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 17 Years of Age) With Mild to Moderate Plaque Psoriasis

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CLINICAL TRIAL PROTOCOL
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Name	Reason for Signing	Date
[redacted]	Medical Advisor	07-Jan-2016

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TITLE PAGE

Title 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		
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This clinical trial will be performed in compliance with applicable regulatory requirements and Good Clinical Practice (GCP). This clinical trial protocol follows guidelines outlined by the International Conference on Harmonisation (ICH) and the GALDERMA template.

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SYNOPSIS

Clinical Trial Title: **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**	
Short Title: Long term safety and efficacy study of calcitriol 3 mcg/g ointment in pediatric subjects with plaque psoriasis	
Clinical Trial phase:	**Clinical Trial Population:**
IV (III*) ** for non US regions*	Plaque psoriasis in pediatric subjects
Clinical Trial objectives:	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 concentrations will be assessed at several time points throughout the study duration in a subset of children 2 to 6 years and 11 months old.
Clinical Trial design:	Multicenter, open-label uncontrolled study.
Total number of subjects (Planned):	As a screen failure rate of approximately 40 percent is expected, screening of approximately 167 subjects is planned in order to achieve the target of 100 subjects enrolled into the study. PK investigations will be conducted in a subset of approximately 9 subjects aged between 2 to 6 years and 11 months old.
Number of clinical trial centers (Planned):	Approximately 30 study centers
Region(s) / country(ies) involved (Planned):	United States, Canada, and Europe
Clinical trial duration:	The planned clinical trial duration (from FSI to LSO) is approximately 40 months.
	The planned duration of recruitment (i.e. from FSI to LSI) is approximately 34 months.
Duration of subject participation:	Clinical trial participation for each subject is approximately 32 weeks.
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.

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.* Subject has hypercalcemia (serum albumin-adjusted calcium level above the upper normal range) at Screening. Subjects with known or suspected disorders of calcium metabolism. Subjects with liver dysfunction, defined as laboratory AST or ALT >2x ULN or total bilirubin >1.5x ULN. Subjects with creatinine clearance <85 mL/min per 1.73 m^2 at Screening. The subject has urinary calcium:creatinine ratio above the upper normal range at Screening. The subject has a history or signs and symptoms of urolithiasis. Subject has secondary hyperparathyroidism or PTH above upper limit of normal 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)[1]. 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).
Investigational product:	
Name:	Vectical®/Silkis™ ointment
Internal code:	CD2027
Pharmaceutical form:	ointment
Strength/Concentration:	Calcitriol 3 mcg/g
Dosage (total daily dose):	Maximum of 0.5 g/kg of body weight or 28 grams daily (whichever is the lower)
Route:	Topical to psoriatic skin
Duration of administration:	26 weeks
Dose regimen:	Twice daily application (morning and evening)
Location of treated area:	Psoriatic skin (excluding face and scalp)

[1] http://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/, National Institutes of Health Office of Dietary Supplements, Strengthening Knowledge and Understanding of Dietary Supplements

Comparator product:	Not Applicable
Name:	
Internal code:	
Pharmaceutical form:	
[*Strength/Concentration*]:	
Dosage (total daily dose):	
Route:	
Duration of administration:	
Dose regimen:	
Location of treated area:	
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.
Safety assessment:	Safety assessments include AE evaluation, vital signs/physical examination, and laboratory evaluations including hematology, chemistry, 1, 25(OH)2D, 25(OH)D, PD serum and urinary assessments (see Pharmacodynamic assessment below), eCRF AE forms will be reviewed periodically to monitor the ongoing safety of the study. An Independent Data Monitoring Committee (IDMC) will be established for this study to monitor general subject safety and specifically parameters relating to calcium metabolism, and biochemistry.
Safety endpoints:	Safety endpoints include: Serum albumin-adjusted calcium, urine calcium:creatinine ratio, phosphorus, and PTH.
Pharmacokinetic assessment:	PK assessment: to evaluate the plasma concentration of calcitriol. One single blood sample at screening and baseline to assess the endogenous levels and its variability, then a single pre-dose blood sample (C_t) will be collected at Week 4, Week 12, Week 26, and Week 30 in approximately 9 subjects 2 to 6 years and 11 months of age.
Pharmacodynamic assessment:	PD Serum (non-fasting): calcium, phosphorus, albumin (in order to calculate the serum albumin-adjusted calcium) and PTH. 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.

Principal statistical method:	No inferential statistics are planned for this study. The Safety Population is defined as comprising all of the subjects who have applied the study drug at least once. All data will be summarized based on the Safety Population. The laboratory parameters at scheduled visits and change from Screening at post-baseline visit(s) will be summarized descriptively by visit. A shift table for lab parameters at Screening versus the Week 26/Early Termination will be provided when appropriate. The categorical variables will be summarized by frequency and percentage for each response category (N, %). The continuous variables will be summarized using means, medians, minimum, maximum, and standard deviations for the data collected at each visit and the changes and percent changes from Baseline at each post-baseline visit when appropriate. Treatment-emergent Adverse Events (TEAEs) will be tabulated in frequency tables by System Organ Class and Preferred Term based on the Medical Dictionary for Regulatory Activities (MedDRA). Additional summary tables will be provided for AEs that are considered serious (SAEs), related to the study drug(s), severe, AESIs, and AEs leading to discontinuation. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE. Subgroup summaries of AEs will be provided based on gender, age group, and race when appropriate. C_t will be submitted, after logarithmic transformation (Ln), to paired comparisons of Baseline and each subsequent time point. Ninety percent confidence intervals of the pairwise differences will be calculated using the Student's t statistic. The limits of the intervals will be back-transformed into exponential to obtain 90% confidence intervals of the ratios of geometric means between time points, on the original scale. PK/PD relationships will be investigated by correlating C_t with appropriate PD parameters, using Spearman coefficient and graphical illustrations.
Sample size:	**Sample Size Justification:** Approximately 167 subjects will be screened to enroll approximately 100 subjects into the study.

Table 1 Clinical trial schematic

Screening (Approximately 167 subjects)	
↓	
100 Subjects assigned to treatment with:	
	Group 1
	n= 100
Treatment	*CD2027 calcitriol 3 mcg/g*
Treatment Frequency	*Twice daily*
Treatment Duration	*26 weeks*

Table 2 Schedule of Assessments

	Clinical Trial Assessments					
	Screening Period	Treatment Period				Follow up Period
	Screening *(Day -14)*[14] *V1*	*Baseline*[16] *(Week 0)* *V2*	Week 4[1] *V3*	Week 12[1] V4	Week 26 / ET[1, 5] V5	Week 30[1] V6
Informed Consent / Assent Form /HIPAA/PIPEDA	X					
Demographics	X					
Medical History	X					
Previous Therapies/Procedures[8]	X					
Physical examination and Vital signs[2]	X	X		X	X	
Inclusion/Exclusion Criteria	X	X[3]				
Urine Pregnancy Test (post menarcheal)	X	X	X	X	X	X
Record % Body Surface Area involved	X	X	X	X	X	X
Routine Blood Chemistry and Hematology	X		X	X	X	X[11]
Urinalysis	X		X	X	X	X
Pharmacodynamic Serum[9]	X	X[18]	X	X	X	X[11]
PK Blood Sampling[17]	X	X	X	X	X	X
Pharmacodynamic Urine[10]	X			X[13]	X[13]	X[11]
25(OH)D & 1,25 (OH)2D	X			X	X	X[11]
IGA	X	X	X	X	X	X
Pruritus	X	X	X	X	X	X
Drug application		Twice a day from Baseline to Week 26 V5[15]				
Study drug Dispensing (D) and Accountability (A)[4]		D	D/A	D/A	A	
Adverse Event information collection[7, 12]	X	X	X	X	X	X
Concomitant Therapies/Procedures[8]	X	X	X	X	X	X
Moisturizer and cleanser dispensed[6]		X	X	X	X	
Exit Form[5]						X

[1] Visit window of ± 3 days.
[2] Physical Examination to include: weight and review of systems: skin, cardiovascular, respiratory, abdomen, head and neck, musculoskeletal, neurological, lymph nodes and psychological. Height is to be evaluated at Screening visit only. Vital Signs to include: blood pressure, pulse rate
[3] Reconfirm that subject continues to meet inclusion/exclusion criteria.
[4] Total amount of Study Drug applied to involved skin should not to exceed 0.5 g/kg of body weight or 28g per day (whichever is the lower). First application to be made under the supervision of the investigator or designee. Record daily administration on dosing calendar. Dosing calendar to be checked at each visit after Baseline.
[5] Or at any time in case of early termination.
[6] The Cetaphil® Moisturizing Cream and Cetaphil® Gentle Skin Cleanser or equivalents will be provided by the Sponsor
[7] Events occurring after the Informed Consent Form and Assent Form (when applicable) have been signed should be recorded as Adverse Events in the eCRF
[8] Any therapy or medication other than study ointment will be noted on the Drugs/Therapies Form. Subjects that require a wash-out period of a prohibited therapy for >2 weeks, should be screen failed and may re-screen 1 time after completion of the washout period.
[9] PD Serum (non-fasting): calcium, phosphorus, albumin (in order to calculate the serum albumin-adjusted calcium) and PTH.
[10] 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 that are toilet-trained should be actively encouraged to complete 24-hour urine collection. A urine collection container/material will be 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.
[11] Laboratory testing (full panel) will be completed at Week 30 for subjects in the PK group. For all other subjects, laboratory testing at Week 30 will be completed at Investigator's discretion.
[12] Subjects with suspected kidney stones should temporarily discontinue study drug and will be referred to their Primary Care Physician (PCP) for care in tandem with Sponsor consultation of the IDMC.
[13] The visit before: Distribute container and provide instructions for 24-hour urine collection to be started 1 day prior to Week 12 and Week 26/ET visits. The study site should contact the parent/legal guardian 48 hours prior to the visit to remind them to start the urine collection.
[14] Subjects may re-screen one time with written approval from the Sponsor prior to re-entry into the study.
[15] At Baseline, the study nurse show the subject's parents how to apply the drug.
[16] Visit window of +/- 5 days.
[17] For subjects in the PK group, a single blood sample at Screening and Baseline will be taken, then a single pre-dose blood sample will be taken at Weeks 4, 12, 26 and 30, to assess the calcitriol plasma concentration. The volume of each blood sample will be 5 mL. A total volume of 30 mL will be collected during the study for PK assessment.
[18] Serum PD will be assessed during Baseline visit only for subjects 2 to 6 years and 11 months of age in whom PK analysis will be conducted in order to assess PK/PD relationships at Baseline for these subjects.

Unscheduled visit: When necessary and exceptionally, because of either an AE needing a specific treatment, AE leading to withdrawal from the study, laboratory result(s) that warrant further testing, or other reason.

