possible, or a urine sample after fasting for 4 hours, in order to calculate urine calcium/creatinine ratio. Pharmacodynamic urine was assessed at Screening, and Weeks 12, 26, and 30.

Other Assessments
Evaluation of 1, 25 dihydroxy vitamin D (1, 25(OH)2 D), and 25-hydroxy Vitamin D (25(OH)D) was performed at Screening, and Weeks 12, 26, and 30.

Efficacy Assessments

- IGA score
- Pruritus

Data Analysis
The Safety Population was defined as all subjects who have applied the study drug at least once.

The statistical analyses were to be performed based on the Safety population. No inferential statistical analysis was planned for safety endpoints of the study.

Efficacy endpoints: No formal inferential statistical analysis was to be performed. IGA was to be summarized by each category and by shift changes over time. In addition, observed changes from baseline of the IGA and Pruritus over time were to be summarized as continuous variables.

Protocol Amendments
The protocol was amended two times:

Amendment 1 (Version 2; dated August 28, 2014): In this amendment, minor changes to the overall study design and conduct were made.

Amendment 2 (Version 3; dated December 2, 2015): Changes were made to include PK assessment in a subset of subjects aged 2 to 6 years and 11 months old as well as changes to facilitate ease of subject enrollment and participation including (among others):

- Added secondary objective of PK assessments in approximately 9 subjects aged 2 to 6 years and 11 months old with plaque psoriasis and a minimum of 3% BSA involvement, to fulfill FDA Phase 4 requirements.
- Added serum PD assessment at Baseline for subjects in the PK group in order to investigate PK/PD relationships.
- Reduced the number of enrolled subjects.
- Removed requirement for equal distribution among age groups.
- Added blood draws at every study visit for subset of subjects in the PK group.
- Removed study visits at Week 8 and Week 20.

7.2.2. Results of Efficacy Assessment

The efficacy objective was to evaluate the long-term efficacy of up to 26 weeks of treatment with calcitriol 3 mcg/g ointment when used twice daily, without occlusion, to treat pediatric subjects (2 to 16 years and 11 months of age, Version R03) with mild to moderate plaque psoriasis. Since this trial was an open-label safety trial, no formal inferential statistical analysis was performed. As the pathophysiology of plaque psoriasis and response to treatment are similar in the pediatric and adult populations, efficacy in the pediatric population was extrapolated from the adult population (Dunne et al. 2011).[1]

As outlined in the protocol, investigators documented IGA scores on all treated areas and evaluated pruritus at all visits. Investigators also estimated the percentage of BSA involvement (methodology of the calculation is described in Appendix 3, section 13.3 Protocol RD.06.SPR.18131 V03 – Dec 3, 2015).

Efficacy Endpoints
Efficacy Endpoints

- Percentage of subjects with an IGA Score of 0 (clear) or 1 (almost clear)
- Change from Baseline in Pruritus
- Change from baseline in % BSA

IGA was to be evaluated on all treated areas by a Board Certified (or any other regional equivalent) dermatologist.

Table 7: Investigator's Global Assessment

Score	Category	Description
0	Clear	No signs of psoriasis except for residual hypopigmentation / hyperpigmentation

[1] Dunne, J, WJ Rodriguez, MD Murphy, et al., 2011, Extrapolation of Adult data and other Data in pediatric Drug-development Programs, Pediatrics, 128(5):e1242-e1249

Score	Category	Description
1	Almost Clear	Just perceptible erythema, no induration, and no scaling
2	Mild	Mild erythema, no induration, and mild or no scaling
3	Moderate	Moderate erythema, mild induration, and mild or no scaling
4	Severe	Severe erythema, moderate to severe induration, and scaling of any Degree

Source: Reviewer's table based on section 7.1.1.1 of Protocol RD.06.SPR.18131 V03 – 02 Dec 2015 eUS

Pruritus was to be evaluated on all treated areas.

Table 8: Pruritus Assessment

Score	Category	Description
0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching that is somewhat bothersome without loss of sleep
3	Severe	Intense itching that has caused pronounced discomfort, night rest interrupted
4	Very Severe	Very severe itching that has caused pronounced discomfort during the night and daily activities

Source: Reviewer's table based on section 7.1.1.2 of Protocol RD.06.SPR.18131 V03 – 02 Dec 2015 eUS

All data were summarized and analyzed based on the Safety population, which comprised all enrolled subjects who received at least one application of the study medication.

IGA

As specified in the protocol, all subjects had an IGA of either 2 (mild) or 3 (moderate) at Baseline, with the majority (39 of 54 subjects, 72.2%) being moderate, with a median IGA score of 3.0. At the Week 26/End of Study visit, 19 subjects (46.3%) had an IGA of clear (0) or almost clear (1). By Week 30 (Follow-Up) visit, 17 subjects (41.5%) had an IGA score of clear (0) or almost clear. The majority (63.4%) of subjects improved from Baseline to Week 26, with most showing a 1- or 2-grade improvement. The median change from Baseline was -1.0, a 1-grade improvement. Change from Baseline at Week 26 is presented in Table 9 (below).

Table 9: Change From Baseline in IGA at Week 26 (Safety Population)

	Change from Baseline at Week 26 N=54
Change = -3 (3-grade improvement)	3 (7.3)
Change = -2 (2-grade improvement)	10 (24.4)
Change = -1 (1-grade improvement)	13 (31.7)
Change = 0 (no change)	13 (31.7)
Change = 1 (1-grade worsening)	2 (4.9)
Change = 2 (2-grade worsening)	0
Change = 3 (3-grade worsening)	0
Total	41 (100.0)
N	41
Mean (SD)	-1.0 (1.04)
Median	-1.0
Min, Max	-3, 1

Abbreviations: IGA = Investigator's Global Assessment; Max = maximum; Min = minimum; SD = standard deviation
Note: The percentage of subjects was calculated based on the number of subjects in the Safety population with available results at each visit.
There were no visits of Week 8 and Week 20 after the protocol amendment
Source: Table 5 Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, p 19.

Pruritus

At Baseline, the majority of subjects had a pruritus score of either 1 "mild" (27.8%) or 2 "moderate" (48.1%), with a median score of 2.0; 6 subjects (11.1%) had no pruritus (score of 0), 5 subjects (9.3%) had a pruritus score of 3 (severe), and 2 subjects (3.7%) had a pruritus score of 4 (very severe). At the Week 26/End of Study visit, 17 (41.5%) subjects had a pruritus score of 0 (none), 17 (41.5%) had a pruritus score of 1 (mild) and 6 subjects (14.6%) had a pruritus score of 2 (moderate). One subject (2.4%) had a pruritus score of 3 (severe) and no subjects had a pruritus score of 4 (very severe)

The majority (70.7%) of subjects improved between Baseline and Week 26, with most showing a 1- or 2-grade improvement. The median change from Baseline was -1.0, a 1-grade improvement. Change from Baseline at Week 26 is presented in Table 10 (below).

Table 10: Change From Baseline in Pruritus at Week 26 (Safety Population)

	Change from Baseline at Week 26 N=54
Change = -4 (4-grade improvement)	0
Change = -3 (3-grade improvement)	1 (2.4)
Change = -2 (2-grade improvement)	9 (22.0)
Change = -1 (1-grade improvement)	19 (46.3)
Change = 0 (no change)	9 (22.0)
Change = 1 (1-grade worsening)	2 (4.9)
Change = 2 (2-grade worsening)	1 (2.4)
Change = 3 (3-grade worsening)	0
Change = 4 (4-grade worsening)	0
Total	41 (100.0)
N	41
Mean (SD)	-0.9 (0.98)
Median	-1.0
Min, Max	-3, 2

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation
Note: The percentage of subjects was calculated based on the number of subjects in the Safety population with available results at each visit.
There were no visits of Week 8 and Week 20 after the protocol amendment.
Source: Table 6 Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, p 21.

BSA

At Baseline, the mean percent BSA was 7.4%, with a median of 6.0, which improved to 3.4% BSA at Week 26 (median 2.0). The improvement in BSA from Baseline was 3.9% and continued to improve through the Week 30 follow-up (4.7%). A summary of percent BSA at Baseline and Week 26 is presented in Table 11 (below).

Table 11: Summary of % BSA at Baseline and Week 26 (Safety Population)

	Baseline	Week 26	Change from Baseline at Week 26
N	54	41	41
Mean (SD)	7.4 (5.63)	3.4 (3.81)	-3.9 (4.52)
Median	6.0	2.0	-3.0
Min, Max	1, 30	0, 15	-20, 2

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation
Source: Table 7 Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, p 23.

7.3. Review of Safety

7.3.1. Safety Review Approach

The review of the safety of Vectical(calcitriol) Ointment in trial RD.06.SRE.18131 involved a pediatric population, 2 to 16 years and 11 months of age, with mild to moderate plaque psoriasis. The safety review included analyses of TEAEs, serious AEs (SAEs), AEs leading to discontinuation, treatment-emergent adverse reactions, and AEs associated with product class, vitamin D analogs.

7.3.2. Review of the Safety Database

Disposition

A total of 88 subjects were screened; 29 subjects were considered screening failures based on eligibility criteria. The study was closed to enrollment in November 2017. At the time of study closure, 54 subjects were enrolled and had received study drug, of which 41 subjects completed the study.

Table 12: Disposition of Subjects

Completion Status	Calcitriol 3 µg/g (N=54) n (%)
Number of subjects enrolled[a]	54 (100.0%)
Number of subjects who completed the study	41 (75.9%)
Number of subjects who prematurely discontinued	13 (24.1%)
Reason for discontinuation	
Lack of efficacy	2 (3.7%)
Adverse Event	0
Subject request	6 (11.1%)
Protocol violation	1 (1.9%)
Lost to follow-up	4 (7.4%)

a) Subjects with at least 1 application of study drug
Note: The percentage of subjects was calculated based on the number of subjects with study drug at least once.
Source: Table 3: Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, p 16.

Exposure

Duration of treatment

The median number of treatment days was 181, and the mean treatment duration was 159.1 days. The majority (75.9%) of subjects received treatment for 162 to 196 days.

Table 13: Summary of Treatment Duration

Treatment Duration (days)	Calcitriol 3 µg/g (N=54)
N	54
Mean (SD)	159.1 (53.17)
Median	181.0
Min, Max	1, 209
≤42 days	4 (7.4)
43 - 70 days	2 (3.7)
71 - 112 days	4 (7.4)
113 - 161 days	0
162 - 196 days	41 (75.9)
>196 days	3 (5.6)

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation
Source: Table 8: Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, p 25.

Extent of Exposure

Actual study drug exposure was calculated as treatment duration in days minus the number of days with no AM or PM application. The mean actual study drug exposure was 155.1 days. Median compliance with study drug in days was 100% (range, 29 to 100 days) and the median study drug exposure was 344.5 doses (98.15%; range, 2 to 415 doses). Study drug supplied was not weighed.

Table 14: Summary of Exposure and Compliance Safety Population

CD2027 (N=54)	
Actual Study Drug Exposure in Days [1]	
N	54
Mean (SD)	155.1 (54.58)
Median	180.0
Min, Max	1, 209
Compliance with Study Drug (%) in days [1]	
N	54
Mean (SD)	96.90 (10.415)
Median	100.00
Min, Max	29.4, 100.0

CD2027 (N=54)	
Actual Study Drug Exposure in Doses [2]	
N	54
Mean (SD)	298.9 (107.45)
Median	344.5 (98.15%)
Min, Max	2, 415

Abbreviations: SD = standard deviation; Min = minimum; Max = maximum
[1]Actual study drug exposure in days = Treatment duration (days) – number of days with no applications in both PM and AM. If the number of missed doses was unknown at a visit, 50% of the duration (rounded up) between the previous visit and the visit was assumed as the days
with no applications in both PM and AM.
[2]Compliance (%) in days = Actual study drug exposure in days /expected study drug exposure in days.
[3]Actual study drug exposure in doses = Treatment duration * 2 – number of missed doses.
If the number of missed doses was unknown at a visit, 50% doses were assumed to be missed between the previous visit and the visit.
Source: Adapted from Table 14.3.1.3: Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, Section 14.3, p 5.

Characteristics of the Safety Population

Demographics and Baseline Characteristics

All data were summarized and analyzed based on the Safety population, which comprised all enrolled subjects who received at least one application of the study medication.

The Safety population comprised 54 subjects, 30 (55.6%) males and 24 (44.4%) females, with a mean age of 10.3 years (range 3 to 17 years). Half of the subjects were 6 to 12 years of age, and approximately one-third of subjects were 13 to 17 years of age. The majority (85.2%) of subjects were White and not Hispanic or Latino (83.3%). The skin phototype for the majority (79.6%) of subjects was Type II and III. The mean involved BSA was 7.4%.

Table 15: Demographics (Safety Population)

		Calcitriol 3 µg/g (N=54)
Age (years)	N	54
	Mean (SD)	10.3 (3.99)
	Median	10.0
	Min, Max	3, 17
Age group n (%)	2-5 years	8 (14.8)
	6-12 years	27 (50.0)
	13-17 years	19 (35.2)
Gender n (%)	Male	30 (55.6)
	Female	24 (44.4)
Race n (%)	White	46 (85.2)
	Black/African American	1 (1.9)
	Asian	4 (7.4)
	Other	3 (5.6)
Ethnicity n (%)	Hispanic or Latino	9 (16.7)
	Not Hispanic or Latino	45 (83.3)
Skin phototype n (%)	I	0
	II	25 (46.3)
	III	18 (33.3)
	IV	10 (18.5)
	V	1 (1.9)
Baseline Body Surface Area Involved	N	54
	Mean (SD)	7.4 (5.63)
	Median	6.0
	Min, Max	1, 30
Location of Affected Area, n(%)	Head and Neck	27 (50.0)
	Left Arm	42 (77.8)
	Right Arm	42 (77.8)
	Anterior Trunk	21 (38.9)
	Posterior Trunk	23 (42.6)
	Left Leg	43 (79.6)
	Right Leg	41 (75.9)

Abbreviations: SD = standard deviation; Min = minimum; Max = maximum
Source: Table 4: Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, p 17.

Concomitant Medications

Concomitant therapies were defined as any therapy/medication usage past first dose of study medication. Approximately half (51.9%) of subjects received concomitant therapies with systemic antihistamines and emollients being the most frequently used. Three subjects (5.6%) used vitamin D and analogues.

Protocol Deviations
In Table 14.1.2.3 of the Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, Section 14.1, p 16, the Applicant reports that 0 subjects had major protocol violations.

Adequacy of the Safety Database
The Applicant did not achieve the enrollment total specified in PMR 973-5 (100 evaluable subjects aged 2 to 16 years and 11 months).

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted was adequate to characterize the safety of Vectical(calcitriol) Ointment applied twice daily for 26 weeks in pediatric subjects (2 to 16 years and 11 months of age. No significant deficiencies were discovered that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events
Adverse events were coded using the Medical Dictionary for Regulatory Activities version 15.0.

The Applicant defined an adverse event (per ICH E2A) as any untoward medical occurrence in a subject or clinical investigation subject who was administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment.

For this trial, the Applicant also designated AEs of special interest including:
1. Typical clinical signs and symptoms consistent with Vitamin D toxicity:
   - polyuria, polydipsia
   - clinically significant mental status changes
2. Out-of-range laboratory result that is identified as clinically significant and related to the study drug
3. Dermatological events such as severe skin irritation as well as severe local and/or generalized pruritus
4. Suspected skin sensitization (contact allergy)
5. Cutaneous AE assessed as related to the study drug and leading to discontinuation of the study drug, including temporary discontinuations

Routine Clinical Tests
Investigators monitored AEs, concomitant medications, local safety, and effects on calcium metabolism.

Routine laboratory values evaluated included:

- Hematology [White blood cell count with differential, red blood cell count, hemoglobin, hematocrit, mean cell volume, and platelet count]
- Blood chemistry (non-fasting) [Total protein, alanine aminotransferase (also called serum glutamic-pyruvic transaminase), aspartate aminotransferase (also called serum glutamic-oxaloacetic transaminase), alkaline phosphatase, blood urea nitrogen, creatinine (calculated creatinine clearance), and bilirubin (total and conjugated)]
- Urinalysis (glucose, ketones, blood, proteins, leukocytes, nitrites)

Pharmacodynamic parameters evaluated included:

- Serum (non-fasting): calcium, phosphorus, albumin (in order to calculate the serum albumin-adjusted calcium), PTH
- Urine: Calcium and creatinine (in order to calculate urine calcium: creatinine ratio) at 24-hour urine collections, when feasible, or fasting (4 hour) urine samples. Subjects who are toilet-trained should be actively encouraged to complete the 24-hour urine collection.

Other Assessments included:

- 1, 25(OH)2D (calcitriol = active form of vitamin D) (Note: this is metabolized from 25(OH)D in kidneys. Calcipotriene is a synthetic derivative of vitamin D.)
- 25(OH)D [25-hydroxyvitamin D = prohormone]

Assessments for routine laboratory values occurred at Screening, Week 4, Week 12, Week 26, and follow-up at Week 30. Assessments for serum pharmacodynamic parameters occurred also at Screening, Week 4, Week 12, Week 26, and follow-up at Week 30 and at Baseline only for subjects 2 to 6 years and 11 months for whom PK analysis was conducted. Urine pharmacodynamic parameters and 1, 25(OH)2D, and 25(OH)D were assessed at Screening, and Weeks 12, 26, and 30.

Measures to evaluate calcium metabolism included albumin-adjusted calcium, intact PTH, alkaline phosphatase, phosphorus, Baseline Serum 25-OH vitamin D concentrations and urinary calcium/creatinine ratios.

7.3.4. Safety Results - Trial RD.06.SRE.18131

Deaths, Serious Adverse Events (SAEs), and Discontinuations Due to AEs
There were no deaths, no SAEs or AEs that led to discontinuation during this trial.

Adverse Events of Special Interest
One subject experienced 2 events of the same adverse events of special interest, skin irritation, on the treated area.

Subject [redacted]; cutaneous AE, skin irritation
Subject [redacted] was a 16-year-old, white, non-Hispanic, non-Latino male. On [redacted] (Study Day 50), the subject experienced moderate skin irritation on the treated area (reported term: irritation skin after drug application). On [redacted] (Study Day 51), he again experienced moderate skin irritation on the treated area (reported term: irritation skin after drug application). Each event lasted 1 day and resolved.

Administration of the study drug was temporarily interrupted on the day of each of the events. The Investigator considered the events to be related to study drug.

Adverse Events
Of the 54 subjects who received calcitriol, 20 subjects (37.0%) reported 49 TEAEs. Of these, 4 subjects had 5 AEs related to the study drug, and 1 subject had an AE related to the study procedure, all of which were experienced in the first 90 days of treatment. All AEs were mild or moderate in severity. No TEAEs were experienced during the follow-up period.

No subjects experienced TEAEs possibly related to calcium metabolism or TEAEs that led to discontinuation from the study. All AEs were mild or moderate in severity. No AEs were assessed as severe.

At least 1 AE was reported by 20 of 54 (37.0%) subjects; 15 subjects experienced AEs that started during the treatment period from Day 1 to 90, and 10 subjects experienced AEs that started during the treatment period from Day 91 to the end of treatment. Overall, AEs were most often reported in the Infections and infestations system organ class (SOC) (12 subjects; 22.2%), followed by the skin and subcutaneous tissue disorders SOC (7 subjects; 13.0%). AEs reported by more than one subject included; nasopharyngitis (6 subjects), skin burning sensation (3 subjects), upper abdominal pain, vitamin D deficiency, skin papilloma, and nasal congestion (2 subjects each). All other AEs were reported by no more than 1 subject each in either study period.