An ongoing dialogue between subject, parent/legal guardian and investigators focusing on all aspects of the trial is encouraged. Any new information that arises in relation to the trial and that might affect the willingness of the subject and/or parent/legal guardian should be discussed. This brief discussion should be documented during each study visit.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
/	Per
%	Percent
°C	Degrees Celsius
°F	Degrees Fahrenheit
1, 25(OH)2D	1, 25 dihydroxyvitamin D
25(OH)D	Vitamin D
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT/ALAT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
approx	Approximately (or use 'about', not C. or ca.)
AST/ASAT (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
AUC	Area under Curve
BID	Twice Daily (Latin: bis in die)
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CDMS	Clinical Data Management System
CI	Confidence Interval
C_{max}	Maximum Concentration
C_{min}	Minimum Concentration
C_t	Pre-dose Plasma Concentration
CNS	Central Nervous System
C_0	Trough Levels
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSO	Clinical Safety Officer
CSR	Clinical Study Report
CV	Coefficient of Variation
DC	Discontinuation
DMP	Data Management Plan
eCRF	Electronic Case Report Forms

Abbreviation	Term
e.g.	For Example (Latin: exempli gratia)
Eq	Equivalent (e.g., as in milli equivalent [mEq])
ET	Early Termination
etc	Et cetera
EU	European Union
Eur. Ph. or EP	European Pharmacopoeia
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GI	Gastro-intestine
Hb	Hemoglobin
Hct	Hematocrit
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
i.e.	That is
IEC	Institutional Ethics Committee
IGA	Investigator's Global Assessment of Disease Severity
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IU	International Units
IUD	Intrauterine Device
IV	Intravenous
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
N/A	Not Applicable
NDA	New Drug Application
NF	National Formulary
N or n	Number
p	Probability (as in significance level)
P	Page(s)
PD	Pharmacodynamics
PE	Physical Examination
PIPEDA	Personal Information Protection and Electronic Documents Act

Abbreviation	Term
PK	Pharmacokinetics
PO	Oral
PP	Per-Protocol
PT	Preferred term
PTH	Parathyroid hormone
PUVA	Psoralen-ultraviolet-light
PR	Pulse Rate
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analyses System
SD	Standard Deviation
SEM	Standard Error of Mean
SIN	Subject Identification Number
SGOT (AST)	Serum glutamic oxaloacetic transaminase
SGPT (ALT)	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SOP	Standard Operating Procedure
$t_{½}$	Half-life
TEAE	Treatment Emergent Adverse Event
t_{max}	Time to Maximum Concentration
UA	Urinalysis
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
US	United States
USP	United States Pharmacopeia
UV	Ultraviolet light
WBC	White Blood Cell

1 BACKGROUND AND RATIONALE

Psoriasis vulgaris is one of the most common chronic skin diseases with a prevalence estimated at between 1.4% and 2.9% of the population. In approximately 35% of adults with psoriasis, the onset occurred in childhood (Farber 1999). In pediatric subjects and adolescents, plaque psoriasis is the most common form encountered, ranging from 34% to 84% in frequency and followed by guttate or "drop-like" psoriasis in 25% of cases (Lewkowicz 2004 and Nanda 1999).

Vitamin D derivatives are well-established, efficacious and safe topical drugs used in the therapy of chronic psoriasis. In the USA, only calcipotriol and calcitriol are on the market; they are indicated for the treatment of mild to moderate plaque psoriasis in adults. The earliest approvals of calcitriol 3 mcg/g ointment occurred in 1995 in The Netherlands and Switzerland. To date, calcitriol 3 mcg/g ointment is approved in 39 countries. It is marketed as Silkis® ointment in 30 countries worldwide, including most European countries. Calcitriol 3 mcg/g ointment was approved in the USA on January 23, 2009 (Vectical®, Galderma Laboratories).

A total of 45 clinical studies have been conducted by the Sponsor to evaluate calcitriol ointment at various concentrations. To date, 2974 subjects have been treated with calcitriol as part of the drug development program. Calcitriol 3 mcg/g ointment has been shown to be effective and safe, without affecting calcium homeostasis parameters in adult subjects. Clinical studies have also shown that calcitriol is less irritating than calcipotriol.

Two pivotal Phase 3 studies (SPR.18053 and SPR.18054) with calcitriol 3 mcg/g ointment were completed in 2002. In both studies, the primary endpoint (Success Rate) was clinically and statistically superior for calcitriol 3mcg/g ointment compared to vehicle at Week 8. The superiority of treatment with calcitriol over vehicle was observed as early as Week 2, and sustained throughout the treatment period of 8 weeks.

A PK/PD study (SPR.18102) was conducted from August 2006 to September 2009 on 25 adolescents (12-17 years old; mean age: 14.7 years) with plaque psoriasis affecting 10 to 35% BSA (mean: 17.8%). Serum calcitriol levels were investigated at baseline and after 21 days of treatment with Vectical® (calcitriol 3µg/g ointment). Subjects received two applications per day and up to 15 g of formulation per application, depending on the total BSA and on the percentage of psoriasis-involved BSA. There was no significant variation of calcitriol levels during treatment. The overall mean (±SD) value of maximum calcitriol plasma levels (Cmax) was 76±24 pg/mL at Baseline (endogenous levels) and 73±22 pg/mL after 3 weeks of treatment. Regarding age stratification, the mean Cmax and $AUC_{0\text{-}9hr}$ or $AUC_{0\text{-}12hr}$ at Baseline were higher in the 12 to <15 years than in the 15 to 17 years (respectively 26% higher for Cmax and 19% higher for $AUC_{0\text{-}9hr}$ and $AUC_{0\text{-}12hr}$). The same tendency was observed after 21 days of application. The plasma calcitriol levels (Cmax) appeared to be 21% higher in the 12 to <15 years age group compared to the 15 to 17 years age group and $AUC_{0\text{-}9hr}$ and $AUC_{0\text{-}12hr}$, were approximately 17% higher. However, in each stratum, the calcitriol levels after 21 days of treatment were similar to the baseline levels. Overall, the repeated application of calcitriol 3 µg/g ointment did not resulted in an increased systemic exposure.

Furthermore, no correlation could be established between percentage of psoriasis-involved BSA and AUC_{0-9h} in this study. Therefore, in study 18131, repeated applications of Vectical® are not expected to increase endogenous levels of calcitriol.

The mean change for PD parameters were very minimal. No subjects had serum calcium or adjusted serum calcium values shifted from within the reference range at Baseline to above this range during the study. Serum PTH levels of one subject (Subject 9017) shifted from within the normal reference range (16 pg/mL) to below the normal reference range (6 pg/mL) at Day 15 but returned to within the reference range at Day 22 of study (19 pg/mL at Day 58). Although PTH levels remained within the normal reference range for the other subjects throughout the study, there was a trend for a decrease over time (mean change = -9.07 pg/mL for 12 to <15 year group and -10.36 pg/mL for 15 to 17 year group). No statistically significant correlations between PK and PD parameters were noted.

PTH will be monitored regularly throughout this study and all abnormal values and downward trends will be reviewed by the study Medical Expert and/or CSO as well as the IDMC.

Additional studies have been conducted to evaluate the effect of calcitriol on calcium homeostasis. One study of 59 subjects treated with calcitriol 3 mcg/g ointment for a total of 20 weeks showed no significant change on calcium levels (Katz 1987). An additional study of 253 subjects treated with calcitriol 3 mcg/g ointment showed long-term efficacy after up to 78 weeks of treatment and 2% (N=5) showed slightly elevated calcium levels. Calcium levels normalized during the treatment period for four of the five subjects with hypercalcemia (Gerritsen 2001).

Galderma R&D has been conducting an extensive pediatric program as a Phase 4 requirement to extend the indication for calcitriol 3 mcg/g ointment to the pediatric population, which includes:

SPR.18102 PK/PD study in adolescents aged 12-17 years (completed in 2009),

SPR.18104 PK/PD study in pediatric subjects aged 2-12 years (closed, 2015),

SPR.18132 Safety and Efficacy study in pediatric subjects aged 2-11 years (closed, 2015),

and SPR.18131 Long-Term Safety (LTS) study in pediatric and adolescent subjects aged 2-16 years and 11 months.

In light of the recruitment challenges faced by the latter 3 studies conducted in parallel, the pediatric program was recently reconsidered by Galderma and reassessed by the US Food and Drug Administration (FDA).

As a result of the discussion with the Agency in July 2015, the ongoing long-term safety study (SPR.18131) is being amended to include a PK assessment in a subset of 9 children aged 2 to 6 years and 11 months old and the 2 ongoing studies (SPR.18104 and SPR.18132) will be closed to subject enrollment. These decisions were suggested and agreed by the Agency for logistical reasons and were not based on any safety concerns regarding the product's use in children.

A summary and rationale of the present amendment follows:

- Inclusion of PK assessments in this long-term safety study. In discussion with FDA, it was agreed that a Pharmacokinetic assessment will be performed in approximately 9 subjects with plaque psoriasis aged 2 to 6 years and 11 months old with a minimum of 3% BSA involvement .
- Addition of serum PD assessment at Baseline for subjects in the PK group so that PK/PD relationships can be investigated.
- Number of enrolled subjects reduced from 140 to 100.
- Study visits at Week 8 and Week 20 were removed.
- Management of parathyroid hormone (PTH) results falling below the lower limit of normal was revised.

The Independent Data Monitoring Committee (IDMC) will supervise the subjects' safety as defined in the IDMC Charter. The IDMC will inform the Sponsor and suggest the action(s) to be taken, if safety signals are observed.

The specific roles of the IDMC include, but are not limited to:

- Meet periodically to review individual data and summary analyses,
- Assess data quality, including completeness,
- Monitor biochemical and pharmacodynamic parameters,
- Suggest additional data analyses,
- Maintain and document any decisions and activities taken during IDMC meetings,
- Recommend to the Sponsor whether recruitment/participation should be suspended for either individual participants or the entire study.

Further details regarding the IDMC's role and activities will be outlined in a separate IDMC Charter document.

1.1 Medical background and short rationale for the clinical trial

Safety and efficacy of calcitriol 3 mcg/g ointment in pediatric subjects under the age of 12 has not been previously studied. The current study of the long-term safety of calcitriol 3 mcg/g ointment applied twice daily for up to 26 weeks is specifically designed to enroll and evaluate pediatric subjects 2 to 16 years and 11 months (Version R03) of age with mild to moderate plaque psoriasis. In addition, this study will allow the evaluation of plasma concentrations of calcitriol in a subset of 9 subjects aged 2 to 6 and 11 months.

1.2 Drug profile

Calcitriol is the naturally occurring and biologically active metabolite of vitamin D_3. Calcitriol inhibits the proliferation and stimulates differentiation of keratinocytes. It inhibits the proliferation of T-cells and normalizes the production of various inflammation factors. For these reasons, calcitriol is an effective drug in the topical treatment of psoriasis.

At the time of writing this amended protocol, there have been no recent updates to the reference safety information for Vectical®/Silkis™, nor are any updates pending.

1.3 Risk/Benefit assessment

As mentioned in Section 1 above, calcitriol 3 mcg/g ointment has shown efficacy over vehicle in studies with adult subjects.

The primary objective of this LTS study is to collect long-term (up to 26 weeks) safety data in children 2-16 years and 11 months of age (Version R03). As a secondary objective, calcitriol levels will be assessed at several time points throughout the study duration in a subset of children aged 2 to 6 years and 11 months old.

As mentioned in Section 1, childhood psoriasis is very prevalent, and an alternative to topical corticosteroid therapy in a pediatric population would be a desirable option. Calcitriol is a corticosteroid-sparing treatment that does not cause known steroid-related side effects such as skin atrophy and hypothalamo-pituitary axis (HPA) suppression.

PK/PD data from adolescent subjects 12-17 years of age in study SPR.18102 are mentioned in Section 1 above, including abnormalities observed in PTH levels in a subset of subjects. PTH will be monitored regularly throughout this study and all abnormal values and downward trends will be reviewed by the study Medical Expert and/or CSO. In addition, an IDMC will be in place for the duration of the study and will monitor laboratory and pharmacodynamic data as defined in the IDMC Charter.

In controlled clinical trials in adults, hypercalcemia was observed in 24% (18/74) of subjects exposed to calcitriol 3 mcg/g ointment, and in 16% (13/79) of subjects exposed to vehicle. However, the increases in calcium and albumin-adjusted calcium levels were less than 10% above the upper limit of normal.

In the two pooled 8-week vehicle-controlled studies in 419 adult subjects, pruritus and discomfort pain were reported in 1% and 3% respectively for subjects treated with calcitriol 3 mcg/g ointment, and 1% and 2% respectively for subjects exposed to vehicle.

In a 52-week open label study of 324 adult subjects, adverse events reported at a rate of greater than or equal to 3% of subjects treated with calcitriol 3 mcg/g ointment were lab test abnormality (8%), urine abnormality (4%), psoriasis (4%), hypercalciuria (3%), and pruritus (3%). Kidney stones were reported in 3 subjects and confirmed in two.

All subjects enrolled in this LTS study will receive active treatment, calcitriol 3 mcg/g ointment. There is a risk of local irritation reactions, hypercalcemia, hypercalciuria and kidney stones associated with study participation. Multiple safety measures including regular monitoring of serum hematology, biochemistry and pharmacodynamic parameters pertaining to calcium homeostasis, as well as urine testing have been implemented to closely monitor subject safety. Further details regarding safety assessments are provided in Section 2.1.

2 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

2.1 Clinical trial objectives

Safety Objectives:

The primary objective of this study is 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 of age, Version R03) with mild to moderate plaque psoriasis. As a secondary objective, calcitriol plasma levels will be assessed at several time points throughout the study duration in a subset of children aged 2 to 6 years and 11 months old.

Safety Assessments:

- Adverse Event recording at each study visit.
- An Independent Data Monitoring Committee (IDMC) will be established for this study and will be responsible for securing the subjects' safety including the review of the subjects' laboratory results for: parathyroid hormone, calcium, phosphorus, albumin, and creatinine levels on an ongoing basis (as defined in the IDMC charter). The IDMC will inform the Sponsor and recommend actions to be taken, if safety signals are observed.
- Systemic Safety Parameters to be completed per the Schedule of Assessments (Table 2).
  - Vital signs (blood pressure and pulse rate)
  - Physical examination (weight, skin, cardiovascular, respiratory, abdomen, head and neck, gastrointestinal, respiratory, musculoskeletal, neurological, lymph nodes and psychological). Height is to be evaluated at the Screening visit only.
  - Routine safety laboratory parameters
    - *Hematology*: red blood cells, white blood cells with differential cell count, hemoglobin, hematocrit, platelets
    - *Blood chemistry (non fasting)* : total protein, ALT (SGPT), AST (SGOT), alkaline phosphatase, blood urea nitrogen, creatinine (calculated creatinine clearance), total and conjugated bilirubin
    - *Urinalysis*: glucose, ketone, blood, protein, nitrite and leukocytes
  - Pharmacodynamic parameters
    - *Serum(non fasting)*: calcium, phosphorus, albumin (in order to calculate the serum albumin-adjusted calcium), PTH
    - *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 that are toilet-trained should be actively encouraged to complete the 24-hour urine collection.

- Other Assessments
  - *1, 25(OH)2D.*
  - *25(OH)D.*
  - *Urine Pregnancy Test for post menarcheal females (including subjects who become post-menarcheal during study participation).*

Efficacy Objectives:

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.

Efficacy Assessments:

- Investigator's Global Assessment of Disease Severity (Will be referred to as the IGA score in this document) [IGA scale is described in Section 7.1.1.1].
- Pruritus.

Pharmacokinetic (PK) Assessment:

- Plasma concentration of calcitriol (1, 25(OH)2D) will be assessed using a single pre-dose blood sample (C_t) in a subset of approximately 9 subjects aged between 2 to 6 years and 11 months old.

Other Assessments:

- Percent Body Surface Area (BSA) involved.
  - The % BSA involved will be assessed using the methodology shown in Section 13.3, Appendix 3.

2.2 Clinical hypothesis

Long term use (26 weeks) of calcitriol 3 mcg/g ointment is safe and efficacious in pediatric subjects (2 to 16 years and 11 months of age, Version R03) with mild to moderate plaque psoriasis.

The calcitriol absorption in pediatric subjects (2 to 6 years and 11 months of age) is expected to be comparable to that in adults and adolescents, with no significant impact on calcium/ phosphorus metabolism.

3 OVERALL CLINICAL TRIAL DESCRIPTION

This is an open-label, uncontrolled, multicenter long-term safety and efficacy study in pediatric subjects (age 2-16 years and 11 months, Version R03) with mild to moderate plaque psoriasis.

Approximately one hundred (100) subjects will be enrolled into this study. A subset of enrolled subjects (approximately 9 among the 100) will meet the PK requirements: pediatric subjects aged 2 to 6 years and 11 months (inclusive at Screening) and with a minimum 3% BSA involvement.

Qualified subjects will receive calcitriol 3 mcg/g ointment for a period of up to 26 weeks. The subject's parent/legal guardian or the subject under the responsibility of the parent/legal guardian will apply a thin film of study drug as needed to cover all involved areas twice daily, without exceeding a maximum of 0.5 g/kg of body weight or 28 g daily (whichever is the lower). If the subject experiences complete clearing of psoriasis per physician assessment (i.e. an IGA of 0), the subject should discontinue the study drug but continue to follow the visit schedule through the Week 26 visit. Treatment with study drug should be resumed if the IGA score is >0 and <4.

Subjects will be evaluated at screening, baseline and Weeks 4, 12, 26, and 30 as described in the Schedule of Assessments (Table 2). A visit window of ± 5 days will be allowed for Baseline and a visit window of ±3 days will be allowed at the visits from Weeks 4 through 30.

4 CLINICAL TRIAL DURATION AND TERMINATION

The planned clinical trial duration (from FSI to LSO) is approximately 40 months. The date of end of the clinical trial is defined as the date of the last visit of the last subject who participates in the clinical trial.

The planned duration of recruitment (i.e. from FSI to LSI) is approximately 34 months.

Clinical trial participation for each subject is approximately 32 weeks.

GALDERMA may decide to prematurely terminate or suspend the participation of a particular clinical trial center (for example, for non-inclusion or non-compliance with clinical trial protocol, regulation, or GCP) or prematurely suspend the clinical trial (for example, for safety, study drug(s) quality, regulatory, efficacy, or logistical reasons) at any time with appropriate notification.

5 SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

5.1 Number of subjects

As a screen failure rate of approximately 40 percent is expected, approximately 167 subjects may have to be screened in order to get 100 subjects enrolled. A subset of approximately 9 subjects will be enrolled to meet the PK requirements (see Section 5.2).

5.2 Clinical trial population characteristics

In order to be eligible for the clinical trial, subjects must fulfill all of the following inclusion criteria and none of the exclusion criteria.

Approximately 100 male or female subjects, 2 to 16 years and 11 months of age (Version R03), diagnosed with mild to moderate plaque psoriasis are to be enrolled in this multicentre open label uncontrolled study of the long term safety and efficacy of calcitriol 3 mcg/g ointment applied twice daily for 26 weeks. A subset of approximately 9 subjects will be enrolled to meet the PK requirements: pediatric subjects 2 to 6 years and 11 months of age (inclusive at Screening) and with a minimum 3% BSA involvement.

5.3 Inclusion criteria

1. Male or female 2 to 16 years and 11 months of age (Version R03).
2. Specific for PK: Pediatric subjects 2 to 6 years and 11 months of age (inclusive at Screening) and with a minimum 3% BSA involvement.
3. Clinical diagnosis of stable mild to moderate plaque type psoriasis.
4. Subjects with an IGA score of 2 or 3 at Screening and Baseline.
5. Female of non-childbearing potential (pre-menarcheal).
6. Female of childbearing potential with a negative urine pregnancy test (UPT) at visit(s) Screening (Day -14) and Baseline (Day 0).
7. Female of childbearing potential who:
   - 7.1. has been strictly abstinent 1 month prior to baseline and agrees to continue for the duration of the clinical trial,
   - 7.2. 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:
     - 7.2.a. combined oral contraceptives (estrogens and progesterone) or implanted or injectable contraceptives with a stable dose for at least 1 month prior to baseline
8. Willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol.
9. Parent or legal guardian must understand and sign an Informed Consent Form (ICF) at screening, prior to any investigational procedures being performed.
10. If capable to give assent to decisions about participation in research, subject may sign an Assent Form to participate. In addition the subject must also have a parent or guardian sign the Informed Consent Form and HIPAA (USA only) or PIPEDA (Canada only) and is willing to share personal information and data as verified by signing a written authorization at Screening visit prior to any study related procedures being performed.

Rationale:

1 to 4: In order to select a suitable pediatric population for the clinical trial. Overall age range is based on recent agreements with FDA and must be followed once the protocol amendment is implemented.

5 to 7: Since the safety of the Investigational Product for pregnant women has not been established yet.

8. To ensure protocol compliance and consistency of study data.

9 to 10: To ensure that all subjects are fully informed of the study requirements and only subjects providing written consent are included in the clinical trial.

5.4 Exclusion criteria

1. 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.*
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 he/she participates 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. Female who is lactating.
5. Female who intends to conceive a child during the clinical trial.
6. Current participation in any other clinical trial of a drug or device OR participated in a clinical trial of a drug or device within 1 month prior to baseline.

7. The subject has received, applied or taken the following treatments within the specified time frame prior to the Baseline visit:

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

8. The subject or subject's parent /legal guardian is unwilling to refrain from use of prohibited medication during the clinical trial (see Section 5.5.5).
9. The subject is vulnerable (such as deprived from freedom) as defined in Section 1.61 of International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP).
10. The subject has hypercalcemia (serum albumin-adjusted calcium above the upper normal range) at Screening.
11. The subject has urinary calcium:creatinine ratio above the upper normal range at Screening.
12. The subject has history or signs and symptoms of urolithiasis.
13. Subjects with known or suspected disorders of calcium metabolism.
14. Subjects with liver dysfunction, defined as laboratory AST or ALT >2x ULN or Total bilirubin >1.5x ULN.
15. Subjects with creatinine clearance <85mL/min per 1.73 m^2 at Screening. (Shull, et al, 1978)

Note:

Creatinine clearance is to be calculated using the Schwartz Equation:

Creatinine Clearance = k x H/Scr.

For children 1-12 and adolescent girls 13-16 years and 11 months old, k=0.55. For adolescent boys 13-16 years and 11 months old, k=0.7. H=height at screening (cm). Scr=serum creatinine (mg/dL) at screening. (Schwartz 1976).

16. Subjects with concomitant medical or dermatological disorder(s), which might preclude accurate evaluation of the psoriasis.
17. 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).
18. 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.).
19. 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).
20. Subjects with clinically significant blood loss within the last 3 months prior to screening, per Investigator discretion.
21. The Subject has clinically significant abnormal values of the safety laboratory parameters at Screening (See Section 7.2.2).
22. The Subject has secondary hyperparathyroidism or PTH above Upper Limit of Normal at Screening.

Rationale:

1: These conditions are not part of the proposed label indications, plaque psoriasis.

2 to 3; 10 to22: These subjects are at risk and in order to enable appropriate evaluation.

4, 5 The safety of the Investigational Product for pregnant or nursing women has not been established yet.

6: To secure integrity of the study.

7 to 8: In order to exclude the influence of concomitant therapies on the evaluation of this study.

9: Protection of subject rights.

5.5 Previous and concomitant therapies

5.5.1 Definition

Previous therapies are defined as therapies that have been stopped within the last 6 months prior to the screening visit for non-psoriasis-related therapies; for psoriasis-related therapies, all medications and procedures must be reported as previous therapy in the e CRF.