Table 16: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

			By period [1]			
	N=54		Day 1 – 90 N=15		Day 91 - EOT N=10	
System Organ Class Preferred term	**Event n**	**Subjects N (%)**	**Event n**	**Subjects N (%)**	**Event n**	**Subjects N (%)**
Total AEs	49	20 (37.0)	30	15 (100.0)	19	10 (100.0)
Gastrointestinal disorders	5	4 (7.4)	3	3 (20.0)	2	1 (10.0)
Abdominal pain upper	3	2 (3.7)	1	1 (6.7)	2	1 (10.0)
Abdominal pain	1	1 (1.9)	1	1 (6.7)	0	0
Gastroesophageal reflux disease	1	1 (1.9)	1	1 (6.7)	0	0

	N=54		By period [1] Day 1 – 90 N=15		Day 91 - EOT N=10	
System Organ Class Preferred term	**Event n**	**Subjects N (%)**	**Event n**	**Subjects N (%)**	**Event n**	**Subjects N (%)**
General disorders and administration site conditions	1	1 (1.9)	1	1 (6.7)	0	0
Pyrexia	1	1 (1.9)	1	1 (6.7)	0	0
Immune system disorders	2	2 (3.7)	0	0	2	2 (20.0)
House dust allergy	1	1 (1.9)	0	0	1	1 (10.0)
Seasonal allergy	1	1 (1.9)	0	0	1	1 (10.0)
Infections and Infestations	16	12 (22.2)	10	8 (53.3)	6	4 (40.0)
Nasopharyngitis	7	6 (11.1)	5	4 (26.7)	2	2 (20.0)
Impetigo	1	1 (1.9)	1	1 (6.7)	0	0
Lice infestation	1	1 (1.9)	0	0	1	1 (10.0)
Oral herpes	1	1 (1.9)	1	1 (6.7)	0	0
Otitis media acute	1	1 (1.9)	0	0	1	1 (10.0)
Pneumonia	1	1 (1.9)	0	0	1	1 (10.0)
Tinea pedis	1	1 (1.9)	1	1 (6.7)	0	0
Upper resp. tract infection	1	1 (1.9)	0	0	1	1 (10.0)
Viral rash	1	1 (1.9)	1	1 (6.7)	0	0
Viral upper resp tract infection	1	1 (1.9)	1	1 (6.7)	0	0
Injury, poisoning and procedural complications	1	1 (1.9)	1	1 (6.7)	0	0
Muscle strain	1	1 (1.9)	1	1 (6.7)	0	0
Investigations	2	2 (3.7)	1	1 (6.7)	1	1 (10.0)
Heart rate irregular	1	1 (1.9)	1	1 (6.7)	0	0
Vit D decreased	1	1 (1.9)	0	0	1	1 (10.0)
Metabolism and nutrition disorders	2	2 (3.7)	2	2 (13.3)	0	0
Vit D deficiency	2	2 (3.7)	2	2 (13.3)	0	0
Musculoskeletal and connective tissue disorders	1	1 (1.9)	0	0	1	1 (10.0)
Myalgia	1	1 (1.9)	0	0	1	1 (10.0)
Neoplasms benign, malignant & unspecified (incl cysts and polyps)	2	2 (3.7)	1	1 (6.7)	1	1 (10.0)
Skin papilloma	2	2 (3.7)	1	1 (6.7)	1	1 (10.0)
Nervous system disorders	2	1 (1.9)	1	1 (6.7)	1	1 (10.0)
Headache	2	1 (1.9)	1	1 (6,7)	1	1 (10.0)
Renal and urinary disorders	1	1 (1.9)	0	0	1	1 (10.0)
Dysuria	1	1 (1.9)	0	0	1	1 (10.0)
Respiratory, thoracic, & mediastinal disorders	5	3 (5.6)	2	1 (6.7)	3	2 (20.0)
Nasal congestion	3	2 (3.7)	0	0	3	2 (20.0)
Sinus congestion	2	1 (1.9)	2	1 (6.7)	0	0

System Organ Class Preferred term	N=54 Event n	N=54 Subjects N (%)	By period (1) Day 1 – 90 N=15 Event n	Day 1 – 90 N=15 Subjects N (%)	Day 91 - EOT N=10 Event n	Day 91 - EOT N=10 Subjects N (%)
Skin and subcutaneous tissue disorders	9	7 (13.0)	8	6 (40.0)	1	1 (10.0)
Skin burning sensation	3	3 (5.6)	3	3 (20.0)	0	0
Erythema	3	3 (5.6)	3	3 (20.0)	0	0
Pityriasis alba	1	1 (1.9)	0	0	1	1 (10.0)
Rash	1	1 (1.9)	2	1 (6.7)	0	0
Skin irritation	2	1 (1.9)	2	1 (6.7)	0	0

Abbreviations: EOT = end of treatment; AE = adverse event
[1] Include subjects with any AE started during each period. The percentage of subjects was calculated based on the number of subjects (N*) with any AE started during the period.
- A subject was counted only once for multiple occurrences within a System Organ Class or Preferred Term.
- MedDRA version 15.0.
Source: Modified from Table 4.3.2.3: Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, Section 14.3, p 24.

Subgroup summaries of TEAEs were performed based on gender, race (white and non-white), and age group (2 to 5 years, 6 to 12 years, and 13 to 17 years). In general, the percentage of subjects who reported at least 1 TEAE was similar for all subgroups. When overviews of TEAEs were compared within each subgroup, the proportion of females who experienced TEAEs was slightly higher than males and the proportion of non-whites who experienced TEAEs was slightly higher than whites. There were a total of 8 subjects in age group 2 to 5, 8 of which experienced events (100%), 27 subjects in age group 6 to 12, 13 of which experienced events (48%), and 19 subjects in age group 13 to 17, 18 of which experienced events (95%). The proportion of subjects aged 6 to 12 years who experienced TEAEs was lower than those in the 13 to 17-year age group. It should be noted that the majority of subjects in the study were white (85%).

Table 17: TEAES by SOC, PT and Age Group (2 to 5 years)

System Organ Class Preferred Term	CD2027 (N = 8) Event n	CD2027 (N = 8) Subject N(%)	By Period[1] Day 1 – Day 90 (N* = 3) Event n	Day 1 – Day 90 (N* = 3) Subject N(%)	Day 91 – EOT (N* = 3) Event n	Day 91 – EOT (N* = 3) Subject N(%)	Follow-up (N* = 0) Event n	Follow-up (N* = 0) Subject N(%)
General disorders and administration site conditions	1	1 (12.5)	1	1 (33.3)	0	0	0	0
Pyrexia	1	1 (12.5)	1	1 (33.3)	0	0	0	0
Immune system disorders	1	1 (12.5)	0	0	1	1 (33.3)	0	0
Seasonal allergy	1	1 (12.5)	0	0	1	1 (33.3)	0	0
Infections and infestations	5	3 (37.5)	1	1 (33.3)	4	2 (66.7)	0	0
Nasopharyngitis	1	1 (12.5)	0	0	1	1 (33.3)	0	0
Otitis media acute	1	1 (12.5)	0	0	1	1 (33.3)	0	0
Pneumonia	1	1 (12.5)	0	0	1	1 (33.3)	0	0
Upper respiratory tract infection	1	1 (12.5)	0	0	1	1 (33.3)	0	0
Viral rash	1	1 (12.5)	1	1 (33.3)	0	0	0	0
Investigations	1	1 (12.5)	0	0	1	1 (33.3)	0	0
Vitamin D decreased	1	1 (12.5)	0	0	1	1 (33.3)	0	0

Renal and urinary disorders	1	1 (12.5)	0	0	1	1 (33.3)	0	0
Dysuria	1	1 (12.5)	0	0	1	1 (33.3)	0	0
Skin and subcutaneous tissue disorders	2	2 (25.0)	2	2 (66.7)	0	0	0	0
Skin burning sensation	2	2 (25.0)	2	2 (66.7)	0	0	0	0

Source: Listing 16.2.7.1
- [1] Include subjects with any AE started during each period. The percentage of subjects was calculated based on the number of subjects (N*) with any AE started during the period.
- A subject was counted only once for multiple occurrences within a System Organ Class or Preferred Term.
- MedDRA version 15.0.

Table 18: TEAEs by SOC, PT and Age Group (6 to 12 years)

	By Period[1]							
	CD2027 (N = 27)		Day 1 – Day 90 (N* = 4)		Day 91 – EOT (N* = 4)		Follow-up (N* = 0)	
System Organ Class Preferred Term	Event n	Subject N(%)	Event n	Subject N(%)	Event n	Subject N(%)	Event n	Subject N(%)
Gastrointestinal disorders	3	2 (7.4)	1	1 (25.0)	2	1 (25.0)	0	0
Abdominal pain	1	1 (3.7)	1	1 (25.0)	0	0	0	0
Abdominal pain upper	2	1 (3.7)	0	0	2	1 (25.0)	0	0
Immune system disorders	1	1 (3.7)	0	0	1	1 (25.0)	0	0
House dust allergy	1	1 (3.7)	0	0	1	1 (25.0)	0	0
Infections and infestations	6	5 (18.5)	4	3 (75.0)	2	2 (50.0)	0	0
Nasopharyngitis	3	3 (11.1)	2	2 (50.0)	1	1 (25.0)	0	0
Lice infestation	1	1 (3.7)	0	0	1	1 (25.0)	0	0
Oral herpes	1	1 (3.7)	1	1 (25.0)	0	0	0	0
Viral upper respiratory tract infection	1	1 (3.7)	1	1 (25.0)	0	0	0	0
Metabolism and nutrition disorders	1	1 (3.7)	1	1 (25.0)	0	0	0	0
Vitamin D deficiency	1	1 (3.7)	1	1 (25.0)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (3.7)	0	0	1	1 (25.0)	0	0
Skin papilloma	1	1 (3.7)	0	0	1	1 (25.0)	0	0
Nervous system disorders	2	1 (3.7)	1	1 (25.0)	1	1 (25.0)	0	0
Headache	2	1 (3.7)	1	1 (25.0)	1	1 (25.0)	0	0
Respiratory, thoracic and mediastinal disorders	2	1 (3.7)	0	0	2	1 (25.0)	0	0
Nasal congestion	2	1 (3.7)	0	0	2	1 (25.0)	0	0
Skin and subcutaneous tissue disorders	1	1 (3.7)	1	1 (25.0)	0	0	0	0
Skin burning sensation	1	1 (3.7)	1	1 (25.0)	0	0	0	0

Source: Listing 16.2.7.1
- [1] Include subjects with any AE started during each period. The percentage of subjects was calculated based on the number of subjects (N*) with any AE started during the period.
- A subject was counted only once for multiple occurrences within a System Organ Class or Preferred Term.
- MedDRA version 15.0.

Table 19: TEAEs by SOC, PT and Age Group (13 to 17 years)

	By Period[1]							
	CD2027 (N = 19)		Day 1 – Day 90 (N* = 8)		Day 91 – EOT (N* = 3)		Follow-up (N* = 0)	
System Organ Class Preferred Term	Event n	Subject N(%)	Event n	Subject N(%)	Event n	Subject N(%)	Event n	Subject N(%)
Gastrointestinal disorders	2	2 (10.5)	2	2 (25.0)	0	0	0	0
Abdominal pain upper	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Gastrooesophageal reflux disease	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Infections and infestations	5	4 (21.1)	5	4 (50.0)	0	0	0	0
Nasopharyngitis	3	2 (10.5)	3	2 (25.0)	0	0	0	0
Impetigo	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Tinea pedis	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Injury, poisoning and procedural complications	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Muscle strain	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Investigations	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Heart rate irregular	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Metabolism and nutrition disorders	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Vitamin D deficiency	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Musculoskeletal and connective tissue disorders	1	1 (5.3)	0	0	1	1 (33.3)	0	0
Myalgia	1	1 (5.3)	0	0	1	1 (33.3)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Skin papilloma	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	3	2 (10.5)	2	1 (12.5)	1	1 (33.3)	0	0
Nasal congestion	1	1 (5.3)	0	0	1	1 (33.3)	0	0
Sinus congestion	2	1 (5.3)	2	1 (12.5)	0	0	0	0
Skin and subcutaneous tissue disorders	6	4 (21.1)	5	3 (37.5)	1	1 (33.3)	0	0
Erythema	1	1 (5.3)	1	1 (12.5)	0	0	0	0
Pityriasis alba	1	1 (5.3)	0	0	1	1 (33.3)	0	0
Rash	2	1 (5.3)	2	1 (12.5)	0	0	0	0
Skin irritation	2	1 (5.3)	2	1 (12.5)	0	0	0	0

Source: Listing 16.2.7.1
- [1] Include subjects with any AE started during each period. The percentage of subjects was calculated based on the number of subjects (N*) with any AE started during the period.
- A subject was counted only once for multiple occurrences within a System Organ Class or Preferred Term.
- MedDRA version 15.0.

Source: Table 4.3.2.4c: Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, Section 14.3, p 39.

Adverse Reactions

The Investigator was to determine whether or not there was a reasonable causal relationship between the study drug and the AE, categorized as either “reasonable possibility” or “no reasonable possibility.” Four subjects experienced 5 AEs that were considered to be related to the study drug, all of which were in the skin and subcutaneous tissue disorders SOC. All related AEs were experienced during the first 90 days of treatment (Day 1 to 90), during which 3 subjects reported skin burning sensation. One subject reported 2 events of skin irritation, which were considered adverse events of special interest.

Table 20: Drug-Related TEAEs (Adverse Reactions)

System Organ Class Preferred Term	By Period[1] CD2027 (N = 54) Event n	 Subject N(%)	Day 1 – Day 90 (N* = 15) Event n	 Subject N(%)	Day 91 – EOT (N* = 10) Event n	 Subject N(%)	Follow-up (N* = 0) Event n	 Subject N(%)
Skin and subcutaneous tissue disorders	5	4 (7.4)	5	4 (26.7)	0	0	0	0
Skin burning sensation	3	3 (5.6)	3	3 (20.0)	0	0	0	0
Skin irritation	2	1 (1.9)	2	1 (6.7)	0	0	0	0

Source: Listing 16.2.7.1
- [1] Include subjects with any AE started during each period. The percentage of subjects was calculated based on the number of subjects (N*) with any AE started during the period.
- A subject was counted only once for multiple occurrences within a System Organ Class or Preferred Term.
- MedDRA version 15.0.

Source: Table 4.3.2.8: Abbreviated Clinical Study Report, RD.06.SRE.18131 – Version March 19, 2019, Section 14.3, p. 52

•Canada [(b) (6)]: Skin burning sensation: 4 y/o male; burning sensation immediately after application for 15 minutes, moderate, no treatment given, no action taken, resolved ([(b) (6)] to same, study day 21)

•Canada/ [(b) (6)]: skin burning sensation: 4 y/o female; burning sensation after application, mild, no treatment given, no action taken, resolved ([(b) (6)] to [(b) (6)], 2 days, study days 4 & 5)

•Canada/ [(b) (6)]: skin burning sensation: 10 y/o female; burning sensation for 10 minutes after application, mild, no treatment given, no action taken, resolved ([(b) (6)] to [(b) (6)], 5 days)

•Germany/ [(b) (6)]: skin irritation: 16 y/o male; irritation of skin after drug application, moderate, no treatment given, drug interrupted, resolved ([(b) (6)] to same, 1 day) Same subject: skin irritation: 16 y/o male; irritation of skin after drug application, moderate, no treatment given, drug interrupted, resolved [(b) (6)] to same, 1 day)

Adverse events related to study procedure
One subject had a TEAE (skin burning sensation) reported that was considered related to the study procedure. Canada / [(b) (6)]: skin burning sensation: 10 y/o female; burning sensation for 10 minutes after application, mild, no treatment given, no action taken, resolved [(b) (6)] to [(b) (6)] 5 days). This event was also considered related to study drug.

Laboratory Findings
Routine laboratory findings
Small changes in hematology, blood chemistry, and urinalysis values from Screening were observed at all timepoints during treatment, none of which were reported as clinically significant abnormalities.

Pharmacodynamic assessments
Safety assessments included pharmacodynamic serum and urine assessments to assess the effect of calcitriol 3 μg/g ointment on calcium homeostasis. Analytes from collected serum and urine were evaluated to assess for any impact of calcitriol treatment on calcium metabolism. Serum (nonfasting) calcium, albumin, phosphorus, and PTH were measured. Urine calcium and creatinine were measured in order to calculate urine calcium/creatinine ratio. No major changes in PD parameters were observed.

Vital Signs
Vital signs (systolic and diastolic blood pressure, pulse rate) and weight were evaluated at Screening and all timepoints in the study. The observed changes from baseline in vital signs and weight were not considered to be clinically significant.

Electrocardiograms (ECGs) and QT
The Applicant did not conduct electrocardiogram monitoring during trial RD.06.SRE.18131. Refer to the Clinical Review of the original application (dated September 29, 2008) for a discussion of the cardiac safety of Vectical(calcitriol) Ointment 3 mcg/g. In the original application, the Division granted the request for a waiver from conducting a thorough QT/QTc study based on low exposure and a lack of a safety signal for the moiety.

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

Pregnancies
No pregnancies occurred during this trial

7.3.5. Analysis of Submission-Specific Safety Issues (Trial RD.06.SRE.1813)

Effects on Calcium Metabolism
Safety assessments included pharmacodynamic serum and urine assessments to determine the effect of calcitriol 3 μg/g ointment on calcium homeostasis. Analytes from collected serum and urine were evaluated to assess for the impact of calcitriol treatment on calcium metabolism. Serum (nonfasting) calcium, albumin, phosphorus, and intact PTH were measured. Urine calcium and creatinine were measured in order to calculate urine calcium/creatinine ratio. No major changes in PD parameters were observed.

25-hydroxy Vitamin D

Mean values for 1,25(OH)2D and 25(OH)D decreased from Screening through Week 12 and Week 26 (Final). These changes were not large in comparison with variability noted in measurements.

Most subjects had normal 1,25(OH)2D and 25(OH)D values at Screening that remained normal at the Week 26 (Final) assessment. Most values that were outside the normal range at Screening (low or high) remained that way at Week 26 (Final), while some shifted from low or high at Screening to normal. 1,25(OH)2D values that were normal at Screening shifted to high at Week 26 (Final) for 6 subjects, while 25(OH)D values that were normal at Screening shifted to low at Week 26 (Final) for 10 subjects.

None of the out-of-normal-range values noted above were considered to be clinically significant, with the exception of Subject (b) (6) (6-year-old male with 7% BSA at Baseline):

Table 21:

25-Hydroxyvitamin D (nmol/L)	Screening	(b) (6)	T10:40	-17	Screening	Y	85	76 - 99999				
	Week 12		T10:40	96	Week 12		85	76 - 99999				
	Week 26		T13:25	180	Week 26		67	76 - 99999	Low			
					Week 26 (Final)		67	76 - 99999	Low			
	Week 30 / Follow-up		T10:50	204	Week 30 Follow-up		60	76 - 99999	Low	Y		
Germany/ (b) (6) (b) (6)	6/M	24-Hour Calcium (mmol/day)	Screening	(b) (6)	T15:00	-16	Screening	Y	0.47	2.5 - 8.03	Low	
			Week 12		T11:11	96	Week 12		1.33	2.5 - 8.03	Low	
			Week 26		T13:45	180	Week 26		2.55	2.5 - 8.03		
							Week 26 (Final)		2.55	2.5 - 8.03		

The 25(OH)D values were flagged as low at Week 26, Week 26 (Final), and Week 30/follow-up. The Week 30 follow-up value (60 nmol/L) was considered to be clinically significant. For this subject 1,25-Dihydroxyvitamin D values were within normal limits; Screening, Week 12, Week 26 and Week 30. This subject did not have any clinical chemistry values outside of reference range. This subject also had no pharmacodynamic serum values outside of reference range (calcium corrected, albumin, intact PTH, phosphate – includes Week 30). This subject did have a low 24-hour urine calcium at Screening and at Week 12, but within normal limits at Weeks 26 and 30.
The 24 hour calcium/creatinine was also normal for this subject including Week 30.

Examination of the laboratory values for this subject, (b) (6), overall, indicates that the low 25(OH)D value at Week 30 was not a sign of a clinically significant disorder of calcium metabolism.

An IDMC was established to monitor this trial on an ongoing basis. The Applicant reports that the IDMC did not find any significant safety signals during the trial.

7.3.6. Safety Analyses by Demographic Subgroups (Trial RD.06.SRE.1813)

In view of the small sample size, the analysis of TEAEs by demographic subgroup has limited utility. There were insufficient numbers of subjects receiving Vectical (calcitriol) Ointment 3 mcg/g of non-white races to provide a meaningful comparison (African American 1/54, Asian 4/54, Other 3/54). The majority of subjects in the study were white 46/54 (85%).

Subgroup summaries of TEAEs were based on gender, race (only white versus non-white), and age group (2 to 5 years, 6 to 12 years, and 13 to 17 years). In general, the percentage of subjects who reported at least 1 TEAE was similar for all subgroups. When overviews of TEAEs were compared within each subgroup, the proportion of females (10/24 or 42%) who experienced TEAEs was slightly higher than males (10/30 or 33%) and the proportion of non-whites who experienced TEAEs (4/8 or 50%) was slightly higher than whites (16/46 or 35%). By age group; for 2 to 5 there were 8 subjects total and 8 experiencing events (100%), for 6 to 12 there were 27 subjects and 13 experiencing events (48%), and for 13 to 17 there were 19 subjects and 18 experiencing events (95%). The proportion of subjects age 6 to 12 years who experienced TEAEs was lower than those in the 13 to 17-year age group.

7.3.7. Supportive Safety Data From Other Clinical Trials

For evaluation of this submission and its impact on labeling safety, data from clinical trial RD.06.SRE.18102 (PMC 973-1), abbreviated clinical trials RD.06.SRE.18104 (PMR 973-2), RD.06.SPR.18132 (PMR 973-3), and RD.06.SPR.18131 [PMR 973-5 (combination of PMRs 973-2, 973-3, and 973-4) were examined.

Table 22: Summary of Subject Disposition - All Trials

	Subjects			
Trial/PMR	**2 to 6 years**	**2 to 12 years**	**13 to 17 years**	**Total**
RD.06.SRE.18102/973-1				
Subjects enrolled	0	2	23	25
Safety population		2	23	25
Subjects who completed trial		2	23	25
RD.06.SRE.18104/973-2				
Subjects enrolled	5	18	0	23
Safety population	5	18	0	23
Subjects who completed trial	5	17[a]	0	22

	Subjects				
Trial/PMR	**2 to 6 years**	**2 to 12 years**		**13 to 17 years**	**Total**
RD.06.SPR.18132/973-3	calcitriol	calcitriol	vehicle		
Subjects enrolled		8	11		19
Safety population	1	8	11		8 (calcitriol)
Subjects who completed trial		8	10[b]		18
RD.06.SPR.18131/973-5					
Subjects enrolled	11	35		19	54
Safety population	11	35		19	54
Subjects who completed trial	7[c]	25[d]		16[e]	41
Safety Population: total	17	63*		42*	105 = (2-12 & 13-17) *

[a] One subject (b) (6); age 11 years; female) was discontinued from the trial because the Vitamin D dose taken was higher than the protocol-allowed 400 IU/day.
[b] One subject in the vehicle group discontinued at the subject's request
[c] Two subjects in this group discontinued due to lost to follow-up, one due to protocol violation and one due to subject request
[d] Four subjects in this group due to subject request, four discontinued due to lost to follow-up, one due to lack of efficacy and one due to protocol violation.
[e] Two subjects in this group discontinued due to subject request and one due to lack of efficacy.
Source: Reviewer's table compiled from Module 2.5 NDA 022087/S009 Clinical Overview, Table 2, p.17 and the study report for trial RD.06.SRE.18102 and abbreviated study reports for clinical trials RD.06.SRE.18104, RD.06.SPR.18132, and RD.06.SPR.18131.

[For PMR 973-5: Of the 54 subjects who received calcitriol, 20 subjects (37.0%) reported 49 TEAEs. Of these, 4 subjects had 5 AEs that were related to the study drug, and 1 subject had an AE related to the study procedure. Adverse reactions were skin burning sensation (4 subjects) and skin irritation (1 subject). All AEs were mild or moderate in severity and are labeled. No subjects experienced TEAEs that were possibly related to calcium metabolism or TEAEs that led to discontinuation from the study.]

For (PMR 973-1): an open-label 8-week safety and PK trial conducted in 25 subjects 12 to 17 years of age. This PMR was reviewed, clinical review into DARRTS March 30, 2011. Clinically significant signals were not seen in this study with regard to AEs, local tolerability, or laboratory assessments (including pharmacodynamic parameters). Adverse events reported for the trial for PMR 973-1 included, skin burning sensation (1 subject) and application site erythema (1 subject)

For (PMR 973-2): an open-label 14-day safety and Maximal use PK trial in 18 subjects 2 to 12 years of age; Adverse events reported for trial for PMR 973-2 included pruritus (1 subject), skin burning sensation (1 subject), peeling of skin/desquamation of trunk versus dry skin (1 subject) and pain of skin (1 subject).

For (PMR 973-3): a vehicle-controlled 8-week trial in 19 subjects 2 to 12 years of age with mild to moderate plaque psoriasis. Adverse events reported in those exposed to Vectical Ointment included skin irritation in 2 subjects.

Analysis of Supplement-Specific Safety Issues (All 4 PMRs/Trials)
Vitamin D (7-dehydrocholesterol) is a fat-soluble vitamin that promotes calcium absorption in the gut and enables bone growth and remodeling (Holick 2007). Calcitriol (1α,25-dihydroxyvitamin D3), also the active ingredient in Vectical Ointment, is endogenously

produced and is the active hormone form of vitamin D3. In humans, calcium and phosphorous levels in plasma are regulated by the vitamin D3/PTH/calcitonin system. The plasma half-life of calcitriol in humans is estimated to be between 3 and 5 days. Treatment with calcitriol (Vectical Ointment) is associated with local cutaneous reactions and the potential for hypercalcemia. These potential reactions are included in current product labeling (revised 1/2009).

Effects on Calcium Metabolism

The primary pharmacodynamic analyses to evaluate the effects of Vectical Ointment on calcium metabolism included:

- Calcium, corrected
- Intact parathyroid hormone
- Urinary calcium/creatinine ratio
- Phosphorous

It is noted that hypercalciuria is one the most sensitive indicators of over treatment with calcium and vitamin D (Pearle et al. 2014). Serum phosphorous and urinary phosphorus may also be elevated. Serum PTH (intact) would be at risk for being decreased. Serum alkaline phosphatase is discussed as a value that sometimes can be a signal for changes in calcium homeostasis. A fall in alkaline phosphatase can precede hypercalcemia.

> For trials RD.06.SRE.18102(PMR 973-1), RD.06.SRE.18104(PMR 973-2), RD.06.SRE.18132(PMR 973-3), and RD.06.SRE.18131(PMR- 973-5) all of the above were evaluated and no significant safety signals were noted.

Additional supportive information from FAERS and medical literature

Jessica Weintraub, PharmD, BCPS, conducted a review of FDA Adverse Event Reporting System and the medical literature for reports of hypercalcemia or hypercalciuria in association with vitamin D analogs (calcipotriene, calcipotriol and calcitriol) from January 2006 to August 7, 2019.

Dr. Weintraub identified 22 cases of hypercalcemia and no cases of hypercalciuria with the use of topical calcipotriene or topical calcitriol. One case involved an infant exposed through secondary transfer from an adult. These cases were primarily from foreign sources and reported in an older adult population. Of the 11 cases reporting use for the indication of plaque psoriasis, psoriasis vulgaris, or unspecified psoriasis, seven cases reported other potential factors that may have contributed to the risk of hypercalcemia. Of the remaining four cases, one reported use of 250 g calcipotriene in 4 days (exceeding the standard dosing recommendations) and the remaining three cases provided limited information for case assessment, including no information on the amount of calcipotriene or calcitriol used or the area of application. See Review by Jessica Weintraub, PharmD, BCPS dated August 7, 2019.

7.3.8. Safety in the Postmarket Setting

Expectations on Safety in the Postmarket Setting

The analysis of the safety data from the clinical trial RD.06.SRE.18102 (PMR 973-1) and from the abbreviated clinical trials RD.06.SRE.18104 (PMR 973-2), RD.06.SPR.18132 (PMR 973-3), and RD.06.SPR.18131 [PMR 973-5 (combination of PMRs 973-2, 973-3, and 973-4)] identified no additional safety signals in the population ages 2 to 17 years.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

Although trial RD.06.18132 was designed to include evaluation of efficacy, study enrollment did not achieve the planned 300 subjects. The small number of subjects enrolled (Intent-To-Treat population: 8 on calcitriol and 11 on vehicle) made meaningful interpretation of efficacy data difficult.

7.4.2. Conclusions and Recommendations

In the current submission (SD #362 September 17, 2019), the Applicant has submitted an efficacy supplement for Vectical(calcitriol) Ointment, that includes a request for release from pediatric postmarketing requirements. The Applicant states that the supplement includes all data collected which is presented for evaluation. Data are also included regarding the PLLR addition to the product insert.

The current submission includes an abbreviated clinical study report for trial RD.06.SRE.18131., intended to fulfill PMR 973-5 (a combination of PMRs 973-2, 973-3, and 973-4). Also included in this submission is the abbreviated clinical study report for trial RD.06.SRE.18104, intended to fulfill original PMR 973-3. In response to Agency information requests, the Applicant provided (SD #365 February 27, 2020) the Clinical Study Report for Trial RD.06.18102 used to fulfill PMR 973-1). The abbreviated clinical study report for trial RD.06.SRE.18132 intended to fulfill original PMR 973-3 was submitted to IND 062151 (SD #95) December 21, 2016.

•For PMR 973-5: An open-label 26-week safety and PK trial in 54 subjects 2 to 17 years of age. Of the 54 subjects who received calcitriol, 20 subjects (37.0%) reported 49 TEAEs. Of these, 4 subjects had 5 AEs that were related to the study drug, and 1 subject had an AE related to the study procedure. Adverse reactions were skin burning sensation (4 subjects) and skin irritation (1 subject). All AEs were mild or moderate in severity and are labeled. No subjects experienced TEAEs that were possibly related to calcium metabolism or TEAEs that led to discontinuation from the study.

Safety information was also obtained from the trials conducted to fulfill PMRs 973-1, 973-2, 973-3. (PMR 974-4 was rolled into PMR 973-5). These included the following:

- For (PMR 973-1): an open-label 8-week safety and PK trial conducted in 25 subjects 12 to 17 years of age. Adverse reactions noted included skin burning sensation (1 subject), application site erythema (1 subject).
- For (PMR 973-2): an open-label 14-day safety and PK trial in 18 subjects 2 to 12 years of age. Adverse reactions noted included pruritus (1 subject), skin burning sensation (1 subject) skin exfoliation [peeling of skin/desquamation of trunk versus dry skin (1 subject)], pain of skin (1 subject).
- For (PMR 973-3): a well-controlled 8-week trial in 19 subjects 2 to 12 years of age with mild to moderate plaque psoriasis; Adverse reactions noted included skin irritation 2 subjects.

Adverse Reactions: these are considered labeled adverse reactions.

For PMR 973-1, 973-2, 973-3, and 973-5: Among subjects exposed to Vectical Ointment– there were no deaths, serious adverse events, or discontinuations due to AEs. There were no TEAEs that were possibly related to calcium metabolism.

Overall
Data from 63 subjects aged 2 to 12 years, and 42 subjects aged 13 to 17 years showed no significant effects on indices of calcium metabolism. The systemic exposure of calcitriol in the pediatric subjects was generally comparable to the endogenous levels observed at baseline. No new safety signals were identified in subjects 2 to 17 years.

Efficacy
Efficacy findings from Trial for PMR 973-3 were inconclusive due to small sample size. We are extrapolating efficacy from adults.

Although the data were limited, the size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions. The submitted PK, PD and safety data support approval of this sNDA which provides for the use of Vectical(calcitriol) Ointment for the topical treatment of mild to moderate plaque psoriasis in adult and pediatric patients 2 years and older.

8. Advisory Committee Meeting and Other External Consultations

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

9. Pediatrics

Under the (PREA (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product triggered PREA as a new indication.

The Applicant conducted clinical trial RD.06.SRE.18102 (PMR 973-1), abbreviated clinical trials RD.06.SRE.18104 (PMR 973-2), RD.06.SPR.18132 (PMR 973-3), and RD.06.SPR.18131 [PMR 973-5 (combination of PMRs 973-2, 973-3, and 973-4) to address the required assessment under PREA and support the use of Vectical(calcitriol) Ointment in the target pediatric population with mild to moderate plaque psoriasis.

On March 10, 2020, the pediatric assessment for Vectical(calcitriol) Ointment was presented to the PeRC.

The Division stated they have enough safety and maximal use data to support labeling down to 2 years of age. The PeRC agreed that the PREA PMRs can be considered fulfilled down to 2 years of age as long as the product is labeled down to age 2 years.

For the pediatric population age 2 to 17 years, efficacy is being extrapolated from adequate and well controlled trials in adults. This is reasonable in view of similar pathophysiology and expected response to treatment.

For pediatric subjects aged 12 to 17 years with psoriasis, the Applicant performed a maximal use PK trial (trial 18102) in 25 subjects and the results of this trial fulfilled PMR #1. See Clinical Pharmacology Review by Dr. Abimbola Adebowale (dated March 3, 2011).

According to the clinical Pharmacology reviewer, although the Applicant did not meet the requirement of assessing PK in 9 subjects under PMR #5; the lack of any systemic safety signals and furthermore lack of any increase in systemic concentrations of calcitriol from baseline in pediatric subjects aged 2 years to 12 years under maximal use conditions suggests that the currently available PK data in 18 subjects (17 subjects from PMR #2 and 1 subject from PMR #5) aged 2 years to 12 years is considered adequate to release the Applicant from PMR #2 and PMR #5.

The safety database for all 4 trials conducted [RD.06.SRE.18102 (PMR 973-1), abbreviated clinical trials RD.06.SRE.18104 (PMR 973-2), RD.06.SPR.18132 (PMR 973-3), and RD.06.SPR.18131 [PMR 973-5 (combination of PMRs 973-2, 973-3, and 973-4)]] includes 63 subjects age 2 to 12 years and 42 subjects age 13 to 17 years. Those exposed to Vectical

(calcitriol) Ointment for 26 weeks included; 11 subjects age 2 to 6 years, 35 subjects age 2 to 12 years, and 19 subjects age 13 to 17 years. In general, the percentage of subjects who reported at least 1 TEAE was similar for the age subgroups. It is the Division's considered opinion that enough patients were studied to support safety in all the populations, and that there are no gaps in safety that would require another postmarketing study to address such as a FDAAA PMR.

A description of trials conducted, and relevant safety findings will be included in Sections 8.4 Pediatric Use and 12 Clinical Pharmacology of labeling to convey to the prescriber that the safety and effectiveness of Vectical(calcitriol) Ointment have been established in pediatric patients 4 to 17 years.

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

10. Labeling Recommendations

10.1. Prescribing Information

Clinical Labeling Summary
Indication
VECTICAL Ointment is a vitamin D analog indicated for the topical treatment of mild to moderate plaque psoriasis in adult and pediatric patients 2 years and older.

Dosage and Administration
Apply VECTICAL Ointment to affected areas twice daily, morning and evening.
Adults:

- The maximum weekly dose should not exceed 200 grams.

Pediatrics

- 2 to 6 years of age: the maximum weekly dose should not exceed 100 grams.
- 7 years of age and older: the maximum weekly dose should not exceed 200 grams.

Warnings and Precautions
5.1 Effects on Calcium Metabolism
In controlled clinical trials hypercalcemia was observed in subjects exposed to VECTICAL Ointment. If aberrations in parameters of calcium metabolism occur, treatment should be discontinued until these parameters have normalized. The effects of VECTICAL Ointment on calcium metabolism following treatment durations greater than 52 weeks have not been evaluated. Increased absorption may occur with occlusive use.

8.4 Pediatric Use

The safety and effectiveness of VECTICAL Ointment have been established in pediatric patients age 2 years and older for topical treatment of mild to moderate psoriasis. Use of VECTICAL Ointment in this age group is supported by two adequate and well-controlled 8-week trials and an open-label trial in adult subjects, and additional data from trials conducted in pediatric subjects from 2 to 17 years of age including:

- a vehicle-controlled 8-week trial in 19 subjects 2 to 12 years of age with mild to moderate plaque psoriasis
- an open-label 8-week safety and PK trial in 25 subjects 12 to 17 years of age
- an open-label 14-day safety and PK trial in 18 subjects 2 to 12 years of age, and
- an open-label 26-week safety and PK trial in 54 subjects 2 to 17 years of age.

Data from 63 subjects ages 2 to 12 years, and 42 subjects ages 13 to 17 years showed no significant effects on indices of calcium metabolism. The systemic exposure of calcitriol in the pediatric subjects was generally comparable to the endogenous levels observed at baseline. No new safety signals were identified in subjects 2 to 17 years *[see Clinical Studies (14), Clinical Pharmacology (12.3) and Adverse Reactions (6.1)].*

The safety and effectiveness of VECTICAL in pediatric subjects below the age of 2 years have not been established.

17 Patient Counseling Information

(b) (4)

Patients using VECTICAL Ointment should receive the following information:

- This medication is to be used as directed by the physician. It is for external use only. This medication is to be applied only to areas of the skin affected by psoriasis, as directed.
- It should be gently rubbed into the skin so that no medication remains visible.
  This medication may affect calcium metabolism. Hypercalcemia has been observed in subjects exposed to this medicine. Increased absorption may occur with use of occlusive dressings.
- Avoid use of more than 200 grams per week in patients ages 7 years and older and use of more than 100 grams per week in patients ages 2-6 years.
- Report any signs of adverse reactions to your physician.
- Avoid contact with eyes, lips, and facial skin.
- Advise breastfeeding women not to apply VECTICAL Ointment directly to the nipple and areola to avoid direct infant exposure *[see Use in Specific Populations (8.2)].*

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

Section	Reviewers Providing Comments & Location in This Review
1 Indications and usage	Clinical team Section: 7.4.2

Section	Reviewers Providing Comments & Location in This Review
6 Adverse reactions	Clinical team Section:7.4.2
8 Use in specific populations	DPMH: Leyla Sahin (pediatrics) sections: 9, 10.1 Clinical pharmacology: Cindy (Liping) Pan/Chinmay Shukla: Section 6
12 Clinical pharmacology	Clinical pharmacology: Cindy (Liping) Pan/Chinmay Shukla: Section 6
13 Nonclinical toxicology	Norman A. See: Section 5

Abbreviations: DPMH = Division of Pediatric and Maternal Health
Source: Reviewer's Table

Pregnancy and Lactation Labeling Rule Conversion

Dr. Leyla Sahin provided recommendations for PLLR Conversion, sections 8.1 (pregnancy), 8.2 (lactation), and 17 (Patient Counseling Information).

10.2. Patient Labeling

Responding to an Agency request, the Applicant submitted (April 15, 2020) a proposed Patient Packet Insert (PPI). Jessica Chung, Division of Medical Policy Programs and Laurie Buonaccorsi, Office of Prescription Drug Promotion assessed the PPI (review dated April 27, 2020).