Concomitant therapies are 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.

5.5.2 Categories

The following two categories are to be considered for previous and concomitant therapies:

- Drugs/therapies including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers, X-rays, etc.

5.5.3 Recording

Previous and concomitant therapies are to be recorded on the Drugs/Therapies form (for drugs/therapies) and/or on the Medical and Surgical Procedures form (for medical/surgical procedures) in the eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

Any new concomitant therapy or modification of an existing therapy may be linked to an adverse event (AE). A corresponding Adverse Event Form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc.

5.5.4 Authorized concomitant therapies

Unless listed under the exclusion criteria (Section 5.4 item 7) or in prohibited concomitant therapies (see Section 5.5.5), all therapies are authorized.

No other topical treatments, other than the test materials, will be permitted on the treated areas. However, emollients on healthy skin areas are permitted during the course of the study. Cetaphil® Moisturizing Cream and Cetaphil® Gentle Skin Cleanser or equivalents (provided by the Sponsor) may be used as needed, on non-treated areas of the skin.

Subjects will be permitted to use medicated shampoos that do not contain corticosteroids or vitamin D derivatives to treat scalp psoriasis. Tar products can be used on the face and scalp areas.

Topical anesthetic creams for the purpose of blood draw comfort may be used on non-treated areas and should be documented in the eCRF.

Sunscreen may be used as needed on non-treated areas of the skin.

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). Subjects are to remain on the same dose throughout the course of the study.

5.5.5 Prohibited concomitant therapies

The following therapies are 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):

- Listed in Section 5.4 item 7
- Listed in Section 13.1, Appendix 1 – Unauthorized therapy

If prohibited therapies become a necessary treatment for the safety or best interest of the subject, GALDERMA must be notified to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical trial, GALDERMA must be notified to discuss the pertinence and the modalities for the subject to continue in the clinical trial.

5.6 Procedures/Reasons for subject discontinuation

An Investigator may decide to discontinue a subject from the clinical trial for safety reasons.

Although the importance of completing the entire clinical trial should be explained to the subject by the clinical trial personnel, any subject is free to discontinue his/her participation in this clinical trial at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated.

When a subject does not complete the clinical trial, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Week 26/Early Termination visit should be completed for all subjects discontinuing the clinical trial and the appropriate Case Report Form eCRF should be completed. All discontinuations and the reason for discontinuation are to be documented by the Investigator on the Exit Form, and also on the Adverse Event Form for discontinuation due to an AE.

For discontinuation due to an AE, the Investigator should ensure that the subject receives suitable therapy for his/her AE.

Subjects who have a 2 grade worsening of their plaque psoriasis per the IGA scale, or who reach an IGA of 4, should be discontinued and complete the Week 26/ET visit. If the subject experiences complete clearing of psoriasis (IGA = 0), per physician assessment the subject should discontinue the study drug but continue to follow the visit schedule through the Week 26 visit. Treatment with study drug should be resumed if the IGA score is >0 and <4.

Subjects whose parathyroid hormone (PTH) results fall below the lower limit of normal will be assessed on a case-by-case basis; study drug application may be temporarily discontinued based on Sponsor and Investigator assessment. Serum PD parameters will be regularly checked (at least within 2 weeks) at Investigator's and Sponsor's discretion until the PTH level is back within the normal range. In addition, the IDMC will be notified of all PTH results that decrease by 30% from the subject's baseline results and will recommend appropriate management of the subject on a case-by-case basis.

For subjects whose parathyroid hormone (PTH) results have fallen below the lower limit of normal, if either:

- The PTH does not return to the normal reference range within two weeks

OR

- The PTH returns to the normal reference range but falls below the lower limit of normal at any other stage during the course of the study

then the IDMC will be contacted for advice on management.

Subjects with abnormal serum albumin-adjusted calcium should temporarily discontinue study drug use immediately: The IDMC will be consulted for each occurrence of hypercalcemia, and depending on the severity and/or duration of the out-of-range serum calcium, will recommend appropriate management of the subject on a case-by-case basis in combination with other lab values and clinical condition of the subject in general.

Subjects with suspected kidney stones should temporarily discontinue study drug and will be referred to their Primary Care Physician (PCP) for care in tandem with Sponsor consultation of the IDMC. If urolithiasis is not confirmed, the subject may resume treatment with study drug. Subjects with confirmed urolithiasis should permanently discontinue study drug use and complete the Week 26/ET visit.

A subject who has been enrolled and assigned a kit number cannot be replaced by another subject if he/she discontinues the clinical trial for any reason.

For subjects not completing the entire study, all used (and unused) study drugs containers should be returned by the subject's parent/legal guardian to the defined personnel at the study center.

GALDERMA may also decide to prematurely terminate or suspend a subject's participation in the clinical trial.

Potential reasons for discontinuation, as listed on the Exit Form, are defined below:

- Pregnancy: **Withdraw the Subject from the clinical trial and follow the procedure described in Section 7.2.3.2.4**
- Lack of Efficacy: Investigator judgment only: based on therapeutic/disease-state expectations. If subject/parent or legal guardian opinion only, mark "subject request" and document it in the comment section of the eCRF Exit Form.
- Adverse Event: Complete an Adverse Event Form.
- Subject Request: Includes consent withdrawal, subject relocation, schedule conflicts. Explain the reason for withdrawal in the comment section of the eCRF Exit Form.
- Protocol Violation: Explain the violation in the comment section of the eCRF Exit Form.
- Lost to Follow-up: Confirmed with two documented phone calls and a certified letter (delivery receipt requested) without answer. Explain in the comment section of the eCRF Exit Form.
- Other: This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the eCRF Exit Form.

If reason for discontinuation is "subject or parent/legal guardian request" or "other", the subject or parent/legal guardian will be questioned to rule out the possibility of an AE and the response will be documented in source documentation.

6 CLINICAL SUPPLIES

6.1 Clinical supply identification and use

6.1.1 Study drug(s) description

Table 3 Description and usage of the study drug(s)

	Investigational product
Trade Name or Equivalent	Vectical® / Silkis™ ointment
Name of Drug Substance	calcitriol
Internal Code	CD2027
Pharmaceutical Form	ointment
Concentration	3 mcg/g
Formula number	0100/B50100
Packaging (type and size)	Aluminum Tube 100 g
Storage Conditions	Store at 25° C (77° F); excursions permitted to 15° -30° C (59°-86° F) Do not freeze or refrigerate.
Dosage (total daily dose)	Maximum of 0.5 g/kg of body weight or 28 grams daily (whichever is the lower)
Route	Topical to psoriatic skin
Dose Regimen	Twice daily application (morning and evening)
Duration of administration	26 weeks
Location of Treated Area	Psoriatic skin (excluding face and scalp)

6.1.2 Subject Identification Number (SIN)

Upon signature of the ICF, each subject will be assigned a Subject Identification Number (SIN) allocated in ascending sequential order for each subject without skipping any number.

For the duration of the entire clinical trial, the subject will be identified by the SIN for all documentation and discussion.

One re-screening is allowed.

6.1.3 Method of treatment assignment

All qualified subjects will receive the study drug. All enrolled subjects will be assigned a kit number using the Interactive Response Technology (IRT) system.

No randomization will be performed for this study.

6.1.4 Kit number/randomization number

Kit numbers will be assigned according to a pre-specified drug kit list.

No randomization numbers will be assigned.

6.1.5 Instructions for use and administration

The first dose will be applied under the supervision of the Investigator, at the Investigative site.

Application should be done either by the subject's parent / legal guardian or by the subject himself. It is the responsibility of the parent/legal guardian to decide if the subject can apply the product himself and if they should supervise the application depending on the capability of the child. After application, the study product tube should be stored out of the reach and the sight of children,

Application will consist of a thin film of study drug as needed to cover all involved areas twice daily (morning/evening), without exceeding a maximum of 0.5 g/kg of body weight or 28 g daily (whichever is the lower). The dosing calendar is to be completed by the subject or subject's parent or legal guardian daily and returned to the site at each visit.

For the subset of subjects with PK evaluations, the drug product MUST NOT be applied on the areas that will be used for blood sampling. These areas will be defined at screening by the Investigator.

In addition, at the week 4, week 12 and week 26 visits, study drug applications will be performed on site after the PK pre-dose blood sampling is obtained. This blood sample has to occur 12 hours (±1 hour) after the last product application.

To avoid potential contamination of the blood sample collected, study drug applications and blood draws must NOT occur in the same room. Additionally, the blood draw area should be clean and kept away from contact with study drug.

Subjects should wait at least six hours after the study treatment application before swimming or bathing.

Cetaphil® Moisturizing Cream or equivalent (provided by the Sponsor and distributed by the Investigator or designee at the Baseline Visit) may be used during the study as needed on non-treated areas of the skin. Cetaphil® Gentle Skin Cleanser or equivalent (provided by the Sponsor) may be used for cleansing.

Subjects will be permitted to use medicated shampoos that do not contain corticosteroids or vitamin D derivatives to treat scalp psoriasis. Tar products can be used on the face and scalp areas.

No other topical treatments, other than the test materials, will be permitted on the treated areas. However, emollients and sunscreen on healthy skin areas are permitted during the course of the study.

Dietary instructions: subjects will be asked to maintain the same dietary habits, especially calcium intake as before the study. Subjects should maintain adequate hydration. Detailed instructions will be provided to the subjects regarding appropriate hydration in the subject instructions document.

It is recommended that the subject use protective clothing and other measures/precautions to protect themselves from excessive sun exposure while participating in this study.

Subjects and parents/legal guardians should wash their hands after each application of study drug.

6.1.6 Other supplies

Adequate supplies of the following items are to be provided to or sourced by each study site:

- Urinary pregnancy tests
- Cetaphil® Moisturizing Cream & Cetaphil® Gentle Skin Cleanser (or equivalents)

Note: Cetaphil® Moisturizing Cream or equivalent may be used during the study as needed on non-treated areas of the skin.

All unused UPTs and undispensed Cetaphil® Moisturizing Cream and Cetaphil® Gentle Skin Cleanser or equivalents, etc. are to be returned to the Sponsor, or sponsor's contract vendor for destruction.

6.2 Study drug(s) packaging and labeling

Kits will be dispensed at the following visits: Baseline (1 kit), Week 4 (2 kits), and Week 12 (4 kits) Each kit will contain 8 100-gram tubes.

The labels will be printed in the languages of participating countries. Labels will contain the information requested by Good Manufacturing Practice, local regulation, kit number and corresponding Week/Visit number.

The labeling will be performed under the responsibility of Galderma R&D, LLC, following the ICH Guidelines.

6.3 Supplies management

6.3.1 Accountability

Upon receipt of the study drug(s), the Investigator or designee will maintain accurate records of the study drug(s) delivery to the clinical trial center using the IRT system. The inventory at the clinical trial center, the use by each subject, the reconciliation of all study drug(s) received from the Sponsor, and the return to the Sponsor or alternative disposal of used and unused study drug(s) will also be tracked in the IRT system.

The Investigator or designee is required to sign the original "Acknowledgement of Receipt of Clinical Supplies" Form (or any acknowledgment of receipt) upon receipt and inspection of the supplies, fax the signed copy to the shipping depot and retain the receipt within the clinical trial file.

All used and unused clinical study drug(s) will be appropriately inventoried by the monitor and returned to the Sponsor, or sponsor's contract vendor for reconciliation, counting and destruction as instructed by GALDERMA/CRO.

All clinical study drug(s) sent to the Investigator/Institution will be accounted for and no unauthorized use is permitted.

6.3.2 Storage of clinical study drug(s)

Study drug(s) must be stored in a safe and secure area with restricted access, under the storage conditions specified by GALDERMA (see Table 3).

6.3.3 Dispensing and return

The Investigator or designee is responsible for dispensing study drug in accordance with the protocol at the Baseline, Week 4 and Week 12 visits. Study drug will only be dispensed to subjects' parent/legal guardian in accordance with the conditions specified in the protocol.

Each subject kit will contain:

- 8 tubes of calcitriol 3 mcg/g ointment to be dispensed

All kits are to be numbered. The kit number is to be recorded in the eCRF. Dispensation and return of test material at each visit, is to be appropriately documented by the designated study personnel. Each subject's parent/legal guardian is to return all dispensed study tubes at each visit as appropriate.

Each subject's parent/legal guardian will receive the initial study drug supply at the Baseline visit and additional supplies at each interim visit. All study drug containers must be inventoried and a record of the dispensing and return of each container for each subject must be appropriately documented by the Investigator or designee using the IRT system. Requirements of all study drug returns will be reinforced for all subjects at each visit during the study. Any dispensing errors must be reported to the Sponsor/CRO and properly documented in the eCRF and source documentation.

Subject's parent/legal guardian will be instructed to return the study drug in order to have new study drug dispensed and the process will be repeated throughout the subject's participation. However, the study drug may be dispensed even if all tubes from previous visits are not returned, but the subject's parent/legal guardian will be instructed on the importance of returning the tubes prior to receiving further supplies.

Subjects/Subject's parents/legal guardians will be instructed by the Investigator or designee on the importance of being compliant with the use of the study drug(s) throughout the clinical trial but also about the importance of returning their study drug(s) (used and/or unused) at each visit.

All used and unused study drug tubes are to be returned to the Sponsor, or sponsor's contract vendor.

In the event of early termination/suspension of the clinical trial, a rapid recall of study drug(s) will be initiated. The Investigator or designee must immediately instruct the subjects to stop the study drug(s) regimen and return the study drug(s) to the clinical trial center.

For subjects who do not complete the entire clinical trial, all used and unused study drug(s) should be returned by the subjects to the defined personnel at the clinical trial center.

6.3.4 Treatment compliance management and record

Subjects / Subjects' parents/legal guardians will be required to fill out a dosing calendar to collect the date and time of each application and to bring back this dosing calendar at each visit. Upon study product return, the study staff will check the dosing calendar and the returned products. In case of bad compliance or missed applications, the study staff will re-instruct the subject / Subjects' parents/legal guardians on the proper use.

6.4 Dose modification

Temporary drug discontinuations and dose modifications may be permitted in instances of out-of-range laboratory results, local tolerability issues, and clearing/worsening of disease.

Subjects whose PTH results fall below the lower limit of normal will be assessed on a case-by-case basis; study drug application may be temporarily discontinued based on Sponsor and Investigator assessment. Serum PD parameters will be regularly checked (at least within 2 weeks) at Investigator's and Sponsor's discretion until the PTH level is back within the normal range (see section 5.6).

Subjects with abnormal serum albumin-adjusted calcium should temporarily discontinue study drug; the IDMC will recommend appropriate management of the subject on a case-by-case basis.

Subjects with other out-of-range laboratory results may temporarily discontinue study drug dosing until the issue resolves according to Investigator or IDMC discretion.

Subjects with suspected urolithiasis should temporarily discontinue study drug. If urolithiasis is not confirmed, the subject may resume treatment with study drug. Subjects with confirmed urolithiasis should permanently discontinue study drug use and complete the Week 26/ET visit.

Dose modifications (i.e. dosing only once a day) will also be permitted for skin tolerability issues according to Investigator discretion. Dose modifications may be made for up to 7 consecutive days and must be documented in the subject source document. In case of study drug dosage modification, an earnest attempt should be made to return the subject to a twice daily treatment regimen as soon as possible. Increasing the dose above 0.5 g/kg of body weight or 28 g/day is strictly prohibited.

Subjects who have a 2 grade worsening of their plaque psoriasis per the IGA scale, or who reach an IGA of 4, should be discontinued and complete the Week 26/ET visit. If the subject experiences complete clearing of psoriasis (IGA = 0), per physician assessment the subject should discontinue the study drug but continue to follow the visit schedule through the Week 26 visit. Treatment with study drug should be resumed if the IGA score is >0 and <4.

Two temporary study drug discontinuations or dose modifications are allowed and must be documented in the subject source documents. Additional study drug discontinuations or dose modifications must be discussed with the Sponsor.

6.5 Blinding

6.5.1 Verification of blinding

Not applicable to this study.

6.5.2 Unblinding during the clinical trial

Not applicable to this study.

7 CLINICAL TRIAL ASSESSMENT

7.1 Efficacy assessments

7.1.1 Efficacy measurements

IGA and Pruritus evaluations will be assessed at each visit on all treated areas.

7.1.1.1 IGA (as evaluated on all treated areas by a Board Certified (or any other regional equivalent) Dermatologist)

The IGA will be evaluated at each visit on a 0 to 4 point scale. The following definitions will be used to score IGA:

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

7.1.1.2 Pruritus (as evaluated on all treated areas)

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

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

7.1.1.3 Other Assessments:

Percent Body Surface Area (BSA) involved will be assessed using the methodology shown in Section 13.3, Appendix 3.

7.1.2 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

7.2 Safety assessment

A safety assessment will be conducted for all subjects at the screening visit (from the Informed consent signature) and every subsequent visit. The safety parameters are AEs, (to be recorded as specified in Section 7.2.3), laboratory safety tests, physical examination, and vital signs.

All abnormal findings at the screening visit identified as clinically significant by the Investigator, will be recorded in the Medical History form. For any clinically significant changes from the screening visit, an AE is to be recorded.

7.2.1 Physical examination and vital signs

7.2.1.1 Physical examination

The following body systems should be evaluated as "normal" or "abnormal" by the Investigator, at the visits per the Schedule of Assessments (Table 2):

- Skin
- Cardiovascular system
- Respiratory
- Abdomen
- Head and neck
- Musculoskeletal system
- Neurological function (mental status exam [level of consciousness, cognitive function], cranial nerve assessment, reflex testing, motor system assessment, sensory system assessment)
- Lymph nodes
- Psychological

Weight will be recorded every time a physical examination is performed and height will be evaluated at Screening Visit only.

The Investigator may choose to further investigate any other sign that he/she observes during the physical examination.

7.2.1.2 Vital signs

Evaluation of vital signs (blood pressure and pulse rate) will be performed after 5 minutes rest in sitting position. It will include measurement of systolic and diastolic blood pressure and pulse rate in the sitting position.

7.2.2 Laboratory safety tests

The following laboratory safety tests will be performed according to the Schedule of Assessments (Table 2).

- Hematology:

White blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin (Hb), hematocrit (hct), mean cell volume (MCV), and platelet count (Plt)

- Blood chemistry (non-fasting):

Total protein, alanine aminotransferase (ALT) (SGPT), aspartate aminotransferase (AST) (SGOT), alkaline phosphatase (ALP), blood urea nitrogen, creatinine (calculated creatinine clearance), and bilirubin (total and conjugated).

The Principal Investigator or another medically qualified Investigator must review and evaluate laboratory values for each subject in a timely manner. The Investigator will initial and date each laboratory report and note directly on the report whether or not each out-of-range laboratory value is clinically significant.

For each out-of-range laboratory result, the Investigator will enter in the eCRF the Investigator judgment on the presence or the absence of a clinical significance.

All out-of-range laboratory values at screening, identified as clinically significant by the Investigator, will be recorded in the medical history (report a diagnosis rather than individual laboratory parameters abnormality whenever possible).

All out-of-range laboratory values after screening, are to be assessed for clinical significance by the Investigator (physician) or another medically qualified Investigator and to be reported as an AE if <u>both of the following conditions</u> are met:

The abnormality suggests a disease and/or organ toxicity, and/or is considered pathological

AND

This abnormality was not present at the screening visit or is assessed as having worsened since the screening visit.

Unscheduled visits may occur due to laboratory result(s) that warrant further testing. If the Investigator observes a clinically relevant laboratory test value, the laboratory tests will be repeated as soon as possible and monitored until the values have returned to normal and/or an adequate explanation for the abnormality is found. This does not apply to screening laboratory test values.

An out-of-range laboratory value that is identified as clinically significant and related to the study drug(s) is considered by the Sponsor to be an Adverse Event of Special Interest (AESI) (see Section 7.2.3.1.3).

For AEs and AESIs, whenever possible, the Investigator is to provide a diagnosis rather than to report individual laboratory abnormalities.

A summary of sample volumes and the number of blood samples is detailed in Section 13.2, Appendix 2.

- Urinalysis:

A semi-quantitative urinalysis will be performed. The following parameters will be 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 collections, when feasible, or fasting (4 hour) urine samples. Subjects that are toilet-trained should be actively encouraged to complete the 24-hour urine collection. In case of Ca:Cr ratio above the normal range on a urine sample after fasting for 4 hours, the measurements should be repeated on a 24–hour urine collection whenever possible.

- Other Assessments
  - 1, 25(OH)2D
  - 25(OH)D
- Urine Pregnancy Test

Post menarcheal female subjects of childbearing potential will have a urine pregnancy test performed at all visits. Additional urine pregnancy tests may be performed at the Investigator's discretion.

For pre-menstrual subjects who begin menses after the Screening visit, pregnancy tests will be performed according to the Schedule of Assessments (Table 2) for females of childbearing potential (Baseline, Week 4, Week 12, Week 26/ET, and Week 30). In addition, subjects must adhere to the contraceptive methods as outlined in Inclusion Criteria 7.

The screening visit laboratory values must be available prior to the Baseline visit.

7.2.2.1 IDMC Case Management

The management of hypercalcemia and PTH-suppressed cases will remain under the responsibility of the IDMC.

All cases of hypercalcemia, confirmed urolithiasis, out of range PTH levels or decreases in PTH of 30% from the subject's Baseline visit will be communicated immediately to the Principal Investigator, to Clinical Safety Officer (see contact detail in section 7.2.3.2.2), and to the IDMC members as alerts, as appropriate. Galderma will receive recommendations from the IDMC on the management of the subject and on the study outcome.

Subjects with microscopic or macroscopic hematuria will be managed according to Investigator discretion. The IDMC will be notified of cases of hematuria as necessary. Management of subjects with suspected urolithiasis will be handled on a case by case basis. Subjects with suspected urolithiasis should temporarily discontinue study drug. If urolithiasis is not confirmed, the subject may resume treatment with study drug. Subjects with confirmed urolithiasis should permanently discontinue study drug use and complete the Week 26/ET visit.

7.2.3 Adverse Events

Adverse events (AEs) are to be monitored throughout the course of the clinical trial. All AEs are to be reported on the Adverse Event Form of the eCRF with complete information as required. If AEs occur, the main concern will be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical trial center personnel for reporting AEs and medical emergencies.

The subject's parent / legal guardian or subject (according to subject's maturity level), should be asked specifically about symptoms of kidney stones e.g. obvious hematuria or pyuria, or vague abdominal or flank pain/discomfort, or possible pain radiating to the groin area at each study visit.

7.2.3.1 Definitions

7.2.3.1.1 Adverse events (AE)

According to ICH E2A, an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Thus any new sign, symptom or disease, or any clinically significant worsening of an existing sign, symptom or disease compared to the condition at the first visit (including disease treated), should be considered as an AE. Lack of efficacy is not considered as an AE.