11. Financial Disclosure

Table 24: Covered Clinical Study [PMR 973-5/RD.06.SRE.18131]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant) See below
Total number of investigators identified: 24		
Number of investigators who are Sponsor employees (including both full-time and part-time employees):0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) NA

Table 25: Covered Clinical Study [PMR 973-1/RD.06.SRE.18102]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant) See below
Total number of investigators identified: 13		
Number of investigators who are Sponsor employees (including both full-time and part-time employees):0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) NA

Table 26: Covered Clinical Study [PMR 973-2/RD.06.SRE.18104]

Was a list of clinical investigators provided: After information request 2/24/20	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 14 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None in list provided		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) N/A

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Table 27: Covered Clinical Study [PMR 973-3/RD.06.SRE.18132]

Was a list of clinical investigators provided: After information request 2/24/20	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 39		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not Applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

Patricia C. Brown, M.D.
Medical Officer/Dermatology

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13. Appendices

13.1. PMR Final Study Report PMR 973-2 /RD.06.SRE.18104

13.1.1. Clinical Pharmacology

The clinical pharmacology reviewer, Cindy (Liping) Pan, Ph.D. evaluated the final study report for a trial (RD.06.SPR.18104 in pediatric subjects 2 to 12 years of age under maximal use conditions) intended to fulfill original PMR 973-2 which was later modified (see regulatory history) to become part of PMR 973-5. The trial was entitled: Pharmacokinetics and pharmacodynamics of calcitriol 3 mcg/g ointment applied twice daily for 14 days under conditions of maximal use in pediatric subjects (2 to 12 years of age) with plaque psoriasis.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology has concluded that the Applicant has fulfilled the PMR #2 and PMR #5 from a Clinical Pharmacology's perspective. The clinical pharmacology reviewer notes that, in this review cycle, labeling revisions to reflect pharmacokinetic (PK) results from PMR#1 and PMR#2 have been submitted in this application.

13.1.1.1. Pharmacokinetics

The primary objective of the trial RD.06.SPR.18104 was to assess calcitriol plasma level under conditions of maximal use of Vectical Ointment twice daily (BID) in pediatric subjects aged 2 to 12 with plaque psoriasis affecting 3% through 35% of body surface area (BSA) (excluding face and scalp). Completers included 5 subjects aged 2-6 and 13 subjects aged 7-12. Principal PK results: Overall, the mean calcitriol plasma concentrations were relatively flat at Baseline (Day 1) and after 2-week treatment application (Day 14). At Baseline, endogenous plasma calcitriol

levels over time in all subjects ranged from 61.3 pg/mL to 172 pg/mL. After 2-week BID treatment, the plasma calcitriol levels over time ranged from 59.3 pg/mL to 208 pg/mL.

13.1.1.2. Pharmacodynamics

Effects of calcitriol treatment on calcium metabolism were evaluated in pediatric subjects with psoriasis following BID application of Vectical Ointment for 2 weeks. Serum (nonfasting) calcium, albumin phosphors, intact parathyroid hormone (PTH), and urine calcium and creatinine were measured. Overall, the majority of subjects had normal serum and/or urine values at Baseline that remained normal at the Day 14 assessment.

No significant correlation between PK and pharmacodynamic (PD) parameters were noted among the 17 subjects who completed the study. There were no correlations between AUC and PD variables evaluated.

13.1.2. Clinical and Evaluation

13.1.2.1. Sources of Clinical Data and Review Strategy

13.1.2.1.1. Table of Clinical Studies

To address PMR 973-2 and support the use of Vectical (calcitriol) Ointment 3mcg/g in younger pediatric patients with (mild to moderate) plaque psoriasis (of the body) the Applicant conducted a study (RD.06.SRE.18104) entitled, “Pharmacokinetics and pharmacodynamics of Calcitriol 3 mcg/g ointment applied twice daily for 14 days under conditions of maximal use in pediatric subjects (2 to 12 years of age) with plaque psoriasis”. The final study design (Amendment 3, June 25, 2014) is summarized below:

Table 28: Clinical Trial RD.06.SPR.18104

Trial Identity	Trial Design	Regimen / Schedule / Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects	Study Population	No. of Centers and Countries
Studies to Support Safety							
RD.06.SPR.18104	Multicenter, open-label, uncontrolled, Maximal use PK/PD	Twice daily, For 14 days	Assess calcitriol plasma level under max use conditions Assess effect of calcitriol 3 mcg/g ointment on calcium homeostasis parameters	14 days	18 enrolled	Pediatric, ages 2 to 12 years inclusive, plaque psoriasis involving 3 to 35% of body, excluding face and scalp (at least 5% of BSA treated)	7 centers in US

Abbreviations: PK = pharmacokinetic, PD = pharmacodynamic
Source: Reviewer's Table

13.1.2.1.2. Review Strategy

The focus of this review was the local and systemic safety of Vectical (calcitriol) Ointment 3mcg/g which included the PK and PD findings.

Data Sources
The sources of data used for the evaluation of the efficacy and safety of Vectical (calcitriol) Ointment 3mcg/g for the proposed indication included a final abbreviated clinical study report submitted by the Applicant, and literature references.

This application was submitted in electronic common technical document (eCTD) format and was entirely electronic. The electronic submission including the protocol and clinical study reports are located in the following network path:
\\CDSESUB1\evsprod\NDA022087\022087.enx

Data and Analysis Quality
In general, the data submitted by the Applicant to support the safety of Vectical (calcitriol) Ointment 3mcg/g for the proposed indication appear adequate.

13.1.2.2. Review of Relevant Trial

13.1.2.2.1. Study Design and Endpoints

Clinical Trial RD.06.spr.18104

Objectives:
Primary objective
To assess calcitriol plasma level (maximum plasma concentration [C_{max}], minimum plasma concentration [Cmin], time drug is present at maximum concentration [T_{max}], and area under the curve [AUC]) under conditions of maximal use (i.e., area of involvement that is representative of the upper level of disease severity and at least 5% BSA treated) of calcitriol 3 mcg/g ointment BID in pediatric subjects (2 to 12 years of age) with plaque psoriasis affecting 3% through 35% of BSA (excluding face and scalp).

Secondary objective
To assess the effect of calcitriol 3 mcg/g ointment on calcium homeostasis and to evaluate safety of calcitriol 3 mcg/g ointment applied twice daily for 14 days in pediatric subjects (2 to 12 years of age) with plaque psoriasis.

Study Population
The Applicant planned to enroll approximately 30 pediatric subjects with plaque psoriasis to allow for 25 subjects to complete the study. The number of subjects were to be equally distributed among the 2- to 6- and the 7- to 12-year-old age groups. At least 12 subjects with ≥10% BSA were to be enrolled.

The study was closed in December 2015 due to slow enrollment. At the time of closure, 18 subjects were enrolled (5 subjects were between the ages of 2 and 6 years, and 13 subjects were between the ages of 7 and 12 years) and 17 subjects had completed the study. One 11-year-old subject received the last application on Day 5 and discontinued the study due to daily use of Vitamin D that was in excess of the protocol-allowed 400 IU per day.

The key entry criteria that defined the study population for the final version of the protocol are as follows:

Key Inclusion Criteria
1. Male or female pediatric subjects, 2 to 12 years of age (inclusive), at Screening.
2. The subject has a clinical diagnosis of plaque type psoriasis involving 3% through 35% of BSA excluding face and scalp (See Appendix 4) at Screening and Baseline. Subjects disqualified from study participation under a previous version of the study protocol due to insufficient involved % BSA, may be re-screened only one time with written approval from the Applicant prior to re-entry into the study. (For subjects with a minimum of 3%,

but less than 5% involved BSA, study drug will be applied on all involved areas and on additional uninvolved skin to reach a total of approximately 5% BSA.)

3. The subject lesions are amenable to a topical treatment with a maximum of 0.5 g of study medication by kg of body weight per day or 28.5g per day (200g per week), whichever is the lower.
4. If the subject is a postmenarcheal female, she has a negative urine pregnancy test at Screening (Day 14 to 7) and Baseline (Day 1).
5. If capable to give assent to decisions about participation in research, subject may sign an Assent Form to participate but must also have a parent or guardian sign the Informed Consent Form and HIPAA (as appropriate) form at Screening visit prior to any study-related procedures being performed.
6. Subject and parent/legal guardian willing and capable of co-operating to the extent and degree required by the protocol.
7. Subject's Body Mass Index (BMI) is greater than or equal to the 10th percentile of the corresponding age population (see Appendix 8). Subjects who were previously disqualified from study participation under a previous version of the study protocol due to BMI greater than the 90th percentile for the corresponding age population may be rescreened only one time with written approval from the Applicant prior to re-entry into the study.

Key Exclusion Criteria

1. Subject with guttate or pustular psoriasis, erythrodermic psoriasis, or active infection (i.e., an infection associated with the fever, swollen lymph nodes, and/or signs of localized inflammation of tissue and/or joints) *Note: allergic or vasomotor rhinitis is not exclusionary*.
2. Subject with known sensitivities to any of the study preparations (for a detailed description of the ingredients of the study medication, refer to clinical investigator's brochure or package insert).
3. The subject has an underlying known disease, a surgical or medical condition which in the investigator's opinion would put the subject at risk (e.g., uncontrolled chronic or serious diseases which would normally prevent participation in any clinical trial such as severe cardiopathy, renal or hepatic impairment, etc.).
4. The subject has clinically significant abnormal values of the safety laboratory parameters at Screening (specified in section 6.4.2 of protocol). The subject has Vitamin D deficiency (25(OH)D <20 ng/mL) at Screening (Note: subjects with 25(OH)D <20 ng/mL at Screening, may undergo re-screening after 4 weeks of Vitamin D deficiency treatment to determine eligibility).
5. The subject has secondary hyperparathyroidism (intact PTH above the upper normal range) at Screening.
6. The subject has hypercalcemia (serum and albumin-adjusted calcium above the upper normal range) at Screening.

7. The subject has urinary calcium/creatinine ratio above the upper normal range at Screening.
8. The subject has history or signs and symptoms of kidney or urinary tract lithiasis.
9. Subject who used any of the following topical treatments listed below within the specified timeframe prior to the Baseline visit:

Table 29: Topical Treatments

Corticosteroids or topical immunomodulators	2 weeks
Tar	2 weeks
Vitamin D derivatives	2 weeks

10. Subject who used any of the following systemic treatments listed below within the timeframe specified prior to the Baseline visit:

Table 30: Systemic Treatments

Homeopathic or herbal preparations	1 week
Calcium containing products	2 weeks
Immunomodulators and biologics known to affect psoriasis	4 weeks
Corticosteroids or ACTH analogs	4 weeks
Phototherapy/PUVA therapy	4 weeks

11. Subjects with any regular systemic or topical treatment that may impact calcium homeostasis (such as, but not limited to, calcium or Vitamin D supplements), except if taken for prophylaxis. Note: subjects taking oral calcium and vitamin D for prophylactic purposes must be on a stable dose for at least 4 weeks before Screening and are not to exceed the Recommended Daily Allowance for calcium (700mg for subjects below 4 years and 1000 mg for subjects over 4 years) or Vitamin D (400 IU). If calcium treatment

is taken for any reason other than prophylaxis, a wash-out period of 2 weeks must be completed prior to the Baseline visit.
12. Subject who is pregnant or nursing.
13. Subject with history of or ongoing physical or psychiatric conditions which, in the investigator's opinion, may put the subject at risk, may confound the study assessments, or may interfere with the subject's participation in the study.
14. The subject is planning excessive exposure to the sun or ultraviolet light during the study (i.e. natural or artificial sunlight, including tanning booths and sun lamp).
15. The subject is unable to comply with the following restrictions: swimming and bathing are restricted for six hours after each study drug application; no swimming on the days of blood sampling.
16. Subject who is unable or unwilling to undergo multiple venipunctures.
17. Subjects who have participated in a clinical drug or device research study within the last 30 days.
18. Subject who has had significant blood loss within the last 3 months.
19. Subject has a history of anemia or Screening lab results indicate anemia.

Study Design

This is an open-label, uncontrolled, multicenter, study to assess the systemic exposure to calcitriol under conditions of maximal use (i.e. area of involvement that is representative of the upper level of disease severity) of calcitriol 3mcg/g ointment applied twice daily in pediatric subjects (2 through 12 years of age) with plaque psoriasis affecting 3% to 35% of BSA, excluding face and scalp. For subjects with a minimum of 3%, but less than 5% involved BSA, study drug was to be applied on all involved areas and on additional uninvolved skin to reach a total of approximately 5% BSA.

The pediatric individual maximal daily dose was based on g/kg of body weight, extrapolated from the adult dose. In adult, the maximal daily dose of calcitriol 3mcg/g ointment is 28.5g (200g per week). Therefore, if the mean adult body weight is 60 kg, it represents a maximal daily dose of approximately 0.5 g/kg and a maximal dose per application of approximately 0.25 g/kg.

The investigator calculated for each subject, the maximal daily dose of calcitriol 3 mcg/g ointment to be applied during the study (0.5 g/kg of body weight or 28.5 g, whichever is the lower) and the maximal dose per application (0.25 g/kg of body weight or 14 g, whichever is the lower). The investigator determined the percent BSA involved (excluding face and scalp) based on the "rule of nine".

The first application was to be performed on site by trained study personnel. The quantity to be applied was determined by the investigator/designee based on the percentage of involved BSA and in order to cover at least 5% BSA. Enough product was to be applied in order to cover the involved areas and a minimum of 5% BSA with a thin layer. When possible, per the investigator's discretion, the study drug was applied to uninvolved skin located near the

psoriasis-involved areas or to uninvolved skin on the subject's back. The surface of uninvolved skin to be treated was estimated using the palm of the subject's hand as a scale. The palm of the hand (including fingers) is considered to represent approximately 1% BSA. The study drug was applied to the same location on the body for each application during the study. The quantity to be applied was not to exceed the maximal dose per application (0.25 g of ointment/kg of weight or 14 g, whichever is the lower). The quantity applied during the first visit was recorded and the parents were instructed to apply the same quantity for each application, regardless of any changes to involved BSA during the study treatment period (twice daily, throughout the study).

To facilitate the dosing, the quantity to be applied was converted into a volume. The relative density of calcitriol 3 mcg/g ointment is 0.85 and a conversion table (weight to volume and volume to weight) was provided. In order to measure the volume, the investigator/designee and the parents used syringes, whose size was be adapted to the quantity of study drug to be applied.

Pharmacokinetic and pharmacodynamic profiles were followed during the study. Final trough concentrations for PK and PD analyses were collected on Day 14. Safety parameters were evaluated and recorded over the course of the study.

Study participation of each subject was approximately 28 days including a Screening period of up to 2 weeks and 14 days (2 weeks) of treatment.

At Day 1 and Day 14 ET visits, the following PK parameters were determined for each subject: C_{max}, C_{min}, T_{max}, AUC0-9h and AUC0-12h.

Concomitant Medications

Authorized Therapy

Therapy considered necessary for the subject's safety and welfare was permitted at the investigator's discretion. Moisturizing lotion (provided by the Applicant) could be used as needed, on non-treated areas of the skin. A gentle cleansing bar (provided by the Applicant) could be used to cleanse both treated and non-treated areas of the skin. Shampoos not containing high potency corticosteroids or vitamin D derivatives were permitted for the treatment of scalp psoriasis. The face and scalp could be treated with low potency corticosteroid such as hydrocortisone cream.

Subjects taking oral calcium and vitamin D for prophylactic purposes were to be on a stable dose for at least 4 weeks before Screening and are not to exceed the recommended daily allowance for calcium (700 mg for subjects below 4 years and 1000 mg for subjects $\geq$4 years) or Vitamin D (400 IU).

Prohibited Therapies
Subjects enrolled in this study were not to receive any treatment impacting on calcium homeostasis other than the drug, (calcitriol 3 mcg/g) ointment under investigation, and prophylactic use of calcium and Vitamin D as discussed under exclusion criteria.

Drugs that may cause alterations in serum or urine calcium levels
The Applicant provided a list in an Appendix to the protocol.

Vitamin D and Vitamin D analogs: The Applicant provided a list in an Appendix to the protocol.

Objectives and Related Endpoints
Objectives:
Primary objective
To assess calcitriol plasma level (maximum plasma concentration [C_{max}], minimum plasma concentration [C_{min}], time drug is present at maximum concentration [T_{max}], and area under the curve [AUC]) under conditions of maximal use (i.e., area of involvement that is representative of the upper level of disease severity and at least 5% BSA treated) of calcitriol 3 mcg/g ointment applied BID in pediatric subjects (2 to 12 years of age) with plaque psoriasis affecting 3% through 35% of BSA (excluding face and scalp).

Secondary objective
To assess the effect of calcitriol 3 mcg/g ointment on calcium homeostasis and to evaluate safety of calcitriol 3 mcg/g ointment applied twice daily for 14 days in pediatric subjects (2 to 12 years of age) with plaque psoriasis.

Investigator(s):

Table 31: Study Sites and Enrollment

Site Number	Principal Investigator	Location	Ages 2 – 6 years	Ages 7 – 12 years	Total Subjects Enrolled (N)
8008	Lawrence Eichenfeld	San Diego, CA	5	13	18
8101	Aida Lugo-Somolinos	Chapel Hill, NC		3	3
8142	Scott Fretzin	Indianapolis, IN		2	2
8247	Yolanda Helfrich	Ann Arbor, MI	1	1	2
8299	Kara Shah	Cincinnati, OH	2	2	4
8333	Elizabeth Tichy	San Antonio, TX		2	21
8434	Heather Brandling-Bennett		1	1	2

Source: Compiled from Applicant table 14.1, Abbreviated Clinical Study Report, RD.06.SPR.18104 and SDN 365, NDA 22087 (response to information request)

Table 32: Enrollment by Center - Safety Population

	2 - 6 years old	7 - 12 years old	Total
Centre no/ Investigator name			
N	5	13	18
- 8008- LAWRENCE EICHENFIELD	1 (20.0%)	2 (15.4%)	3 (16.7%)
- 8101- AIDA LUGO-SOMOLINOS		3 (23.1%)	3 (16.7%)
- 8142- SCOTT FRETZIN		2 (15.4%)	2 (11.1%)
- 8247- YOLANDA HELFRICH	1 (20.0%)	1 (7.7%)	2 (11.1%)
- 8299- KARA SHAH	2 (40.0%)	2 (15.4%)	4 (22.2%)
- 8333- ELIZABETH TICHY		2 (15.4%)	2 (11.1%)
- 8434- HEATHER BRANDLING-BENNETT	1 (20.0%)	1 (7.7%)	2 (11.1%)

Source: Abbreviated Clinical Study Report, RD.06.SPR.18104, Table 14.1, IND 062151 Seq 0087, page 44 of 155.

Table 33: Schedule of Assessments

	STUDY VISITS					
	Screening Visit (Day -14 to Day -7)	Treatment Period 2 weeks				
PROCEDURES		Baseline Day 1	Day 3 Telephone Contact	Day 7 Telephone Contact	Day 10 Telephone Contact	Final/ET Day 14 +1 Day
Informed consent / Assent form, HIPAA	X					
Demographics, Medical history	X					
Inclusion/exclusion criteria	X	X[a]				
Record percent BSA involved and applied[b]	X	X				X
Physical examination[c]	X	X				X
Vital signs[c]	X	X				X
Calculate maximum applicable quantity[d]		X				
Previous therapies/ Procedures[e]	X					
Concomitant therapies/Procedures[e]	X	X	X	X	X	X
25(OH)D	X[f]					
Routine: Hematology[g], blood chemistry[h], and urinalysis[i]	X[f]					X[j]
Urine pregnancy test[k]	X	X				X
PD: Serum [l]	X[f]	X				X[j]
PD: Urine[m]	X	X				X[j]
PK: Blood sampling[n]		X				X[j]
Application of investigational product (time and quantity)[o]		X				X
Investigational product dispensed[p]		X				
Investigational product returned						X
Dosing calendar review[q]		X	X	X	X	X
Dispensing moisturizing lotion and cleansing bar[r]		X				
Adverse events[s]		X	X	X	X	X
Exit form						X

Abbreviations: BSA = body surface area; HIPAA = Health Insurance Portability and Accountability Act; PD = pharmacodynamics; PK = pharmacokinetic; ET = end of treatment
Note: Unscheduled visit: When necessary and exceptionally, unscheduled visits were allowed (because of either an AE that needed a specific treatment, or an adverse event that led to withdrawal from the study).
Note: Subjects who were previously disqualified from study participation due to Vitamin D deficiency, insufficient involved % BSA, or out-of-range BMI were allowed to be rescreened only 1 time with written approval from the Applicant prior to re-entry into the study.

a) Criteria were rechecked to confirm eligibility of the subject.
b) Body surface area (%) involved and BSA applied (%) was recorded on the source document and eCRF at Screening, Baseline, and Day 14.
c) Physical examination included: weight and review of systems: general, skin, cardiovascular, gastrointestinal, respiratory, musculoskeletal, neurological, psychological, and hematolymphatic. Height was measured at Screening only. Vital signs included: blood pressure, heart rate, temperature, and respiration rate.
d) After determination of the body weight, the investigator calculated and recorded the maximal daily dose of study drug (0.5g of ointment/kg of body weight or 28.5g, whichever was lower) on the source document and the CRF.
e) Any therapy or medication other than study ointment, was noted on the Drug/Therapies Therapy Form.
f) Blood samples were collected at Screening and results had to be available for the Baseline visit.
g) Routine hematology: red blood cells, white blood cells with differential cell count, platelets, hemoglobin, hematocrit
h) Routine blood chemistry (nonfasting): total protein, ALT (SGPT), AST (SGOT), alkaline phosphatase, blood urea nitrogen, creatinine, total and conjugated bilirubin
i) Routine urinalysis: glucose, ketone, blood, protein, nitrite, and leukocytes
j) In case of early termination, all efforts were made to perform blood tests prior to completion of the exit form.
k) Urine pregnancy test for postmenarcheal females
l) PD Serum (nonfasting): calcium, phosphorus, albumin (in order to calculate the albumin-adjusted calcium) and Intact PTH
m) PD Urine: Urine calcium and creatinine on 24H urine specimen (whenever feasible) in order to calculate urine calcium /creatinine ratio. Urine collection for 24H urine specimen was to start the day prior to the visit (no later than 15H prior to the visit).
n) PK: Blood sampling for determination of plasma calcitriol levels were taken.
o) On Day 1, first application was performed by the investigator/designee immediately after T9hr PK blood draw. The quantity to be applied was determined by the investigator/designee based on the percentage of involved BSA. The quantity to be applied could not exceed the maximal dose per application of 0.25 g of ointment / kg of weight or 14 g, whichever was lower). The maximal daily dose was not to exceed 0.5 g of ointment / kg of weight or 28.5 g, whichever was the lower and was to remain constant during the treatment period. For subjects with less than 5% involved BSA, study drug was to be applied on all involved areas and on additional uninvolved skin to reach a total of approximately 5% BSA. When possible, per the investigator's discretion, the study drug applied to uninvolved skin would be located near the psoriasis-involved areas. If this was not possible, the additional study drug could be applied to uninvolved skin on the subject's back. Study drug was to be applied to the same location on the body for each application during the study. The Day 14 dose was applied at the Investigative site. Daily treatments from Day 2 to Day 13 were applied by the parent/legal guardian. Application time and quantity were recorded on the calendar. Each study drug tube was returned to and weighed by the Applicant.
p) Additional tubes could be dispensed at an unscheduled visit, if needed.
q) Time of application and compliance was recorded on the dosing calendar.
r) Cetaphil® Moisturizing Lotion and Cetaphil® Gentle Cleansing Bar were provided by the Applicant.
s) Adverse events occurring after the Informed Consent Form had been signed were recorded as adverse events in the eCRF
Source: Abbreviated Clinical Study Report for RD.06.SRE.18104, section 9.1, pages 5.6.

Data Analysis

All data were summarized and analyzed based on the Safety population, which comprised all enrolled subjects who received at least 1 application of the study medication.

Protocol Amendments

The original protocol RD.06.SPR.18104, dated 21 Aug 2012, was amended 3 times. The first treatment was applied on 17 Jul 2013. No changes to the protocol-specified analyses were made during finalization of the Statistical Analysis Plan.

Amendment 1 (dated May 07, 2013)

- Modified PK sampling schedule for subjects with a body weight of <15 kg at Screening to reduce the total blood volume collected, in response to an FDA request.
- Clarified procedures performed at the Screening visit by adding that weight is measured as part of the physical examination at this visit.

Amendment 2 (dated Nov 19, 2013)

- Updated the enrolled subject population to include at least 12 subjects with ≥10% BSA.
- Removed a PK sample collection (9 hours) to minimize blood volume collected for subjects with lower body weight (<15 kg at Screening).

- Added AUC0-6h PK parameter due to the removal of the T9 hour PK sampling for subjects weighing <15 kg.
- Added that T0 PK timepoint was applicable only to Day 14.
- Deleted mention of timing for the additional postmarketing studies in response to an FDA request.
- Modified exclusion criterion #12 to allow calcium or Vitamin D if taken for prophylaxis.
- If calcium treatments were taken for any reason other than prophylaxis, a 2-week wash-out period was to be completed before the Baseline visit was added. Corresponding language was added to "Unauthorized therapy" in Appendix 1.
- Added exclusion criterion #20 to exclude subjects with a history of anemia or laboratory results at Screening that indicated anemia to ensure the safety of subjects.
- Removed recording of demographics and medical history from the Baseline visit.
- Removed dipstick from urinalysis procedure.
- Clarified safety procedures and updated best practice for PD urine assessments per consultation with a pediatric endocrinologist.
- Provided instructions for 24-hour urine collection to be started on Day 13 and not more than 15 hours prior to the Day 14 visit (when applicable).
- Changed the Day 7 visit from a clinic visit to a telephone contact to facilitate scheduling. To ensure study medication compliance, and recording of Adverse Events (AEs) and any new concomitant therapies/procedures, additional telephone contacts at Days 3 and 10 were added.
- Removed Day 7 physical examination and vital sign assessments.
- Added that unscheduled visits could be utilized for any concerns that arose from the telephone contacts or to dispense any additional study medication.
- Added that requirements of all study drug returns were to be reinforced for all subjects at the Day 3, 7, and 10 telephone contacts.
- Added subject instructions regarding hydration to ensure safety of subjects.
- Added a +1 day window to the Day 14 visit to facilitate scheduling.
- Added "or equivalent" for all references to Cetaphil™ Moisturizing Lotion and Cetaphil™ Gentle Cleansing Bar.
- Added "or sourced by" to allow study materials to be sourced by sites or vendors.

Amendment 3 (dated Jun 25, 2014)

- Included subjects with a minimum of 3% BSA involved. However, the conditions for maximal use were unchanged and at least 5% of BSA was to be treated.
- Added instructions as to where to apply study drug for subjects with <5% involved BSA.
- Allowed subjects who were disqualified from study participation previously based on <5% of BSA involved, to be rescreened one time for re-entry into the study.
- Modified Inclusion criterion #7 to allow subjects with BMI greater than the 90th percentile of the corresponding age population to participate in the study. Subjects who were disqualified previously from study participation based on BMI were allowed to be rescreened 1 time for re-entry into the study.

13.1.3. Results of Efficacy Assessment

Trial RD.06.SRE.18104 was not designed to evaluate efficacy.

13.1.4. Review of Safety

13.1.4.1. Safety Review Approach

The review of the safety of Vectical (calcitriol) Ointment 3 mcg/g in trial RD.06.SRE.18131, pediatric population, 2 to 16 years and 11 months of age, Version R03, with mild to moderate plaque psoriasis, included analyses of treatment emergent adverse events (TEAEs), serious AEs (SAEs), AEs leading to discontinuation, treatment emergent adverse reactions, AEs associated with product class, and vitamin D analogs.

13.1.4.2. Review of the Safety Database

Disposition
A total of 32 subjects were screened; 14 subjects were considered screening failures based on eligibility criteria. The study was closed in (b) (6) At the time of closing, 18 subjects had been enrolled into the study. Of the 18 subjects enrolled, 17 subjects completed the study. Subject (b) (6) was discontinued from the study, due to daily use of Vitamin D that was in excess of the protocol-allowed 400 IU per day. According to the protocol, subjects were to be equally distributed among the 2 to 6-year-old and 7 to 12-year-old age groups. As the study was closed, this goal was not achieved. Of the 17 subjects who completed the study, 5 subjects were in the 2 to 6-year-old group, and 12 subjects were in the 7 to 12-year-old group. One subject in the 7 to 12-year-old age group discontinued from the trial and is included in the Safety population.

Table 34: Disposition of Subjects (Safety population)

	2-6 years old	7-12 years old	Total)
Number of subjects enrolled	5	13	18
Number of subjects who completed the study	5 (100.0%)	12 (92.3%)	17 (94.4%)
Number of subjects who discontinued	0	1 (7.7%)	1 (5.6%)
Reason for discontinuation			
Protocol violation[a]	0	1 (7.7%)	1 (5.6%)

a) Subject (b) (6) (age 11 years; female) was discontinued from the study because the Vitamin D dose taken was higher than the protocol-allowed 400 IU/day.
Source: Abbreviated Clinical Study Report, RD.06.SRE.18104, Table 4, section 10.1, page 10 of 30.

Exposure
The Safety population comprised 18 subjects who received at least 1 application of study drug.

Extent of Exposure
The duration of treatment was comparable between the 2 age groups (2 to 6; 7 to 12). The median number of treatment days was 15.0 days for both groups. The mean treatment duration was 14.6 days for the 2 to 6 year group and 14.1 days for the 7 to 12 year group.

For all subjects, the mean maximal daily dose (calculated as .5g/kg body weight) was 17.09±6.81 g (range: 6.70 to 28.50 g). The actual mean daily medication calculated from the total dispensed and returned tube weights was 8.4±4.1 g (range: 1.9 to 16.7 g).

The median study drug usage during the study was greater for the 7 to 12 year group (133.21 g) compared with the 2 to 6 year group (117.72 g).

Daily study drug usage was calculated as total study drug usage/treatment duration (days). The mean daily usage ranged from 7.01±2.44 g/day for the 2 to 6 year age group to 8.98±4.59 g/day for the 7 to 12 year age group.

Dosing
From Clinical Pharmacology Review by Cindy (Liping) Pan, Ph.D., dated March 24, 2020: "The approved maximum weekly dose for adults is 200 g. Based on data in Table 35, in the maximal use study, the observed maximum weekly dose studied in the pediatric patients aged 2 to 6 years was 103.6 g (14.8 g x 7 days) and in subjects 7 to 12 years was 199.5 g (28.5 g x 7 days). Based on this information, the proposed maximum weekly dosing will be limited to not more than 100 g in subjects 2 to 6 years old and not more than 200 g in subjects 7 years of age and older. This information is proposed to be added in the label."

Table 35: Summary of Treatment Duration, Daily Dose, and Medication Usage (Safety Population)

	Statistic	Age 2-6 years N=5	Age 7-12 years N=13	Total N=18
Treatment duration (days)	N	5	13	18
	Mean ± SD	14.6 ± 0.5	14.1 ± 2.8	14.2 ± 2.3
	Median	15.0	15.0	15.0
	Min, Max	14, 15	5, 15	8, 15
Maximal daily dose (g)	Mean ± SD	9.66 ± 3.06	19.94 ± 5.55	17.09 ± 6.81
	Median	8.70	19.50	16.70
	Min, Max	6.7, 14.8	12.2, 28.5	6.7, 28.5
Total usage of investigational product[a]	Mean ± SD	101.68 ± 34.02	126.37 ± 71.35	119.51 ± 63.21
	Median	117.72	133.21	120.99
	Min, Max	63.1,137.3	28.5,250.2	28.5,250.2
Daily usage of investigational product (g/day)[b]	Mean ± SD	7.01 ± 2.44	8.98 ± 4.59	8.43 ± 4.13
	Median	8.41	8.88	8.59
	Min, Max	4.20,9.15	1.90,16.68	1.90,16.68

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation
Note: Study duration = Date of the last visit-date of Baseline +1
Maximal daily dose calculated as .5 mg/kg
a) Total study drug usage = total dispensed weight (g) - total returned weight (g).
b) Daily study drug usage = total study drug usage / Treatment duration (day).
Source: Abbreviated Clinical Study Report, RD.06.SRE.18104, Table 10, section 12.1.1, page 20 of 30.

Characteristics of the Safety Population

Demographic and Baseline Characteristics

The Safety population was defined as all enrolled subjects who received at least one application of the study medication.

The Safety population comprised 18 subjects, 10 (55.6%) males and 8 (44.4%) females, with a mean age of 8.4 years (range 2 to 12 years). More than twice as many subjects 7 to 12 years of age (N=13) were enrolled compared to those 2 to 6 years of age (N=5). Demographic characteristics were generally similar between the two age groups. The majority of subjects were white in both groups (age 2 to 5 years, 100%; age 7 to 12 years 77%; 83.3% all ages). There were more females (4 or 80%) than males (1 or 20%) in the 2- to 6-year-old group and more males (9 or 69%) than females (31%) in the 7- to 12-year-old group.

At Baseline, the mean BSA affected was 7.8±1.9% (ranging from 5% to 10%) in the 2- to 6-year-old group and 8.8±4.7% (ranging from 3% to 18%) in the 7- to 12-year-old group. 8.6±4.1%. Of note, as per protocol amendment #3, for subjects with less than 5% involved BSA, the study drug was applied to all involved areas and additional uninvolved skin to treat up to approximately 5% BSA as per maximal condition of use. Two subjects had less than 5% of affected BSA (3% for Subject (b) (6) and 4% for Subject (b) (6)). For these 2 subjects, the investigational product was applied on all involved areas and surrounding uninvolved skin to reach a total of 5% BSA. Therefore, at Baseline, the mean BSA treated was 8.7±3.9% (ranging from 5% to 18%).

Table 36: Demographics (Safety Population)

		Age 2-6 years N=5	Age 7-12 years N=13	Total N=18
Age	N	5	13	18
	Mean ± SD	4.2 ± 1.5	10.0 ± 1.5	8.4 ± 3.0
	Median	4.0	10.0	9.5
	Min, Max	2, 6	7, 12	2, 12
Age group	Children (2-11 years)	5 (100.0%)	11 (84.6%)	16 (88.9%)
	Adolescents (12 years)	NA	2 (15.4%)	2 (11.1%)
	Total	5	13	18
Sex	Male	1 (20.0%)	9 (69.2%)	10 (55.6%)
	Female	4 (80.0%)	4 (30.8%)	8 (44.4%)
Race	White	5 (100.0%)	10 (76.9%)	15 (83.3%)
	Black/African American	0	2 (15.4%)	2 (11.1%)
	Other	0	1 (7.7%)	1 (5.6%)
Ethnicity	Hispanic or Latino	0	3 (23.1%)	3 (16.7%)
	Not Hispanic or Latino	5 (100.0%)	10 (76.9%)	15 (83.3%)
Skin phototype	I	1 (20.0%)	1 (7.7%)	2 (11.1%)
	II	2 (40.0%)	3 (23.1%)	5 (27.8%)
	III	2 (40.0%)	4 (30.8%)	6 (33.3%)
	IV	0	4 (30.8%)	4 (22.2%)
	VI	0	1 (7.7%)	1 (5.6%)
BSA involved at Baseline	Mean ± SD	7.8 ± 1.9	8.8 ± 4.7	8.6 ± 4.1
	Median	8.0	8.0	8.0
	Min, Max	5, 10	3, 18	3, 18
Maximal daily dose (g)	Mean ± SD	9.66 ± 3.06	19.94 ± 5.55	17.09 ± 6.81
	Median	8.70	19.50	16.70
	Min, Max	6.7, 14.8	12.2, 28.5	6.7, 28.5
BMI (kg/m2) at Screening	Mean ± SD	15.94 ± 1.22	20.14 ± 4.33	18.97 ± 4.16
	Median	15.80	18.70	17.80
	Min, Max	14.5, 17.8	15.6, 30.4	14.5, 30.4

Abbreviations: BSA = body surface area; BMI = body mass index; NA = not applicable; SD = standard deviation
Source: Abbreviated Clinical Study Report, RD.06.SRE.18104, Table 5, section 11.1, page 12 of 30.

Concomitant Medications

Concomitant therapies were defined as any ongoing therapies at the time of the Screening visit, and any new therapies started after the Screening visit. Of the 18 subjects, all but 1 subject in the 2 to 6 year group received concomitant therapies. The most commonly reported concomitant therapy taken by 8 (44.4%) subjects was Cetaphil (class of "other emollients and protective")

In addition, the investigator was expected to review all concomitant medications taken by the subjects that might have an impact on calcium homeostasis. With the exception of 1 subject in the 7- to 12-year-old group, no concomitant medications that could impact calcium homeostasis were taken. Subject (b) (6) had received glucocorticoids (fluticasone propionate) for the treatment of asthma since 2008 and continued during the study.

Protocol Deviations
The Applicant documented 40 protocol deviations of which 6 were considered major and 34 were considered minor. The major deviations involved Investigational product compliance, such as missing doses 94), exclusion criteria – one subject enrolled in study with current Vitamin D daily use in excess of 400 IU per day and one subject with daily intake of Vitamin D was 1400 IU at time of Screening. Source: Table 16.2.2 Clinical Study report RD.06.SRE.18104

Adequacy of the Safety Database
The Applicant did not achieve enrollment total desired for PMR 973-2 (approximately 30 pediatric subjects with plaque psoriasis to allow for 25 subjects to complete the study).

13.1.4.2.1. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
Overall, the quality of the data submitted was adequate to characterize the safety of Vectical (calcitriol) Ointment 3mcg/g applied twice daily for 2 weeks in pediatric subjects (2 to 12 years inclusive).

Categorization of Adverse Events
Adverse events were coded using the Medical Dictionary for Regulatory Activities version 15.0.

According to the protocol, AEs could include events based on laboratory values. All out of range laboratory values obtained after Screening were to be assessed for clinical significance by an investigator (physician) and reported as an AE, if both of the following conditions were met:

- The abnormality suggested a disease and/or organ toxicity, and/or was considered pathological

AND

- This abnormality was not present at Screening or was assessed as having worsened since the Screening visit.

An out-of-range laboratory value that was identified as clinically significant and related to the study drug(s) was considered by the Applicant to be an Adverse Event of Special Interest (AESI).

In this study, an AESI was defined as:

- Typical clinical signs and symptoms consistent with Vitamin D toxicity:
  - polyuria, polydipsia

  - mental status changes including confusion
  - hypercalcemia, urine calcium/creatinine ratio above the upper normal range, and kidney stones
- Dermatological events such as severe skin irritation, as well as severe local and/or generalized pruritus, suspected skin sensitization (contact allergy)
- Cutaneous AE assessed as related to the study drug and leading to discontinuation of the study drug, including temporary discontinuations.
- Out-of-range laboratory result identified as clinically significant and related to the study drug

Routine Clinical Tests
Investigators monitored adverse events, physical examination, vital signs, and laboratory parameters.