Each new episode of a chronic disease (e.g., hay fever, allergy, etc) should be reported as a new AE.

Notes:

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should also be reported as an AE.
- There should be an attempt to report a diagnosis rather than the signs, symptoms or abnormal laboratory values associated with the report of an AE. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain. Otherwise, symptoms, signs, or laboratory values should be used to describe the AE.
- Pregnancy is not to be considered as an AE; however, is an important medical event that must be monitored as described in Section 7.2.3.2.4.

7.2.3.1.2 Serious Adverse events (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

Note:

The term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of a diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrolment in the clinical trial, admission to a day-care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination).

7.2.3.1.3 Adverse Events of Special Interest (AESIs)

An AESI is a noteworthy event for the particular study drug that can be appropriate to monitor closely. It could be serious or non-serious and AESIs could include events that might be potential precursors or prodromal symptoms for more serious medical conditions in susceptible individuals.

AEs of special interest for this study are defined as:

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

For AESIs, the Investigator is required to complete the Adverse Event Form on the eCRF and follow the AESI reporting procedures in Section 7.2.3.2.3 even if the event is considered non-serious according to the usual regulatory criteria.

7.2.3.1.4 Unexpected adverse drug reaction

According to ICH E6, an unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study drug information (e.g., Investigator's Brochure for an unapproved investigational product or the package insert/summary of product characteristics for an approved product).

7.2.3.1.5 Adverse event reporting period

The clinical trial period during which AEs must be reported is the period from when the subject signed the Informed Consent Form to the end of the subject's participation.

The Sponsor should be informed if the Investigator becomes aware of any unusual safety information or any safety information that appears to be drug-related involving a subject who has participated in a clinical trial, even after a subject has completed the clinical trial. The Investigator should be diligent in looking for possible latent safety effects that may not appear until a medication has been discontinued.

7.2.3.1.6 Severity

Severity is a clinical determination of the intensity of an AE and not of a disease.

The Investigator is to classify the intensity of AEs using the following definitions as a guideline for all AEs occurring during clinical trials conducted or sponsored by GALDERMA. For this classification, the Investigator will take into account the possible range of the intensity of the event and report the grade of intensity which is the most appropriate according his medical judgment.

Mild	Awareness of signs or symptom, but easily tolerated.
Moderate	Discomfort, enough to cause interference with usual activity
Severe	Incapacitating with inability to work or perform usual activity

7.2.3.1.7 Relationship to the study drug(s)

The Investigator is to determine whether there is a reasonable causal relationship between the study drug(s) and the AE. Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction, temporal relationships, positive dechallenge or rechallenge, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during clinical trials conducted or sponsored by GALDERMA:

Reasonable possibility:

According to the reporting Investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered between:

- The study drug (investigational product, active comparator, or placebo/vehicle, etc.) and the AE,
- The clinical trial protocol procedure (such as UV-induction, biopsy, xylocaine injection, blood test or intraocular pressure measurement, etc) and the AE.

No Reasonable Possibility:

No suggestive evidence or arguments can be identified regarding a causal relationship between the study drug or the clinical trial protocol procedure and the AE.

7.2.3.2 Reporting procedures

7.2.3.2.1 Procedures for reporting Adverse Events

The collection of AEs is from the time that a subject signs the ICF to their final visit.

At each post-enrollment visit, the Investigator (or sub-Investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example "Have you noticed any change in your health since the last visit?" Directed questioning and examination will then be performed as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the study drug(s) or not, will be recorded immediately in the source document, and described on the Adverse Event Form of the eCRF along with the date of onset, severity, relationship to the study drug(s), and outcome, without omitting any requested and known information. Additional information may be requested under certain circumstances. Adverse Events (AEs) assessed as related to the treatment will be monitored until they are completely or satisfactorily resolved. Other AEs will be monitored until the last visit if they are not resolved or satisfactorily resolved.

The Investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow-up of the subject. If necessary, the Investigator will contact the subject's personal physician or hospital staff to obtain further details.

For SAEs (see Section 7.2.3.2.2), AESIs (see Section 7.2.3.2.3), cases of urolithiasis and pregnancies (see Section 7.2.3.2.4), the CSO is to be informed immediately by e-mail/fax. The event must be reported by fax or sent by e-mail to the CSO within 24 hours of receipt of the information (contact details in Section 7.2.3.2.2).

7.2.3.2.2 Procedure for reporting a Serious Adverse Event

For an SAE occurring during the period of the clinical trial, regardless of whether it is related to the treatment or not, and of whether it is expected or not, the Investigator must do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.
2. Immediately inform the CSO of the event by e-mail or by fax and discuss further actions to be taken.

Clinical Safety Officer
For North America: Phone: (+1) (609) 235-6035 - Fax: (+1) (609) 228-6153
E-mail: pharmacovigilance@galderma.com

For EU: Phone: +33 (4) 92 95 29 69 – Fax: +33 (4) 93 95 70 92
E-mail: pharmacovigilance@galderma.com

For regions outside of North America and the EU, a Clinical Safety Officer will be designated as necessary. Additional contact details are provided in the Investigator's site file.

3. Complete the Adverse Event Form provided in the eCRF as fully as possible.
4. Ensure that the event is classified as an SAE.
5. Print and complete the Serious Adverse Event Form (available in the EDC system as PDF document). Fax or scan and send by e-mail the completed form, accompanied by any other relevant information or medical records (e.g., laboratory test results) within 24 hours of receipt of the information to the GALDERMA CSO. The demographics, medical history, previous and concomitant therapies, and adverse event pages of the eCRF must be completed and available for review in the EDC system at the time of the report.
6. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all additional follow-up evaluations, fax or scan and send by e-mail all additional follow-up information to the GALDERMA CSO within 24 hours of receipt of the updated information. Serious Adverse Events (SAEs) will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
7. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
8. Inform the CSO of the final outcome of the event. Send a revised or updated Serious Adverse Event Form and Adverse Event Form, if appropriate.
9. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC).

7.2.3.2.3 Procedure for reporting an Adverse Event of Special Interest

For any AESI (see Section 7.2.3.1.3) occurring during the period of the clinical trial, whether related to the treatment or not, and whether expected or not, the Investigator is to do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of subjects is the first priority.
2. Immediately inform the CSO by e-mail or fax of the event.
3. **Investigator contact: Refer to Section 7.2.3.2.2**
4. Complete the Adverse Event Form provided in the eCRF as fully as possible.
5. Ensure that the event is classified as an AESI.
6. Print the Adverse Event form. Fax or scan and send by e-mail the completed form, accompanied by any other relevant information or medical records (e.g. laboratory test results) within 24 hours of receipt of the information to the GALDERMA CSO. The demographics, medical history, previous and concomitant therapies, and adverse event pages of the eCRF must be completed and available for review in the EDC system at the time of the report.
7. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all the additional follow-up evaluations, first inform the CSO of the outcome by fax or send the additional follow-up information by e-mail to the GALDERMA CSO within 24 hours of receipt of the updated information. AESIs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
8. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further information such as anonymized medical records.
9. Inform the CSO of the final outcome of the event. Send a revised or updated Adverse Event Form, if appropriate.

7.2.3.2.3.1 Procedure for suspected sensitization (Challenge and Rechallenge Patch Test procedures)

If a subject experiences a suspected skin sensitization (contact allergy), follow this procedure to characterize the event:

1. Stop the study drug
2. **Document the event as an AESI, phone the CSO immediately and report the event within 24 hours as described in Section** 7.2.3.2.2**.**
3. After all signs and symptoms have resolved (after a minimum of two weeks), perform a re-challenge with the assigned study drug.
4. Apply the assigned study drug to a naive area on the back (approximately 1 inch in diameter, 2.54 cm) and cover it with non-occlusive gauze (dressing) for 48 hours.
5. After 48 hours, remove the gauze and evaluate the site:
   - at approximately 15 to 30 minutes (1st reading) and,
   - at 48 hours (2nd reading) .
   - A facultative 3rd reading must be performed at 96 or 120 hours after removal of the gauze if the second reading is equivocal.

Duration of study drug application	1st Reading	2nd Reading	3rd Reading
48 hours	15 to 30 minutes (after gauze removal)	48 hours (after gauze removal)	96 or 120 hours (after gauze removal)

6. Use the following numerical (0 to 4) grading system at each reading:

0	No reaction	No reaction
1	Mild erythema	Slight redness
2	Moderate erythema	Definite redness easily recognized
3	Severe erythema OR erythema with edema	Intense redness or redness associated with local swelling
4	Erythema with vesicles or erosion or bullae	Redness with small or large blisters or skin abrasion (can be accompanied by weeping/oozing, crusting)

7. At last reading, the investigator will provide an assessment regarding a possible sensitization reaction using the following scale:

Sensitization Reaction	
0	Negative (might include an irritative reaction)
1	Equivocal
2	Positive

8. Report the results from the re-challenge test as directed by the sponsor and document with photographs.
9. If the re-challenge is negative, the subject may resume treatment.
10. If the re-challenge is positive or equivocal, notify the CSO immediately and initiate a skin sensitization patch test as directed by the sponsor (with the study drug and possibly individual ingredients) after an additional 2 weeks and after all signs and symptoms have resolved. Follow the same procedure for the patch test as for the rechallenge.

7.2.3.2.4 Procedures for reporting pregnancies

Any pregnancy occurring during clinical trials, where the fetus could have been exposed to the study drug(s), must be monitored until its outcome in order to ensure the complete collection of safety data on GALDERMA products.

If a subject becomes pregnant, the Investigator is to do the following:

1. **Withdraw the subject from the clinical trial.**
2. Complete the Pregnancy Surveillance Form – Part I: History and Start of Pregnancy, provided by the CRA at the beginning of the clinical trial, as fully as possible. Fax or send by e-mail this pregnancy form along with the Exit Form within 24 hours of receipt of the information to the GALDERMA CSO.
3. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask regular follow-up information.
4. Inform the GALDERMA CSO of the progress by tri-monthly updates until the final outcome of the pregnancy. For all the additional follow-up evaluations, fax or send by e-mail the additional follow-up information to the GALDERMA CSO within 24 hours of receipt of the information. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with two phone calls and a letter (certified with return receipt) is required.
5. At the outcome of the pregnancy, complete the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy, as fully as possible. Inform the CSO by e-mail/fax, then fax or send by e-mail this pregnancy form to the GALDERMA CSO within 24 hours of receipt of the information.
6. If the pregnancy leads to an abortion (voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for declaration of an SAE (see Section 7.2.3.2.2).

7.3 Pharmacodynamic assessments

The following Pharmacodynamic assessments will be performed according to the Schedule of Assessments (Table 2):

- *Serum (non fasting):* calcium, phosphorus, albumin (in order to calculate the serum albumin-adjusted calcium), PTH.
- *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 that are toilet-trained should be actively encouraged to complete the 24-hour urine collection.

7.4 Pharmacokinetic assessment

7.4.1 Blood sampling

The systemic level of calcitriol will be assessed at each visit using a single blood sample (C_t) according to the Schedule of Assessments (Table 2). To avoid tube contamination, drug product application and blood draws have to be performed in different rooms. Blood samples will have to be collected in either the morning or evening (to be determined at screening according to the subject's lifestyle). In addition, for the blood samples to be drawn during the treatment period (i.e. at Week 4, Week 12 and Week 26), the sampling has to occur 12 hours (±1 h) after the last product application. Blood sampling procedure and handling of samples will be described in a separate document.