The following safety clinical laboratory testing was performed:

- Safety laboratory parameters to be evaluated at Screening and Day 14/ET:
  - *Hematology*: red blood cells, white blood cells with differential cell count, hemoglobin, hematocrit, platelets
  - *Blood chemistry (non-fasting)*: total protein, alanine aminotransferase (ALT), (serum glutamate pyruvate transaminase (SGPT), aspartate aminotransferase (serum glutamic oxalacetic transaminase), alkaline phosphatase, blood urea nitrogen, creatinine, total and conjugated bilirubin
  - *Urinalysis*: glucose, ketone, blood, protein, nitrite and leukocytes
- Pharmacodynamic parameters (on Screening, Day 1 and Day 14/ET)
  - *Serum (non-fasting):* calcium, phosphorus, albumin (in order to calculate the albumin-adjusted calcium), intact PTH
  - *Urine:* calcium and creatinine (in order to calculate urine calcium/creatinine ratio) on 24H urine specimen (whenever feasible) or fasting (4 hours) random urine sample. Subjects who were toilet-trained were to be actively encouraged to complete 24-hour urine collection. A fasting (4 hour) random urine sample could be collected for the Screening Visit, however, if calcium/creatinine ratio results were abnormal, a 24-hour urine collection was to be completed prior to the Baseline Visit.
- Other Assessments included:
  - *25(OH) D* (at Screening) [25-hydroxyvitamin D = pre-hormone]
  - *Urine Pregnancy Test* at Screening, Baseline (Day 1), and Day 14/ET for post menarcheal females

13.1.4.2.2. Safety Results

Deaths, Serious Adverse Events (SAEs), and Discontinuations Due to Adverse Events (AEs)
There were no deaths, no SAEs, or AEs that led to premature withdrawal from the trial.

Adverse Events

Of the 18 subjects who received calcitriol, half of the subjects (9 [50.0%]) reported 11 AEs. All 5 subjects in the 2 to 6 year group and 4 subjects (30.8%) in the 7 to 12 year group experienced at least 1 AE. All were in the "skin and subcutaneous tissue disorder" System Organ Class (SOC).

Three (60.0%) subjects 2 to 6 years of age reported 1 cutaneous AE each and 2 (15.4%) subjects 7 to 12 years of age reported 1 cutaneous AE each. All events were considered to be related to the investigational product, except for 1 cutaneous event experienced by a subject in the 2- to 6-year-old group.

All AEs were mild or moderate in severity

AESI's were predefined for this study (see above). No subjects experienced AESIs.

Overall, AEs were most commonly reported in the skin and subcutaneous tissue disorders SOC (4 subjects; 22.2%). With the exception of headache reported by 2 subjects in the 7- to 12-year-old group, all other AEs were reported by 1 subject each.

Table 37: Adverse Events by System Organ Class and Preferred Term (Safety Population)

		Age				Total N=18	
		2 - 6 years N=5		7 - 12 years N=13			
System Organ Class	Preferred Term	Event n	Subjects[a] N (%)	Event[b] n	Subjects[a] N (%)	Event n	Subjects[a] N (%)
Any adverse event		5	5 (100.0%)	6	4 (30.8%)	11	9 (50.0%)
Gastrointestinal disorders	All	2	2 (40.0%)	0	0 (0.0%)	2	2 (11.1%)
	Abdominal pain upper	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
	Vomiting	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
Infections and infestations	All	0	0 (0.0%)	2	2 (15.4%)	2	2 (11.1%)
	Rhinitis	0	0 (0.0%)	1	1 (7.7%)	1	1 (5.6%)
	Viral infection	0	0 (0.0%)	1	1 (7.7%)	1	1 (5.6%)
Injury, poisoning, and procedural complications	ALL	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
	Sunburn	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
Nervous system disorders	ALL	0	0 (0.0%)	2	2 (15.4%)	2	2 (11.1%)
	Headache	0	0 (0.0%)	2	2 (15.4%)	2	2 (11.1%)

		Age				Total N=18	
		2 - 6 years N=5		7 - 12 years N=13			
System Organ Class	Preferred Term	Event n	Subjects[a] N (%)	Event[b] n	Subjects[a] N (%)	Event n	Subjects[a] N (%)
Skin and subcutaneous tissue disorders	ALL	2	2 (40.0%)	2	2 (15.4%)	4	4 (22.2%)
	Pain of skin	0	0 (0.0%)	1	1 (7.7%)	1	1 (5.6%)
	Pruritus	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
	Skin burning sensation	1	1 (20.0%)	0	0 (0.0%)	1	1 (5.6%)
	Skin exfoliation	0	0 (0.0%)	1	1 (7.7%)	1	1 (5.6%)

Note: Multiple occurrences within an SOC by a subject were counted once per SOC. Multiple occurrences of a PT by a subject were counted once per PT.
a) Number of subjects with at least 1 event
b) Subject (b) (6) had 1 AE in the skin and subcutaneous tissue disorders SOC and 1 AE in the infections and infestations SOC. Subject (b) (6) had 1 AE in the nervous system disorders SOC and 1 AE in the skin and subcutaneous tissue disorders SOC.
Source: Abbreviated Clinical Study Report, RD.06.SRE.18104, Table 12, section 12.2.3, page 23 of 30.

Adverse Reactions

The investigator was to determine whether or not there was a reasonable causal relationship between the study drug and the AE, in terms of either "reasonable possibility" or "no reasonable possibility". Two subjects in each age group experienced an AE that was considered to be related to the investigational product, all of which were in the skin and subcutaneous tissue disorders SOC. In the 2 to 6 year group, pruritus and skin burning sensation were each reported by 1 subject, and in the 7 to 12 year group, pain of skin and skin exfoliation were each reported by 1 subject.

Table 38: Summary of Adverse Events Related to Study Drug by System Organ Class and Preferred Term - Safety Population

		2 - 6 years old (N=5)		7 - 12 years old (N=13)		Total (N=18)	
		Event n	Subject* N(%)	Event n	Subject* N(%)	Event n	Subject* N(%)
ANY ADVERSE EVENTS		2	2 (40.0%)	2	2 (15.4%)	4	4 (22.2%)
Skin and subcutaneous tissue disorders	ALL	2	2 (40.0%)	2	2 (15.4%)	4	4 (22.2%)
	Pain of skin			1	1 (7.7%)	1	1 (5.6%)
	Pruritus	1	1 (20.0%)			1	1 (5.6%)
	Skin burning sensation	1	1 (20.0%)			1	1 (5.6%)
	Skin exfoliation			1	1 (7.7%)	1	1 (5.6%)

Adverse events are defined as events that occurred on the day of, or after, the first use of study drug.
*= Number of subjects with at least one event
Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class. Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.
Safety population: All enrolled subjects having received the treatment at least once
Source: table 14.3.2.6: Abbreviated Clinical Study Report RD.06.SPR.18104, Table 14.3.2, IND 062151 Seq 0087, page 9 of 62.

Adverse reactions

- Subject (b) (6) in the 2-6 age group reported increased pruritus, starting on Study Day 8 and ongoing at Day 14 visit. The event was evaluated as moderate in severity, the dose of study drug was not changed and assessed as having a reasonable possibility of being related to study drug.

- Subject (b) (6) in the 2-6 age group reported pain of hands/skin burning sensation, starting on Study Day 8 and ending on Study Day 14. The event was judged to be mild in severity and assessed as having a reasonable possibility of being related to study drug. The dose of study drug was not changed, and the subject recovered.

- Subject (b) (6) in the 7-12 age group reported peeling skin/desquamation of trunk, starting on Study Day 5 and ending the same day. The event was judged to be of mild severity and assessed as having a reasonable possibility of being related to the study drug. The dose of the study drug was not changed, and the subject recovered. A comment related to this event states it was unclear if this was linked to skin dryness. Note that the event was only observed on one study day.

- Subject (b) (6) in the 7-12 group age, reported pain of skin/stinging, starting on Study Day 2 and ending on Study Day 5. The event was judged to be of mild severity. The dose of study drug was not changed, and the subject recovered.

Pruritus, skin discomfort, and skin burning sensation are labeled as adverse events. Regarding peeling skin/desquamation of trunk, a comment related to this event states it was unclear if this was linked to skin dryness. Note that the event was only observed on one study day.

Laboratory Findings
Routine laboratory findings:
Hematology, Blood Chemistry, Urinalysis
Although some hematology parameters were flagged as outside normal range at Screening or following treatment, none were considered to be clinically significant by the investigator. There were few changes in urinalysis parameters from Screening to Day 14, none of which was considered clinically significant by the investigator.

Laboratory values over time:
Hematology
There were few shifts among hematology parameters during the study. The majority (>76%) of subjects had normal hematology values at Baseline that remained normal at the Day 14 assessment. Most values that were outside the normal range at Screening (low or high) remained that way at Day 14. None of the values outside of normal range at any timepoint were considered to be clinically significant by the investigator.

Blood Chemistry

There were few shifts among blood chemistry parameters during the study. With the exception of; ALT (SGPT) and total Bilirubin; chemistry values within the normal range at Baseline remained normal at the Day 14 assessment for all subjects. Most values that were outside the normal range at Screening (low or high) remained that way at Day 14. Of the 7 to 12 years old subjects who had normal ALT/SGPT values at Screening, 60% had low values at Day 14. Among subjects 2 to 6 years with total bilirubin values within normal range at Screening, two-thirds had low values at Day 14, while half of subjects with low values at Screening had values within normal range by Day 14. Similarly, among 7- to 12-year old subjects, 40% who had values within normal range at Screening had low values at Day 14, while one-third of subjects with low values at Screening increased to values within normal range by Day 14. However, meaningful conclusions cannot be drawn regarding these shifts due to the small numbers of subjects in each age group. None of the values outside of normal range at any timepoint were considered to be clinically significant by the investigator.

There were no individual clinically significant laboratory abnormalities during the study.

25-hydroxy Vitamin D

The levels of 25-hydroxy Vitamin D (25 (OH) D) were assessed at Screening only.

Pharmacodynamic Assessments

A secondary objective of this study was to assess the effect of calcitriol 3 mcg/g ointment on calcium homeostasis. Analytes from collected serum and urine were evaluated to assess for any impact of calcitriol treatment on calcium metabolism. Serum (non-fasting) calcium, albumin, phosphorus, intact PTH, and urine calcium and creatinine were measured. No major changes in PD parameters were observed.

Pharmacodynamic values over time

Serum

There were few shifts among PD serum parameters during the study. The majority (>83%) of subjects had normal serum values at Baseline that remained normal at the Day 14 assessment. Most values that were outside the normal range at Screening (low or high) remained the same at Day 14.

Urine

Of the subjects with calculated calcium/creatinine ratio, all had normal values at Baseline that remained normal at Day 14.

Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, temperature, and respiratory rate) and weight were evaluated at Screening, Baseline, and Day 14. Small changes in vital signs and weight were observed at each timepoint within each group, and were comparable between the 2 age groups. Mean change in heart rate from Baseline was notably greater for 2- to 6-year-olds compared with that of 7- to 12-year-olds.

Pregnancies
No pregnancies occurred during this study.

PK Findings
From Clinical Pharmacology Review by Cindy (Liping) Pan, Ph.D., dated 3/24, 2020: "Although the applicant did not meet the requirement of assessing PK in 9 subjects under PMR#5; the lack of any systemic safety signals and furthermore lack of any increase in systemic concentrations of calcitriol from baseline in pediatric subjects aged 2 years to 12 years under maximal use conditions suggests that the currently available PK data in 18 subjects (17 subjects from PMR # 2 and 1 subject from PMR # 5) aged 2 years to 12 years is considered adequate to release the Applicant from PMR #2 and PMR# 5."

13.1.4.2.3. Analysis of Submission-Specific Safety Issues

DISCUSSED with Main section of review

13.2. PMR Final Study Report PMR 973-3/RD.06.SRE. 18132

13.2.1. Clinical and Evaluation

13.2.1.1. Sources of Clinical Data and Review Strategy

13.2.1.1.1. Table of Clinical Studies

To address PMR 973-3 and support the use of Vectical (calcitriol) Ointment 3mcg/g in younger pediatric patients with (mild to moderate) plaque psoriasis (of the body) the Applicant conducted a study (RD.06.SRE.18132) entitled, "A multicenter, randomized, double blind, parallel group, vehicle controlled study of the safety and efficacy of Calcitriol 3 µcg/g ointment applied twice daily for 8 weeks in pediatric subjects (2 to 12 years of age) with mild to moderate plaque psoriasis." The final study design (Amendment 1, September 10, 2014) is summarized below:

Table 39: Clinical Trial RD.06.SPR.18132

Trial Identity	Trial Design	Regimen / Schedule / Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects	Study Population	No. of Centers and Countries
Studies to Support Safety							
RD.06.SPR.18132	Multicenter, randomize	Twice daily,	Compare the safety and efficacy of	Up to 8 weeks/ 4	19 enrolled	Pediatric, ages 2 to 12 years	13 centers total; US

Trial Identity	Trial Design	Regimen / Schedule / Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects	Study Population	No. of Centers and Countries
	d, double-blind, vehicle controlled, safety and efficacy	For up to 8 weeks	calcitriol 3 mcg/g ointment versus its vehicle, assess effect of calcitriol vs vehicle on calcium metabolism	weeks follow-up		inclusive, plaque psoriasis involving 3 to 35% of body, excluding face and scalp (at least 5% of BSA treated)	(6), and foreign (5); Canada, Italy, Belgium, Spain, Hungary

Abbreviations: BSA = Body Surface Area
Source: Reviewer's Table

13.2.1.1.2. Review Strategy

The focus of this review was the efficacy and local and systemic safety of Vectical (calcitriol) Ointment 3mcg/g which included pharmacodynamic findings.

Data Sources
The sources of data used for the evaluation of the efficacy and safety of Vectical (calcitriol) Ointment 3mcg/g for the proposed indication included a final abbreviated clinical study report submitted by the Applicant, and literature references.

This application was submitted in electronic common technical document (eCTD) format and was entirely electronic. The electronic submission including the protocol and clinical study report are located at the following network path:
\\CDSESUB1\evsprod\NDA022087\022087.enx

Data and Analysis Quality
In general, the data submitted by the Applicant to support the safety of Vectical (calcitriol) Ointment 3mcg/g for the proposed indication appear adequate. The number of subjects evaluated for efficacy was too small to draw meaningful conclusions.

13.2.1.2. Review of Relevant Trial

13.2.1.2.1. Study Design and Endpoints

Clinical Trial RD.06.SPR.18132
Objectives:
Primary objectives
To compare the safety and efficacy of up to 8 weeks of treatment with c calcitriol 3 mcg/g ointment versus its vehicle, when used twice daily, without occlusion, to treat children aged 2 to 12 years, with plaque psoriasis (excluding the face and scalp).

To evaluate the effect of twice daily use of calcitriol 3 mcg/g ointment versus vehicle on calcium metabolism in children aged 2 to 12 years with plaque psoriasis (excluding face and scalp).

Study Population
The study was planned to screen approximately 400 pediatric subjects in order to achieve a minimum of 300 randomized subjects. However, due to slow enrollment the study was closed to enrollment in (b) (6). At the time of closing, 29 subjects were screened; 19 subjects were randomized into the study, 8 in the calcitriol 3 mcg/g ointment group and 11 in the Vehicle group.

The key entry criteria that defined the study population for the final version of the protocol are as follows:
Key Inclusion Criteria

8. Male or female pediatric subjects, 2 to 12 years of age (inclusive), at Screening.
9. The subject has a clinical diagnosis of stable mild to moderate plaque psoriasis with an Investigator's Global Assessment (IGA) score of 2 or 3 at Screening and at Baseline.
10. Female of non-childbearing potential (pre-menarcheal).
11. Female of childbearing potential with a negative urine pregnancy at the Screening and Baseline visits.
12. Female of childbearing potential who:
    a) Has been strictly abstinent 1 month prior to baseline and agrees to continue for the duration of the clinical trial,
    b) And/or agrees to use a highly effective and approved contraceptive method(s) during the study and for at least 1 month after the last study drug application. A highly effective method of contraception is defined as:
        - combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month prior to baseline.

Key Exclusion Criteria

1. Subjects with guttate psoriasis, erythrodermic psoriasis, or active infection (i.e., an infection associated with fever, swollen lymph nodes, and/or signs of localized

inflammation of tissue and/or joints) Note: allergic or vasomotor rhinitis is not exclusionary.

2. Any newly diagnosed genetic or congenital condition, uncontrolled or serious disease, or any medical or surgical condition that may either interfere with the interpretation of the clinical trial results, and/or put the subject at significant risk (according to Investigator's judgment) if the subject continues to participate in the clinical trial.
3. Known or suspected allergies or sensitivities to any components of any of the study drugs (see Investigator's Brochure/Product label).
4. Subjects who have participated in a clinical drug or device research study within the last 30 days, except for study SPR.18104. Subjects who participated in the pediatric PK SPR.18104 study, may be included in the study if:
    a) They have had no clinically significant safety and/or laboratory issues in Study SPR.18104, per Investigator's discretion.
    b) They have completed a 2-week wash-out of the calcitriol 3 mcg/g ointment received during SPR.18104 participation.
    c) They meet all Inclusion and no Exclusion criteria of SPR.18132.
5. The subject has received, applied, or taken the following treatments within the specified time frame prior to the Baseline visit:

Table 40: Topical Treatments Received, Applied, or Taken by the Subjects Prior to the Baseline Visit

TOPICAL treatments:	
▪ Corticosteroids or topical immunomodulators	2 weeks
▪ Tar (on areas to be treated with study drug)	2 weeks
▪ Vitamin D derivatives	2 weeks
▪ Vitamin A derivatives	2 weeks
▪ Intralesional Steroids Injection	4 weeks

Table 41: Systemic Treatments Received, Applied, or Taken by the Subjects Prior to the Baseline Visit

SYSTEMIC treatments:

▪ Homeopathic or herbal preparations	1 week
▪ Calcium containing products	2 weeks
▪ Immunomodulators and biologics known to affect psoriasis	4 weeks
▪ Corticosteroids or ACTH analogs	4 weeks
▪ Phototherapy/PUVA therapy	4 weeks
▪ Laser Therapy	4 weeks

6. The subject has hypercalcemia (serum albumin-adjusted calcium above the upper normal range) at Screening.
7. The subject has urinary calcium: creatinine ratio above the upper normal range at Screening.
8. The subject has history or signs and symptoms of urolithiasis.
9. Subjects with known or suspected disorders of calcium metabolism.
10. Subjects with liver dysfunction, defined as laboratory AST or ALT >2x ULN or total bilirubin >1.5x ULN.
11. Subjects with creatinine clearance <85mL/min per 1.73 m2 at Screening (Shull et al. 1978).
12. Subjects with concomitant medical or dermatological disorder(s), which might preclude accurate evaluation of the psoriasis.
13. Subjects with underlying systemic or other dermatological conditions that require the use of systemic supplements of calcium or vitamin D. (Subjects taking oral calcium and Vitamin D for prophylactic purposes must be on a stable dose for at least 4 weeks prior to Screening and are not to exceed the Recommended Daily Allowance for calcium (1,000 mg) or Vitamin D (600 IU).
14. The Subject has Vitamin D deficiency (25(OH)D <20 ng/mL) at Screening. (Note: Subjects with 25(OH)D <20 ng/mL at Screening may undergo re-screening after 4 weeks of Vitamin D deficiency treatment to determine eligibility.)
15. The subject is planning excessive exposure to the sun or ultraviolet light during the study (i.e. natural or artificial sunlight, including tanning booths and sun lamp).
16. Subjects with clinically significant blood loss within 3 months prior to Screening, per Investigator's discretion.
17. The subject has clinically significant abnormal values of the safety laboratory parameters at Screening.
18. The subject has secondary hyperparathyroidism (parathyroid hormone [PTH] above Upper Limit of Normal) at Screening.

Study Design
This is a multicenter, randomized, vehicle-controlled, double-blind parallel group study.

Qualified subjects were randomized to receive either calcitriol 3 mcg/g ointment or its vehicle for a period of 8 weeks. The subject or subject's parent/legal guardian applied a thin film of study drug as needed to cover all involved areas twice daily (morning and evening), without exceeding a maximum of 0.5 g/kg of body weight or 28 g daily (whichever is the lower).

The first dose was applied under the supervision of the study staff, at the Investigative site. The application was to be made either by the subject's parent/legal guardian or by the subject under parent/legal guardian's supervision for the remainder of the study.

Subjects visits were at Screening, Baseline, Weeks 2, 4, 6, 8/ET, and 12. Follow-up visits were conducted as described in the study flow chart (Table 32). A visit window of ±5 days was allowed for Baseline, and a visit window of ±3 days will be allowed at the Weeks 2, 4, 6, 8/ET, and 12 visits.

Concomitant Medications
Authorized Therapy
Therapy considered necessary for the subject's safety and welfare was permitted at the Investigator's discretion. Moisturizers use was documented in the eCRF. Subjects were permitted to use medicated shampoos that do not contain corticosteroids or vitamin D derivatives to treat scalp psoriasis. Tar products could be used on the face and scalp areas.

Subjects taking oral calcium and vitamin D for prophylactic purposes were to be on a stable dose for at least 4 weeks before Screening and were not to exceed the Recommended Daily Allowance for calcium (1,000 mg) or Vitamin D (600 IU). Subjects were to remain on the same dose throughout the course of the study.

Prohibited Therapies
Certain therapies were prohibited because they may interfere with the efficacy and/or safety (for example interaction with the study drug(s) metabolism) assessment of the study drug(s): See exclusion criteria.

Subjects enrolled in this study were not to receive any treatment impacting on calcium homeostasis other than the drug, (calcitriol 3 mcg/g) ointment under investigation

Drugs that may cause alterations in serum or urine calcium levels
The Applicant provided a list in an Appendix to the protocol.

Vitamin D and Vitamin D analogs
The Applicant provided a list in an Appendix to the protocol.

Objectives and Related Endpoints

Objectives

- To compare the safety of up to 8 weeks of treatment with calcitriol 3 mcg/g ointment versus its vehicle, when applied twice daily, without occlusion, for the treatment of children aged 2 to 12 years, with plaque psoriasis (excluding the face and scalp).
- To evaluate the effect of twice daily applications of calcitriol 3 mcg/g ointment versus vehicle on calcium metabolism in children aged 2 to 12 years with plaque psoriasis (excluding face and scalp).
- To compare the efficacy of up to 8 weeks of treatment with calcitriol 3 mcg/g ointment versus its vehicle, when applied twice daily, without occlusion, to treat children aged 2 to 12 years, with plaque psoriasis (excluding face and scalp).

Table 42: Study Sites and Enrollment (Safety Population)

Site Number	Principal Investigator	Location	Calcitriol	Vehicle	Subjects Enrolled (N)
			8	11	Total 19
5447	Sofie De Schepper	Gent, Belgium		1	1
5448	Pierre-Dominique Ghislain	Bruxelles, Belgium	1	1	2
5893	Zsuszanna Szalai	Budapest, Hungary	2	1	3
5895	Giuseppi Fabrizi	Parma, Italy		1	1
5896	Maria Asuncion Vicente	Esplugues de Llobregat, Spain	1	1	2
8076	Michael Jarrat	Austin, TX		1	1
8154	Jill Keddy-Grant	Winnipeg, Canada		1	1
8183	Adelaide Herbert	Houston, TX	1		1
8333	Elizabeth Tichy	San Antonio, TX		1	1
8412	Steven Cohen	Bronx, NY	1	1	2
8444	Douglass Forsha	West Jordan, Utah		1	1
8456	David Stoll	Beverly Hills, CA	2	1	3

Source: Compiled from Applicant Table 14.1.2, Abbreviated Clinical Study Report, RD.06.SPR.18132 and SDN 365 92/27/2020, NDA 22087 (response to Information request)

Table 43: Schedule of Assessments: SPR 18132

	CLINICAL STUDY VISITS						
	Screening Period[14]	TREATMENT PHASE[10]					Follow-up Period
Procedures	Screening[11] (Day -14) V1	Baseline[17] (Day 0) V2	Week 2[6] V3	Week 4[6] V4	Week 6[6] V5	Week 8[6] / Early Termination visit V6	Week 12[6, 12] V7
Informed Consent / Assent Form / HIPAA /PIPEDA	X						
Demographics	X						
Medical History	X						
Previous Therapies/Procedures[8]	X						
Vital Signs / Physical Examination[1]	X					X	X
Inclusion/Exclusion Criteria	X	X[2]					
Urine Pregnancy Test (post-menarcheal)	X	X		X		X	X
Record % Body Surface Area involved (excluding face and scalp)	X	X	X	X	X	X	X
Pharmacodynamic Serum[9]	X		X	X	X	X	X
Pharmacodynamic Urine[9] (D) Dispensing collection container	X		D[15]	X	D[15]	X/D	X
Routine Blood chemistry and hematology	X			X		X	X[13]
Routine Urinalysis	X		X	X	X	X	X
25(OH)D & 1,25 (OH)2D	X			X		X	X[13]
IGA	X	X	X	X	X	X	X
Pruritus	X	X	X	X	X	X	X
Investigational product(s) Dispensing (D) and Accountability (A)[3]		D[16]	D/A	D/A	D/A	A	

	CLINICAL STUDY VISITS						
	Screening Period[14]	TREATMENT PHASE[10]					Follow-up Period
Procedures	Screening[11] (Day -14) V1	Baseline[17] (Day 0) V2	Week 2[6] V3	Week 4[6] V4	Week 6[6] V5	Week 8[6] / Early Termination visit V6	Week 12[6, 12] V7
Adverse Event information collection[7]	X	X	X	X	X	X	X
Concomitant Therapies/Procedures[8]	X	X	X	X	X	X	X
Moisturizer and cleanser dispensed[5]		X					
Exit Form[4]						X[12]	X

1 Physical Examination included: weight and review of systems: skin, cardiovascular, respiratory, abdomen, head and neck, musculoskeletal, neurological, lymph nodes and psychological. Height was evaluated at Screening visit only. Vital Signs included blood pressure and pulse rate.
2 Reconfirmed subject met inclusion/exclusion criteria.
3 Total amount of Investigational product applied did not exceed 0.5 g/kg of body weight or 28g per day (whichever was the lower). First application was made at Baseline under the supervision of the investigator or designee, who also dispensed dosing calendar. Subject and/or parent/guardian recorded daily administration on calendar. Dosing calendar was checked at each post Baseline visit by study staff.
4 Or at any time in case of early termination.
5 Cetaphil® Moisturizing cream and Cetaphil® Gentle Skin Cleanser or equivalents were provided by the Applicant.
6 +/- 3 day window.
7 Events occurring after the Informed Consent Form and Assent Form (when applicable) had been signed were recorded as AEs in the eCRF. Asked open-ended question assessing for symptoms of kidney stones (urolithiasis) at each scheduled visit.
8 Any therapy or medication other than study ointment was noted on the Previous or Concomitant Therapy Form.
9 PD Serum (non-fasting): calcium, phosphorus, albumin (in order to calculate the serum albumin-adjusted calcium) and parathyroid hormone (PTH). PD Urine: Urine calcium and creatinine on 24-hour urine specimen, when feas ble, or fasting (4 hours) random urine sample in order to calculate Urine calcium: creatinine ratio.
Subjects who were toilet-trained were actively encouraged to complete 24-hour urine collection. At Screening, urine collection container/materials were given to the subject/subject's parent/legal guardian with the instruction to start collecting urine as of this visit and to bring the container back after the 24-hour/4-hour collection, the results were available for the Baseline visit.
10 Unscheduled visits: When necessary and exceptionally, unscheduled visits could take place (because of either an AE needing a specific treatment, or AE leading to withdrawal from the study).
11 Subjects could re-screen one time with written approval from the Applicant prior to re-entry into the study. For these subjects the screening period may be >2 weeks therefore overall study participation may be >14 weeks.

12 Subjects who met all inclusion criteria and no exclusion criteria and had no clinically significant safety issues could enroll in the SPR.18131 Long-Term Safety Study at sites participating in both clinical studies. Subjects enrolling into the Long-Term Safety study SPR.18131 completed the Week 8 visit for SPR.18132 and proceeded to the Baseline visit for the Long-Term Safety Study after receipt of all required lab results and confirmation that the subject met all inclusion and no exclusion criteria. Only subjects not rolling over into SPR.18131 must have completed the Week 12 visit and evaluations.
13 Lab assessment was only done at the Week 12 visit if results were abnormal at the Week 8/ET visit. Subjects enrolling into SPR.18131 with abnormal Week 8 labs were followed in SPR18131 and did not require the Week 12 lab assessment.
14 Subjects who completed the SPR.18104 PK study and had no clinically significant safety issues could screen for this study. Subjects must have met all Inclusion / Exclusion Criteria and complete a 2 week wash-out of the calcitriol 3 mcg/g ointment received during SPR.18104 participation.
Source: Abbreviated Clinical Study Report for RD.06.SRE.18132, section 9.1, pages 5,6.

Data Analysis
The ITT Population was defined as comprising all subjects who were randomized and to whom study medication was dispensed (19, but only 18 completed trial). Subjects in the ITT Population were to be analyzed according to the treatment group they are randomized to.

The Safety Population was defined as comprising the ITT Population subjects who applied the study drug(s) at least once (19). In practice, only the subjects who returned their study drug(s) unopened were to be excluded from the Safety Population. All safety data was to be summarized based on the Safety Population.

Protocol Amendments
The original protocol RD.06.SPE.18132, dated March 18, 2014, was amended 1 time.

Amendment 1 (dated September 10, 2014)
Significant changes included:

- Synopsis - Reduction of number of sites and clarification of study regions
- Synopsis and Section 4 - update of clinical trial duration.
- Synopsis and Section 9.1.4.5 – update statistical section for secondary efficacy endpoints
- Table 43Schedule of assessments Section 3 Clinical Description and Section 4 Clinical Trial Duration and Termination – Baseline time window
- Section 5.5.4 – Clarification of authorized medications and their documentation.
- Section 7.2.2 Laboratory safety tests, Urine Pregnancy Test – Addition of language related to female subjects getting first period during the study.

*additional editorial edits made for clarification of protocol wording and understanding.

13.2.1.3. Results of Efficacy Assessment

Efficacy results were summarized descriptively and graphically versus time and analyzed for Week 8 for the ITT population. Efficacy analyses were repeated for the PP population. For subjects with missing data, the last observation carried forward approach was used as the primary method for analyzing primary and secondary efficacy endpoints. All efficacy data summarized in the abbreviated clinical study report were based on last observation carried forward analyses.

The study enrollment was stopped before achieving the planned 300 subjects. Therefore, the small number of subjects enrolled made meaningful interpretation of the efficacy data difficult.

The primary efficacy parameter was the success rate at Week 8, defined as the proportion of subjects with a minimum improvement of 2 grades from baseline in the IGA score and a severity rating of 0 (clear) or 1 (almost clear). The success rate was not statistically significantly different (p =0.370) for the calcitriol 3 mcg/g ointment group compared with the Vehicle group, with 3 subjects (37.5%) of the calcitriol 3 mcg/g ointment group achieving success and 7 subjects (63.6%) of the Vehicle group. The observed success rate at Week 8 for the ITT population were similar to those for the PP population.

Summary analyses of the success rate by gender, race, age group, country, and analysis center for the ITT population were not performed because of the small numbers of subjects in each treatment group.

Efficacy Endpoints

- Primary Efficacy Variable Endpoint
  The primary endpoint variable is success rate defined as the percentage of subjects with an IGA of 0 (clear) or 1 (almost clear), and at least a 2-grade improvement from baseline.

Secondary Efficacy Endpoints/Variables

- Change from Baseline in Pruritus
- Change from Baseline in % body surface area (BSA)

The IGA was to be evaluated at each visit on a 0 to 4-point scale. The IGA was to be performed by a Board-Certified Dermatologist or any other regional equivalent, unless otherwise allowed by the Applicant. The definitions used to score IGA are in the table below:

Table 44: Investigator's Global Assessment

0	**Clear**	No signs of psoriasis except for residual hypopigmentation / hyperpigmentation
1	**Almost Clear**	Just perceptible erythema, no induration, and no scaling
2	**Mild**	Mild erythema, no induration, and mild or no scaling
3	**Moderate**	Moderate erythema, mild induration, and mild or no scaling
4	**Severe**	Severe erythema, moderate to severe induration, and scaling of any degree

Abbreviations: IGA = Investigator's Global Assessment

Pruritus was to be evaluated at each visit and scored on a 0 to 4-point scale. The following definitions were to be used to score Pruritus:

Table 45: Pruritus Assessment
Pruritus: an itching sensation.

0	**None**	No-itching
1	**Mild**	Slight itching, not really bothersome
2	**Moderate**	Definite itching that is somewhat bothersome without loss of sleep
3	**Severe**	Intense itching that has caused pronounced discomfort, night rest interrupted
4	**Very Severe**	Very severe itching that has caused pronounced discomfort during the night and daily activities

Percent Body Surface Area involved was to be assessed using the methodology shown in Section 13.3, Appendix 3 of the protocol, based on 'rule of nines.'

Secondary endpoints
Secondary efficacy analyses included evaluation of pruritus at each visit, with scoring on a 0 to 4 point scale, and analysis of the change from baseline. The majority of ITT population subjects in both groups had a score of 0 (none) by Week 8, 6 subjects (75%) and 7subjects (63.6%) for the calcitriol 3 mcg/g ointment group and Vehicle group, respectively. The mean change from baseline at Week 8 was -1.4 for the calcitriol 3 mcg/g ointment group and -0.7 for the Vehicle group.

An additional secondary efficacy endpoint was the evaluation of the change from baseline in the percentage BSA involved at Week 8. Subjects randomized to the calcitriol 3 mcg/g ointment group showed a mean reduction in percentage BSA involvement of -1.5 at 8 weeks compared with -3.4 for the Vehicle group.

13.2.1.4. Review of Safety

13.2.1.4.1. Safety Review Approach

The review of the safety of Vectical (calcitriol) Ointment 3 mcg/g in trial RD.06.SRE.18132, pediatric population, 2 to 12 years (inclusive) with mild to moderate plaque psoriasis, included analyses of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, treatment emergent adverse reactions and AEs associated with product class, vitamin D analogs.

13.2.1.4.2. Review of the Safety Database

Disposition of Subjects
A total of 29 subjects were screened from 13 sites in the US, Canada, and Europe. Ten subjects were considered screening failures based on eligibility criteria (n=6), the subject's request (n=2), or "other" (n=2) The 19 randomized subjects received either calcitriol 3 mcg/g ointment

(n=8) or vehicle (n=11) See Table 46 below. The ITT and Safety populations include all randomized subjects.

Table 46: Disposition of Subjects

	Calcitriol (N=8) N (%)	Vehicle (N=11) N (%)	Total (N=19) N (%)
ITT population	8 (100.0)	11 (100.0)	19 (100.0)
PP population	5 (62.5)	9 (81.8)	14 (73.7)
Safety population	8 (100.0)	11 (100.0)	19 (100.0)
Number of subjects who completed the study (ITT Population)	8 (100.0)	10 (90.9)	18 (94.7)
Number of subjects who discontinued	0	1 (9.1)	1 (5.3)
Reason for discontinuation			
- Subject's Request[a]	0	1 (9.1)	1 (5.3)

a) The subject refused blood test at the Week 8 visit; the skin signs of the scalp worsened
Source: Table 3: Abbreviated Clinical Study Report, RD.06.SRE.18132, (IND 062151 Seq 0087), p 11 of 46

Table 47: Summary of Medication Exposure and Compliance (Safety Population)

	Statistics	Calcitriol (N= 8)	Vehicle (N= 11)	Total (N= 19)
Actual study drug exposure in days	N	8	11	19
	Mean	55.0	56.0	55.6
	SD	5.3	1.3	3.5
	Median	57.0	56.0	57.0
	(Min,Max)	(42,58)	(54,58)	(42,58)
Actual study drug exposure in doses	N	8	11	19
	Mean	106.5	109.6	108.3
	SD	10.4	3.9	7.3
	Median	109.5	110.0	110.0
	(Min,Max)	(83,114)	(103,114)	(83,114)

Note: Actual study drug exposure in days = Treatment duration (days) – number of days with no applications in both PM and AM.
Actual study drug exposure in doses = Treatment duration *2 – number of missed doses.
Source: Abbreviated Clinical Study Report, RD.06.SRE.18132, Table 6, section 12.1.2, page 18 of 46.

The mean of number of doses used by subject is 106.5 in the calcitriol 3 mcg/g ointment group and 109.6 doses in the Vehicle group (Table 47). This dosing represented nearly 100% compliance (mean of 96.28% for the calcitriol 3 mcg/g ointment group and 97.41% for the Vehicle group.

[A thin film of study drug was applied as needed to cover all involved areas twice daily (morning and evening), without exceeding a maximum of 0.5 g/kg of body weight or 28 g daily

(whichever is the lower)]. (Weight in grams of study drug applied is not described in the study report.)

Characteristics of the Safety Population

Demographic and Baseline Characteristics

All data was summarized and analyzed based on the Safety population, which comprised all enrolled subjects who received at least 1 application of the study medication.

Demographic data were similar for the 2 treatment groups. Of the 19 subjects randomized, 12 (63.2%) were females; 17 (89.5%) were White. The mean age was similar in both treatment groups: 9.6 years for subjects treated with calcitriol 3 mcg/g ointment and 9.8 years for subjects treated with the vehicle. The majority of subjects randomized were between 7 and 12 years of age (18 [94.7%]). Demographic and baseline characteristics are summarized for the ITT population (same as safety population) in Table 48 below.

Table 48: Summary of Subject Demographics and Baseline Characteristics (ITT Population)

	Statistics	Calcitriol (N= 8)	Vehicle (N= 11)	Total (N= 19)
Age	N	8	11	19
	Mean	9.6	9.8	9.7
	SD	1.8	1.8	1.8
	Median	9.5	10.0	10.0
	(Min,Max)	(6,12)	(7,12)	(6,12)
Age Group	2 - 6	1 (12.5%)		1 (5.3%)
	7 - 12	7 (87.5%)	11 (100.0%)	18 (94.7%)
	Total	8	11	19
Age for EudraCT	Children (2-11 years)	7 (87.5%)	9 (81.8%)	16 (84.2%)
	Adolescents (12-17 years)	1 (12.5%)	2 (18.2%)	3 (15.8%)
	Total	8	11	19
Sex	Male	3 (37.5%)	4 (36.4%)	7 (36.8%)
	Female	5 (62.5%)	7 (63.6%)	12 (63.2%)
	Total	8	11	19
Race	White	6 (75.0%)	11 (100.0%)	17 (89.5%)
	Black or African American	1 (12.5%)		1 (5.3%)
	Asian	1 (12.5%)		1 (5.3%)
	Total	8	11	19
Ethnicity	Hispanic or Latino	2 (25.0%)	3 (27.3%)	5 (26.3%)
	Not Hispanic or Latino	6 (75.0%)	8 (72.7%)	14 (73.7%)
	Total	8	11	19

BSA Involved at baseline	N	8	11	19
	Mean	7.0	8.0	7.6
	SD	6.5	5.6	5.9
	Median	6.0	10.0	7.0
	(Min,Max)	(2,22)	(1,16)	(1,22)
Maximal daily dose (g)	N	8	11	19
	Mean	17.55	20.20	19.08
	SD	3.34	6.34	5.34
	Median	16.20	20.00	19.95
	(Min,Max)	(14.0,22.5)	(11.0,28.0)	(11.0,28.0)
Maximal Dose per Application (g)	N	8	11	19
	Mean	8.791	10.105	9.552
	SD	1.658	3.170	2.664
	Median	8.165	10.000	10.000
	(Min,Max)	(7.00,11.25)	(5.50,14.00)	(5.50,14.00)

Abbreviations: Min = minimum; Max = maximum; SD = standard deviation; BSA = body surface area
Source: Abbreviated Clinical Study Report, RD.06.SRE.18132, Table 4, section 11.1., page 13 of 46.