7.4.2 Plasma concentrations

Calcitriol plasma concentrations will be determined using an appropriately validated method by the sponsor or its representative. A bioanalytical protocol describing the details of the bioanalytical process will be written prior to the samples assays to specify the method and the acceptance criteria that will be used for the bioanalytical part of the study. The results will be described in a bioanalytical report which will be included in the Clinical Study Report (CSR).

7.4.3 Pharmacokinetic measurements

The pharmacokinetic analysis will be carried out by GALDERMA R&D, Sophia Antipolis, France. The C_t mean values and the standard deviation (SD), will be calculated and reported.

Assessments occurring at screening and baseline (before product application) will allow determining calcitriol endogenous levels variability. Pre-dose samples performed at Weeks 4, 12, and 26 will document the calcitriol plasma concentration during the treatment period. Blood sample drawn at week 30 visit allow determining the calcitriol plasma concentration one month after the last drug product application.

7.5 Other assessments

Percent Body Surface Area (BSA) involved will be assessed at each visit using the methodology shown in Section 13.3, Appendix 3.

7.6 Appropriateness of measurements

The measurements used in this study are based on the pivotal Phase 3 studies, completed in 2002, confirming safety and efficacy of calcitriol 3 mcg/g ointment in adult subjects.

8 CLINICAL TRIAL VISITS DESCRIPTIONS AND PROCEDURES

8.1 Description of clinical trial visits

Please refer to the Schedule of Assessments table in the Synopsis (Table 2).

A written, signed ICF, Assent form for minors, and HIPAA/PIPEDA authorization must be obtained prior to performing any clinical trial-related evaluations and/or procedures.

8.1.1 Screening visit

1. Review and explain the nature of the study to the subject (to the extent of his/her maturity) and to the subject's parent/legal guardian and record this process in the subject's file.
2. 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 or PIPEDA (as appropriate) form at Screening visit prior to any study related procedures being performed. Provide the parent/legal guardian with a signed copy of each.
3. Assign a subject identification number using the IRT system (Section 6.1.2).
4. Verify inclusion/exclusion criteria.
5. Ask the subject's parent/legal guardian or subject (according to subject's maturity level) about previous therapy/procedures, concomitant therapy/procedures, demography and medical history including the history of psoriasis (date of psoriasis onset, previous treatment, success of treatment).
6. For post menarcheal females, collect a urine sample from the subject and perform a urine pregnancy test.
7. Perform a physical examination and record vital signs.
8. Record the % BSA involved with psoriasis (excluding face and scalp) (See Section 13.3, Appendix 3).
9. Evaluate pruritus.
10. Evaluate IGA.
11. Obtain serum samples for routine blood chemistry, hematology, 1,25(OH)2D, 25(OH)D, and serum pharmacodynamic sampling. Prepare them according to the Central Laboratory manual.
12. For selected subjects enrolled in the PK analysis: Collect blood sample for PK assessment.
13. Obtain urine sample for urinalysis.

14. Distribute the container for urine collection and provide instructions for 24-hour urine collection, as necessary. Subject/subject's parent/legal guardian can start collecting urine as of the screening visit day and subject's parent will bring the container back to the site 24 hours later. If the urine sample after fasting for 4 hours could not be performed on site, the subject's parent/legal guardian will be given the necessary material to perform it at home, and the parent will be asked to bring it back afterwards.

Note: all Screening labs must be reviewed by the Investigator prior to the Baseline visit.

15. Question the subject's parent/legal guardian or the subject (according to subject's maturity level) about the occurrence of Adverse Events. Events occurring after the Informed Consent Form has been signed should be recorded as Adverse Events in the eCRF.
16. Schedule an appointment for the Baseline Visit.

8.1.2 Baseline visit

1. Confirm the subject continues to meet the inclusion/exclusion criteria.
2. Document discussion with subject and parent/legal guardian(s) in regard to continued willingness to participate in the study.
3. Confirm laboratory results from screening meet study entry requirements.
4. For post menarcheal females, collect a urine sample and perform a urine pregnancy test.
5. Ask the subject and parent/legal guardian whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Drugs/Therapies form in the eCRF.
6. Perform a physical examination and record vital signs.
7. Question the subject's parent / legal guardian or subject (according to subject's maturity level) about the occurrence of AEs. Non-persuasive open ended questions are to be asked, such as "Have you noticed any change in your health since last visit?".
8. Question the subject's parent / legal guardian or subject (according to subject's maturity level) specifically about symptoms of kidney stones e.g. obvious hematuria or pyuria, or vague abdominal or flank pain/ discomfort, or possible pain radiating to the groin area.
9. Record the % BSA involved with psoriasis (excluding face and scalp) (See Section 13.3).
10. For subjects in the PK group only, collect blood for serum pharmacodynamic assessment. Prepare the sample according to the Central Laboratory Manual.
11. For selected subjects enrolled in the PK analysis: Collect blood sample for PK assessment.
12. Evaluate IGA.
13. Evaluate pruritus.

14. Assign the subject a study drug kit using the IRT system (Section 6.1) and provide the subject and parent/legal guardian with study medication as well as instructions for application and dosing calendar. .
15. Demonstrate to the subject's parent / legal guardian how to apply the study medication and how to document application on dosing calendar.
16. Ask the subject's parent / legal guardian to bring back the study medication on the next visit whether used or unused and to bring back the completed dosing calendar.
17. Provide Cetaphil® Moisturizing Cream and Cetaphil® Gentle Skin Cleanser or equivalents to the subject and parent/legal guardian.
18. Schedule an appointment for the Interim visits (Weeks 4 and 12).). For subject with PK assessments, the sampling should occur within 12±1 hour after the last product application., Therefore, remind the subject and parent/guardian that no applications should be performed at home just before the PK blood sampling (AM or PM application depending on scheduled appointment time).

8.1.3 Interim visits (Weeks 4 and 12)

1. Evaluate IGA.
2. Evaluate pruritus.
3. Document discussion with subject and parent/legal guardian in regards to continued willingness to participate in the study.
4. Record the % BSA involved by psoriasis (excluding face and scalp) (See Section 13.3).
5. Obtain laboratory samples according to the Central Laboratory Manual.

5.1. Blood

5.1.a. Weeks 4 and 12: Obtain serum samples for routine blood chemistry and hematology.

5.1.b. Weeks 4 and 12: Obtain samples for pharmacodynamics parameters (serum sample for all subjects) and PK assessment (plasma sample only for selected subjects included in the PK evaluation). Sample obtained within 12±1 hour after the last product application. Therefore, remind the subject and parent/guardian that no applications should be performed at home just before the PK blood sampling (AM or PM application depending on scheduled appointment time).

5.1.c. Week 12: Obtain serum sample for 25(OH)D and 1, 25(OH)2D.

5.2. Urine

5.2.a. Weeks 4 and 12: Obtain urine sample for urinalysis and for post menarcheal females, also perform a urine pregnancy test on the urine sample collected.

5.2.b. Weeks 4 and 12: Distribute container and provide instructions for 24-hour urine collection to be started 1 day prior to Week 12 and Week 26/ET visits, respectively. The study site should contact the parent/legal guardian 48 hours prior to the visit to remind them to start the urine collection.

5.2.c. Week 12: For PD urine, get the 24-hour urine collection from subject or collect fasting (4 hour) urine sample when 24-hour collection is not possible.

6. Question the subject and parent/legal guardian about the occurrence of AEs. Non-persuasive open ended questions are to be asked, such as "Have you noticed any change in your health since last visit?"

7. Question the subject's parent / legal guardian or subject (according to subject's maturity level) specifically about symptoms of kidney stones e.g. obvious hematuria or pyuria, or vague abdominal or flank pain/ discomfort, or possible pain radiating to the groin area.

8. Week 12 only: Perform physical examination and record vital signs

9. Ask the subject and parent/legal guardian whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Drugs/Therapies form in the eCRF.

10. Collect the study medication that was dispensed at the previous visit.

11. Review medication compliance and review dosing calendar for completeness.

12. Weeks 4 and12: Dispense study medication to the subject's parent/legal guardian using the IRT system.

13. Weeks 4 and12: Provide Cetaphil® Moisturizing Cream and Cetaphil® Gentle Skin Cleanser or equivalents to the subject's parent/legal guardian.

14. Ask the subject's parent/legal guardian to return the study medication for the next visit even if used or unused.

15. Schedule an appointment for the Week 26/Early Termination Visit and remind the subject and parent/guardian to bring the completed dosing calendar.

8.1.4 Week 26 Visit / Early Termination visit

1. Document discussion with subject and parent/legal guardian in regards to continued willingness to participate in the study.
2. For post menarcheal females, collect a urine sample and perform a urine pregnancy test.
3. Record the % BSA involved by psoriasis (excluding face and scalp) (See Section 13.3).
4. Perform physical exam and record vital signs.
5. Obtain serum samples for routine blood chemistry, hematology, 1, 25(OH)2D, 25(OH)D and serum pharmacodynamic sampling and urine samples for urinalysis. Prepare them according to the Central Laboratory manual.
   - 5.1. For PD urine, get the 24-hour urine collection from subject or collect fasting (4 hour) urine sample when 24-hour collection is not possible.
   - 5.2. Provide a new container and instructions for 24-hour urine collection to be started 1 day prior to Week 30 Follow-up visit (for all subjects in the PK group and at the Investigator's discretion for all other subjects, such as in the case where the PD urine assessment from week 26 would be abnormal). The study site should contact the parent/legal guardian 48 hours prior to the visit to remind them to start the urine collection.
6. For selected subjects enrolled in the PK analysis: Collect blood sample for PK assessment.
7. Evaluate IGA.
8. Evaluate pruritus.
9. Question the subject's parent/legal guardian or subject (according to subject's maturity level) about the occurrence of Adverse Events. Non-persuasive open ended questions are to be asked, such as "Have you noticed any change in your health since last visit?"
10. Question the subject's parent / legal guardian or subject (according to subject's maturity level) specifically about symptoms of kidney stones e.g. obvious hematuria or pyuria, or vague abdominal or flank pain/ discomfort, or possible pain radiating to the groin area.
11. Ask the subject and parent/legal guardian whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Drugs/Therapies form in the eCRF.
12. Check that the subject and/or parent/legal guardian has brought back all the study medication, even if unused, and check on compliance and review the dosing calendar.
13. Provide Cetaphil® Moisturizing Cream and Cetaphil® Gentle Skin Cleanser or equivalents to the subject's parent/legal guardian.

8.1.5 Week 30 Follow-up visit

1. For post menarcheal females, collect a urine sample and perform a urine pregnancy test.
2. Record the % BSA involved by psoriasis (excluding face and scalp) (See section 13.3, Appendix 3).
3. Obtain serum samples for laboratory testing (full panel) for subjects in the PK group. For all other subjects, obtain serum samples for laboratory testing at the Investigator's discretion (all subjects). Obtain urine for urinalysis (all subjects).
4. Obtain serum samples for 1,25(OH)2D, 25(OH)D and serum PD parameters for subjects in the PK group. For all other subjects, obtain serum samples at the Investigator's discretion. Prepare them according to the Central Laboratory manual.
5. Obtain 24-hour urine sample for PD urine for subjects in the PK group and send it to the central lab for analysis. For all other subjects, obtain 24-hour urine sample at the Investigator's discretion and send it to the central lab for analysis.
6. For selected subjects enrolled in the PK analysis: Collect blood sample for PK assessment.
7. Evaluate IGA.
8. Evaluate pruritus.
9. Question the subject's parent/legal guardian or subject (according to subject's maturity level) about the occurrence of Adverse Events. Non-persuasive open ended questions are to be asked, such as "Have you noticed any change in your health since last visit?"
10. Question the subject's parent / legal guardian or subject (according to subject's maturity level) specifically about symptoms of kidney stones e.g. obvious hematuria or pyuria, or vague abdominal or flank pain/ discomfort, or possible pain radiating to the groin area.
11. Ask the subject and parent/legal guardian whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Drugs/Therapies form in the eCRF.
12. After collecting all data from the subject (including laboratory samples results), complete the Exit form of the eCRF.