Concomitant Medications

Concomitant therapies were defined as follows: any existing therapies ongoing at the time of the Screening visit, any changes to existing therapies (such as changes in dose or formulation) during the course of the clinical trial, or any new therapies received by the subject since the Screening visit.

All 8 (100%) subjects in the calcitriol 3 mcg/g ointment group and 10 (90.0%) subjects in the Vehicle group reported concomitant therapies. The most frequently reported concomitant therapy was for the use of Cetaphil (class of "other emollients and protective"), with 5 (62.5%) and 5 (45.5%) subjects for the calcitriol 3 mcg/g ointment group and the Vehicle group, respectively. The majority of subjects, 6 (75%) in the calcitriol 3 mcg/g ointment group and 9 (81.8%) in the Vehicle group, had used a previous therapy. Overall, the most common classes of previous therapies were Group III or IV corticosteroids and other anti-psoriatics for topical use.

Protocol Deviations

At least one major protocol deviation leading to exclusion from the PP population was reported in 5 (26.3%) subjects. Of these 5 subjects, 3 (37.5%) received calcitriol 3 mcg/g ointment and 2 subjects (18.2%) received vehicle.

These deviations were the result of issues with the informed consent form (3 deviations), laboratory specimens (2 deviations), or the collection of a laboratory specimen that was never sent to the lab (1 deviation).

Table 49: Protocol Deviations Occurring in ≥1 Subject

Deviation	No. (%) of Subjects	
	calcitriol	vehicle
ICF Issue	2 (25.0%)	1(9.1%)
Laboratory Specimens	1 (12.5%)	0
Other: Lab specimen collected Week 12 but not sent to lab		1(9.1%)
Total:	3 (37.5%)	2 (18.2%)

Abbreviations: ICF = intermediate care facility
Source: Adapted from table 14.1 Clinical Study Report RD.06.SPR.18132, section 14.1, p. 5 of 13.

Adequacy of the Safety Database
The Applicant did not achieve enrollment total desired for PMR 973-3 (approximately 400 pediatric subjects with plaque psoriasis to allow for a minimum of 300 subjects to complete the study). (Due to slow enrollment the study was closed to enrollment in December 2015. At the time of closing, 29 subjects were screened; 19 subjects were randomized into the study, 8 in the calcitriol 3 mcg/g ointment group and 11 in the Vehicle group.)

13.2.1.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
Overall, the quality of the data submitted was adequate to characterize the safety of Vectical (calcitriol) Ointment 3mcg/g applied twice daily for up to 8 weeks in pediatric subjects (2 to 12 years inclusive). We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events
Adverse events were coded using the Medical Dictionary for Regulatory Activities version 15.0.

According to the protocol, AEs could include events based on laboratory values. All out of range laboratory values obtained after Screening were to be assessed for clinical significance by an Investigator (physician) or another medically qualified Investigator and reported as an AE, if both of the following conditions were met:

- The abnormality suggested a disease and/or organ toxicity, and/or was considered pathological

AND

- This abnormality was not present at Screening or was assessed as having worsened since the Screening visit.

An out-of-range laboratory value that was identified as clinically significant and related to the study drug(s) was considered by the Applicant to be an Adverse Event of Special Interest (AESI).

In this study, an AESI was defined as:

- Typical clinical signs and symptoms consistent with Vitamin D toxicity:
  - polyuria, polydipsia

- clinically significant mental status changes

- Out-of-range laboratory result identified as clinically significant and related to the study drug
- Dermatological events such as severe skin irritation, as well as severe local and/or generalized pruritus,
- Suspected skin sensitization (contact allergy)
- Cutaneous AE assessed as related to the investigational product and leading to discontinuation of the investigational product, including temporary discontinuations.

Routine Clinical Tests
Investigators monitored adverse events, physical examination, vital signs, and laboratory parameters.

The following safety clinical laboratory testing was performed:
Hematology

- White blood cell count with differential, red blood cell count, hemoglobin, hematocrit, mean cell volume, and platelet count

Blood chemistry (non-fasting)

- Total protein, alanine aminotransferase (serum glutamate pyruvate transaminase), aspartate aminotransferase (serum glutamic oxalacetic transaminase), alkaline phosphatase, blood urea nitrogen, creatinine, and bilirubin (total and conjugated).

Urinalysis

- A semi-quantitative urinalysis was performed. The following parameters were evaluated: glucose, ketones, blood, proteins, leukocytes, and nitrites.

Pharmacodynamic parameters

- Serum (non-fasting): calcium, phosphorus, albumin (in order to calculate the serum albumin-adjusted calcium), PTH
- Urine: Calcium and creatinine (in order to calculate urine calcium:creatinine ratio) on 24-hour urine specimens, when feasible, or fasting (4 hours) urine samples. Subjects that are toilet-trained were actively encouraged to complete the 24-hour urine collection. In case of Ca:Cr ratio above the normal range on a 4 hour fasting collection, the dosing should have been repeated on a 24-hour urine collection whenever possible.

Other Assessments included

- 25(OH) D (at Screening) [25-hydroxyvitamin D = prehormone]
- 1,25 (OH)2D
- Urine Pregnancy (Test for post menarcheal females)

13.2.1.4.4. Safety Results

Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events
There were no deaths, no SAEs, or AEs that led to premature withdrawal from the trial.

Adverse Events
Overall 14 subjects (73.7%) reported at least 1 AE; 6 subjects (75.0%) reported at least 1 AE while receiving Vectical Ointment and 8 subjects (72.7%) reported at least 1 AE while receiving vehicle. Four subjects in the Vectical Ointment group reported 1 cutaneous AE each, 2 of which were considered related to treatment (both AEs of skin irritation), compared with 3 subjects of the Vehicle group who each reported 1 cutaneous AE, with 1 of those events considered treatment-related (worsening pruritus). The Vehicle group subject with the AE of worsening pruritus also had treatment-related AEs of hypercalciuria and urine calcium/creatinine ratio increased. In addition to these related events, one other Vehicle group subject had an AE considered related to investigational product (urinary tract infection). The treatment-related AE of worsening pruritus in the Vehicle group was considered severe in intensity. No subjects in the Vectical Ointment group reported a severe AE.

AESIs were predefined for this study and all that were reported were assessed as related to investigational product. One (1, 12.5%) subject in the Vectical Ointment group experienced 1 AESI of skin irritation compared with 2 (18.2%) subjects in the Vehicle group who experienced a total of 4 AESI: urinary tract infection, urine calcium/creatinine ratio increased, hypercalciuria, and pruritis.

A similar proportion of subjects in both treatment groups experienced AEs. Adverse events were most common in the system organ class (SOC) of infections and infestations (Vectical Ointment: 25%; Vehicle: 54.5%). Two or more subjects of the Vectical Ointment group experienced AEs for the following system SOCs: gastrointestinal disorders, infections and infestations, and skin and subcutaneous tissue disorders. Two or more subjects from the Vehicle group also reported AEs for infections and infestations and skin and subcutaneous tissue disorders, in addition to the SOCs of investigations and respiratory, thoracic and mediastinal disorders.

For the skin and subcutaneous tissue disorders SOC, 3 subjects experienced AEs related to local tolerance, 1 subject in the Vehicle group had worsening pruritus and 2 subjects in the Vectical Ointment group had AEs of skin irritation. All 3 of these events were considered related to investigational product.

Table 50: AEs by SOC and PT (Safety Population)

		Calcitriol (N=8)		Vehicle (N=11)		Total (N=19)	
		Event n	Subject[a] N (%)	Event n	Subject[a] N (%)	Event n	Subject[a] N (%)
ANY ADVERSE EVENTS		**10**	**6 (75.0)**	**18**	**8 (72.7)**	**28**	**14 (73.7)**
Gastrointestinal disorders	**ALL**	**3**	**2 (25.0)**	**0**	**0**	**3**	**2 (10.5)**
	Abdominal pain upper	1	1 (12.5)	0	0	1	1 (5.3)
	Diarrhoea	2	1 (12.5)	0	0	2	1 (5.3)
Infections and infestations	**ALL**	**4**	**2 (25.0)**	**8**	**6 (54.5)**	**12**	**8 (42.1)**
	Conjunctivitis bacterial	1	1 (12.5)	0	0	1	1 (5.3)
	Gastroenteritis	1	1 (12.5)	0	0	1	1 (5.3)
	Laryngitis	0	0	1	1 (9.1)	1	1 (5.3)
	Lice infestation	1	1 (12.5)	0	0	1	1 (5.3)
	Molluscum contagiosum	1	1 (12.5)	0	0	1	1 (5.3)
	Nasopharyngitis	0	0	4	2 (18.2)	4	2 (10.5)
	Upper respiratory tract infection	0	0	1	1 (9.1)	1	1 (5.3)
	Urinary tract infection	0	0	1	1 (9.1)	1	1 (5.3)
	Viral infection	0	0	1	1 (9.1)	1	1 (5.3)
Injury, poisoning and procedural complications	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Arthropod bite	0	0	1	1 (9.1)	1	1 (5.3)

		Calcitriol (N=8)		Vehicle (N=11)		Total (N=19)	
		Event n	Subject[a] N (%)	Event n	Subject[a] N (%)	Event n	Subject[a] N (%)
Investigations	**ALL**	**0**	**0**	**3**	**2 (18.2)**	**3**	**2 (10.5)**
	Blood pressure increased	0	0	2	1 (9.1)	2	1 (5.3)
	Urine calcium/creatinine ratio increased	0	0	1	1 (9.1)	1	1 (5.3)
Musculoskeletal and connective tissue disorders	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Myalgia	0	0	1	1 (9.1)	1	1 (5.3)
Renal and urinary disorders	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Hypercalciuria	0	0	1	1 (9.1)	1	1 (5.3)
Respiratory, thoracic and mediastinal disorders	**ALL**	**1**	**1 (12.5)**	**2**	**2 (18.2)**	**3**	**3 (15.8)**
	Cough	0	0	2	2 (18.2)	2	2 (10.5)
	Oropharyngeal pain	1	1 (12.5)	0	0	1	1 (5.3)
Skin and subcutaneous tissue disorders	**ALL**	**2**	**2 (25.0)**	**2**	**2 (18.2)**	**4**	**4 (21.1)**
	Pruritus	0	0	1	1 (9.1)	1	1 (5.3)
	Psoriasis	0	0	1	1 (9.1)	1	1 (5.3)
	Skin irritation	2	2 (25.0)	0	0	2	2 (10.5)

Abbreviations: AE = adverse event; SOC = system organ class; PT = preferred term

Note: Adverse events are defined as events that occurred on the day of, or after, the first use of investigational product. Multiple occurrences within an SOC by a subject were counted once per SOC. Multiple occurrences of a PT by a subject were counted once per PT.
a) Number of subjects with at least 1 event
Source: Abbreviated Clinical Study Report, RD.06.SRE.18132, Table 8, section 12.2.2, page 21 of 46. (IND 062151 seq 0087)

Subgroup Analyses

Subgroup analyses were not performed because of the small numbers of subjects in the 2 treatment arms.

Adverse Reactions

Regarding adverse events related to treatment, the Investigator was asked to assess if there was a "reasonable possibility" or "no reasonable possibility" that there was a causal relationship between investigational product dosing and an AE.

In the Vectical Ointment group, 2 subjects ([(b) (6)] and [(b) (6)] experienced cutaneous AEs of skin irritation that were considered related to investigational product (Table 10 and Data Source: Table 14.3.2.12, Section 14.3).

Subject [(b) (6)] had an AE of skin irritation that occurred from study Day 43 to study Day 57, was mild in severity, and considered related to investigational product. The event resolved and was not considered serious; dosing was not changed. This event was not classified as an AESI.

For subject [(b) (6)], the skin irritation AE was assessed as mild in severity and was considered an AESI. Subject [(b) (6)] was a 6-year-old Black or African-American female who experienced the AE of skin irritation specifically in bilateral axilla which was part of the treated area, from study Day 4 to study Day 48. The reaction occurred specifically on bilateral axilla and not on other treated areas (head, neck, left and right arms, anterior and posterior trunk and left legs). This reaction was considered an AESI as it led to the temporary study drug discontinuation on axilla, but study drug was still applied on other treated areas.

In the Vehicle group, 2 subjects [(b) (6)] and [(b) (6)]) experienced non-cutaneous and cutaneous AEs of urinary tract infection, increased urine calcium/creatinine ratio, hypercalciuria, and pruritis that were considered related to investigational product as well as AESIs

Subject [(b) (6)], a 12-year-old White female: The urinary tract infection event was mild in severity, related to investigational product, not serious, and did not result in a change in dosing and did not lead to any treatment. This event was considered an AESI as it was an abnormal laboratory result identified as clinically significant and related to the study drug.

Subject [(b) (6)], an 11-year-old White male: He experienced AEs of pruritus (worsening) (Day 26 [(b) (6)] to Day 145 [(b) (6)]), hypercalciuria (Day 54 [(b) (6)] to Day 103 [(b) (6)]), and urine calcium/creatinine ratio increased (Day 54 to Day 103). The urine calcium value at AE onset was 10.73 mmol/day (reference range: 2.5 to 8.03); the urine calcium/creatinine ratio was 0.803 mmol/mmol cr (reference range: 0 to

0.621). By Day 103 (b) (6)), the calcium/creatinine ratio was within the reference range, and the calcium level was elevated (8.18 mmol/day) but not considered clinically significant. None of the AEs was considered serious; all were considered related to investigational product and to be AESIs. The 3 AEs resolved and did not result in changes in dosing. The pruritus AE was classified as severe in intensity and the other AEs were mild in intensity. During the end-of-study visit on (b) (6) the pruritus was reduced but not completely resolved, although the clinical site indicated resolution in the database for the worsening of the pruritus. Psoriasis was treated with calcipotriol 50 µg/g gel daily and betamethasone 0.5 mg/g gel since (b) (6).

Table 51: Adverse Reactions by SOC and PT (Safety Population)

		Calcitriol (N=8)		Vehicle (N=11)		Total (N=19)	
		Event n	Subject[a] N (%)	Event n	Subject[a] N (%)	Event n	Subject[a] N (%)
ANY ADVERSE EVENTS		**2**	**2 (25.0)**	**4**	**2 (18.2)**	**6**	**4 (21.1)**
Infections and infestations	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Urinary tract infection			1	1 (9.1)	1	1 (5.3)
Investigations	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Urine calcium/creatinine ratio increased			1	1 (9.1)	1	1 (5.3)
Renal and urinary disorders	**ALL**	**0**	**0**	**1**	**1 (9.1)**	**1**	**1 (5.3)**
	Hypercalciuria			1	1 (9.1)	1	1 (5.3)
Skin and subcutaneous tissue disorders	**ALL**	**2**	**2 (25.0)**	**1**	**1 (9.1)**	**3**	**3 (15.8)**
	Pruritus			1	1 (9.1)	1	1 (5.3)
	Skin irritation	2	2 (25.0)			2	2 (10.5)

Abbreviations: SOC = system organ class; PT = preferred term
Adverse events are defined as events that occurred on the day of, or after, the first use of study drug. Multiple occurrences within a System Organ Class by a subject were counted once per System Organ Class. Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.
a = Number of subjects with at least one event
Source: table 9: Abbreviated Clinical Study Report RD.06.SRE.18132, Section 12.2.3.2, IND 062151 Seq 0087, page 24 of 46.

Adverse events by severity

Most AEs were mild in intensity for either treatment group. One subject in the Vehicle group (Subject (b) (6)) experienced an AE of pruritus (worsening) that was considered severe in intensity and related to investigational product; this event was also classified as an AESI. No subjects in the Vectical Ointment group had a severe AE.

Laboratory Findings

Routine laboratory findings

Laboratory values over time

Hematology

Only one subject in the Vehicle group had a clinically significant laboratory value for a hematology parameter following treatment. In the Vehicle group, Subject (b) (6) had high leukocytes at the Week 8 visit on the same start date as an AE of urinary tract infection as well as clinically significant urinalysis results. The leukocytes were within the reference range at the Week 12 follow-up assessment even though the urinary tract infection AE was still described as ongoing. The subject was lost to follow-up after Week 12.

At Screening, one subject (b) (6)) in the Vectical Ointment group had elevated platelets that was considered clinically significant. The subject was retested at an unscheduled visit 8 days later during Screening and the platelet value was high but not considered clinically significant at that time.

Blood Chemistry

Only one subject in the Vehicle group had clinically significant laboratory values for a chemistry parameter following treatment. In the Vehicle group, Subject (b) (6) had elevated calcium and calcium/creatinine ratio in urine at Week 8.

At Screening, one subject (b) (6)) in the Vectical Ointment group had high creatinine that was considered clinically significant. The subject was retested 12 days later during the Screening period and the value was within normal at that time. The creatinine level was high at one other time point in the study (Week 4) but that finding was not considered clinically significant.

Urinalysis

Only one subject in the Vehicle group had clinically significant laboratory values for urinalysis following treatment. In the Vehicle group, Subject (b) (6) had bacteria, crystals; high epithelial cells and erythrocytes; high leukocytes (via sediment analysis and urinalysis), and occult blood and protein in urine. These clinically significant results were reported at Week 8, as well as a clinically significant leukocyte hematology assessment and the AE of urinary tract infection.

25-hydroxy Vitamin D, 1,25-Hydroxyvitamin D

The levels of 25-Hydroxyvitamin D and 1,25-Hydroxyvitamin D were also assessed during the study. The mean 25-Hydroxyvitamin D levels and 1,25-Hydroxyvitamin D levels remained stable and no clinically significant increase of calcitriol (1,25-Hydroxyvitamin D) or other laboratory parameters were observed

Pharmacodynamic Assessments

In addition to evaluation of AEs that could be possibly related to calcium metabolism, analytes from collected serum and urine were evaluated to assess for any impact of calcitriol treatment on calcium metabolism. Serum (non-fasting) calcium, phosphorus, albumin, and PTH and urine calcium and creatinine were measured.

Only one subject in the Vehicle group had laboratory values that were considered clinically significant for parameters possibly related to calcium metabolism. Subject (b) (6) experienced laboratory-defined AEs at Week 8 of hypercalciuria study Day 54 to study Day 103, (assessed as mild) and urine calcium/creatinine ratio increased study Day 54 to study Day 103 (assessed as mild) that were considered possibly related to calcium metabolism and to investigational product. At the Week 12 Follow-up visit, retesting of these parameters showed laboratory values that were no longer considered clinically significant, although the calcium level was still higher than the reference range.

Pharmacodynamic values over time

All of the pharmacodynamics parameters remained stable during the study. Mean serum calcium and corrected calcium were within the reference range (2.1 to 2.55 mmol/L) throughout the study and no clinically significant intact PTH decrease was observed post-treatment.

Vital Signs

Vital signs ((systolic and diastolic blood pressure, heart rate) and weight were evaluated for changes at each scheduled or post-baseline visit from Screening. One subject in the Vehicle group (b) (6)) had clinically significant diastolic and systolic blood pressure measurements and pulse rate at the Week 8/Early Termination visit. The subject did not attend the Week 12 Follow-up visit because of withdrawal from the study by subject decision. According to comments on the study exit form from the Investigator, the subject refused the blood test at the Week 8 visit and the “skin signs of the scalp worsened”.

Pregnancies

No pregnancies occurred during this study.

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

/s/

CRAIG H JOHNSON
07/15/2020 02:41:58 PM

BARBARA J GOULD
07/15/2020 04:53:36 PM

GORDANA DIGLISIC
07/15/2020 05:28:31 PM
Signing on behalf of Dr. P. Brown