8.1.6 Unscheduled visits

When necessary and exceptionally, unscheduled visits could take place due to an advent event (AE) needing a specific treatment, AE leading to withdrawal from the study, laboratory result(s) that warrant further testing, or other reason. Please complete appropriate eCRF AE form if necessary. Assessments to be performed will be at the Investigator's discretion according to the reason for the Unscheduled visit.

8.2 Subject instructions (other than study drug(s) administration)

Subjects should wait at least six hours after the study treatment application before swimming or bathing.

The Cetaphil® Moisturizing Cream or equivalent (provided by the Sponsor) may be used during the study as needed on non- treated areas of the skin. A Cetaphil® Gentle Skin Cleanser or equivalent (provided by the Sponsor) may be used for cleansing.

Subjects will be permitted to use medicated shampoos that do not contain corticosteroids or vitamin D derivatives to treat scalp psoriasis. Tar products can be used on the face and scalp areas.

No other topical treatments, other than the test materials, will be permitted on the treated areas. However, emollients and sunscreen on healthy skin areas are permitted during the course of the study.

Dietary instructions: subjects will be asked to maintain the same dietary habits, especially calcium intake as before the study. Subjects should maintain adequate hydration. Detailed instructions will be provided to the subjects regarding appropriate hydration in the subject instructions document.

It is recommended that the subject use protective clothing and other measures/precautions to protect themselves from excessive sun exposure while participating in this study.

9 STATISTICAL METHODS PLANNED

9.1 Statistical and analytical plans

A Statistical Analysis Plan (SAP) will be developed as a separate document. The SAP will contain a more detailed and technical description of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in the sections of the clinical trial protocol below. Any change to the primary objective of the study or to the statistical method of primary endpoint will require the protocol and the SAP to be amended prior to database lock. Changes to the planned analyses of other non-primary endpoints, as well as any additional and unplanned statistical analyses will be documented in the clinical study report, and in an amended SAP if these changes occur before database lock. Any further change to the planned analyses (such as, addition of post-hoc analyses) made to the finalized SAP will be documented in the clinical trial report.

9.1.1 Analysis Endpoints

9.1.1.1 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

9.1.1.2 Key Safety Endpoints

- Laboratory: Serum albumin-adjusted calcium, urine calcium : creatinine ratio, phosphorus, and PTH.
- Adverse Events

9.1.1.3 Pharmacokinetic Endpoint

- C_t

9.1.2 Populations analyzed, evaluability and limitation / evaluation of bias

Prior to the final database lock of the study, a data review will occur to assess the potential bias of any data issues for final statistical analyses; and to determine the final subject populations for statistical analyses. Decisions made from the data review will be documented and any changes to the SAP will be made before database can be locked.

The statistical analyses will be performed based on the safety population.

9.1.2.1 Safety Population

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

9.1.3 Data presentation and graphics

In general, the categorical variables will be summarized by frequency and percentage for each response category (N, %). The continuous variables will be summarized using means, medians, minimum, maximum, and standard deviations for the data collected at each visit

9.1.4 Efficacy analysis methods

9.1.4.1 Handling of missing data

No missing data handling will be performed. All data will be summarized as observed.

9.1.4.2 Analyses of the efficacy endpoints

No formal inferential statistical analysis will be performed. IGA will be summarized by each category and by shift changes over time.

In addition, observed and changes from baseline of the IGA and Pruritus over time will be summarized as continuous variables.

9.1.5 Safety analysis methods

No inferential statistical analysis is planned for safety endpoints of the study.

The laboratory parameters at scheduled visits and change from Screening at post-baseline visit(s) will be summarized descriptively by treatment and by visit. A shift table for lab parameters at Screening versus Week 26/ET will be provided when appropriate.

Only Treatment-emergent Adverse Events (TEAEs) will be summarized. A TEAE is defined as an AE with an onset date on or after the first application of the study drug.

TEAEs will be tabulated in frequency tables by System Organ Class and Preferred Term based on the Medical Dictionary for Regulatory Activities (MedDRA). Additional summary tables will be provided for TEAEs that are considered serious (SAEs), related to the study drug(s), and severe. TEAEs that are AESIs, as well as TEAEs leading to discontinuation will also be summarized. For a given TEAE, a subject will be counted once even if he/she has experienced multiple episodes of that particular TEAE. Subgroup summaries of TEAEs will be provided based on gender, age group, and race when appropriate.

Prior and concomitant therapies and procedures will be summarized. A prior therapy/procedure is one that ends at or before baseline; and a concomitant therapy/procedure is one starting after the baseline visit.

Extent of study drug exposure and compliance will also be summarized.

9.1.6 Pharmacokinetics analysis

C_t will be submitted after logarithmic transformation (Ln), to paired comparisons of Baseline and each subsequent time point. Ninety percent confidence intervals of the pairwise differences will be calculated using the Student's t statistic. The limits of the intervals will be back-transformed into exponential to obtain 90% confidence intervals of the ratios of geometric means between time points, on the original scale.

PK/PD relationships will be investigated by correlating C_t with appropriate PD parameters, using Spearman coefficient and graphical illustrations.

9.1.7 Subject disposition and baseline demographics

Subjects in each analysis population, treated, discontinued and reasons for discontinuation will be summarized.

Demographics and baseline characteristics will also be summarized.

9.1.8 Subgroup analyses

Subgroup analyses for safety data will be performed by age group, gender, and race. Details will be provided in the SAP.

9.1.9 Interim analyses and data monitoring

No interim analysis is planned in the study.

There will be an Independent Data Monitoring Committee (IDMC) to safeguard the interests of the study participants. Details of the IDMC are described in Section 7.2.2.1.

Frequency and type of statistical analyses to be performed for IDMC review will be detailed in the IDMC Charter.

9.2 Sample size determination

9.2.1 Assumptions

No formal sample size calculation has been performed.

9.2.2 Sample size calculation

As a screen failure rate of approximately 40 percent is expected, screening of approximately 167 subjects is planned in order to achieve the target of 100 subjects enrolled into the study.

10 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

10.1 Personnel training

Site initiation visits will be conducted for all Principal Investigators and Study Coordinators to review and discuss protocol, study procedures, eCRF completion and basic GCP Regulations and ICH Guidelines. Evaluation scales will also be reviewed by the Sponsor's Medical Expert or a clinical expert at Investigator Training Meetings. Laboratory collection and processing procedures and other study required procedures will also be discussed.

Prior to enrolling any participants, each site will have a site initiation visit conducted. All CRAs responsible for study monitoring will receive the appropriate study specific training. The training will focus on the treatment indication, protocol, monitoring guidelines, SOPs, and study specific logistics.

An Investigator Site File will be provided to each site.

10.2 Clinical monitoring

The conduct of the clinical trial will be closely monitored by representatives of GALDERMA to verify adherence to the clinical trial protocol, ICH-GCP guidelines, and applicable SOPs.

The Investigator will allow the CRO/Sponsor's representatives, to have direct access to all clinical trial records, eCRFs, corresponding subject medical records, study drug(s) dispensing records, study drug storage area, clinical trial facilities, and any other documents considered source documentation.

The Investigator also agrees to assist the representative if required.

10.3 Data management

All data management procedures will be detailed in a Data Management Plan (DMP).

The DMP will describe the Electronic Data Capture (EDC) system that will be used to collect data, and whether the data management activities are performed internally or outsourced. Computerized edit checks and review processes will be performed on an ongoing basis as outlined in the DMP until all data clarifications are resolved. The data will be exported to be stored in SAS datasets. After all data clarifications are resolved, coding is approved, and subject's evaluability is determined, the database will be locked.

10.4 Quality assurance / audit / inspection

The clinical trial is conducted under the sponsorship of GALDERMA in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines and in accordance with the SOPs for clinical trial conduct and monitoring from GALDERMA and/or the Contract Research Organization (CRO).

Audits of clinical trial centers may be conducted by the Sponsor/CRO representatives, and inspection may be performed by Regulatory Authority inspectorates or IRBs/IECs before, during, or after the clinical trial.

The Investigator will allow and assist the CRO/Sponsor's representatives, IRBs/IECs and any regulatory agency to have direct access to all requested clinical trial-related records.

For the audits performed by, or on behalf of, GALDERMA auditors, acknowledgement letters(s) will be provided by Quality Assurance.

10.5 Changes in clinical trial conduct / amendments

10.5.1 Clinical trial conduct

With the exception of eliminating an immediate hazard to a subject, the Investigator should not deviate from the clinical trial protocol or implement any changes without written approval from the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment.

Changes that involve only logistical or administrative changes to the clinical trial protocol are authorized. The Investigator should document and explain any deviation from the clinical trial protocol.

10.5.2 Amendments

The Sponsor may modify the clinical trial protocol at any time for ethical, medical, or scientific reasons.

No amendment can be implemented at clinical trial centers, unless to eliminate an immediate hazard to the subjects, without having been submitted to FDA for its review and having obtained approval from the IRB with responsibility for review and approval of the clinical trial.

Once this amended protocol is implemented by each study center, it will apply to newly enrolled subjects at that site. Current subjects will continue to follow the original protocol through to completion.

11 ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

11.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This clinical trial protocol and all amendments will be reviewed and approved by the appropriate IECs/IRBs.

11.2 Ethical conduct of the clinical trial

This clinical trial will be conducted in accordance with the protocol, the HELSINKI declaration (1964) and subsequent amendments, and the ICH GCP, and in compliance with applicable regulatory requirements.

The Health Insurance Portability and Accountability Act (HIPAA) will apply to the study centers within the U.S.A. and the Personal Information Protection and Electronic Documents Act (PIPEDA) will apply to the sites in Canada.

11.3 Subject information and consent

All subjects who participate in this clinical trial are required to be fully informed about the clinical trial in accordance with GCPs guidelines, federal regulations, HIPAA or PIPEDA (when applicable) and guidelines and in accordance with local requirements.

The ICF and Assent Form, approved by an IRB/IEC, will be fully explained to the subject and/or their parent/legal guardian.

Prior to enrollment into the clinical trial, the subject and the subject's parent/legal representative will sign and date the consent form and assent form(s). The Investigator is responsible for maintaining each subject's consent form(s) in the Investigator's site file and providing each subject, or his/her parent legal representative, with a copy of the signed and dated consent form(s).

11.4 Contractual requirements

A contractual agreement will be signed between the CRO/Sponsor and each Investigator/Institution. This document will contain supplementary information, including financial terms, confidentiality, the clinical trial schedule, third party responsibility, and publication rights.

11.5 Data collection and archiving

11.5.1 Data collection

The Investigator must maintain all required records for all subjects. Data for this clinical trial will be recorded in the subject's source documents and on the eCRFs provided by the Sponsor. All data should be recorded on the eCRFs completely and promptly.

11.5.2 Source documentation

The Investigator must keep accurate separate records (other than the eCRFs) of all subject visits, being sure to include all pertinent clinical trial-related information. A statement should be made indicating that the subjects have been included in this clinical trial and have provided signed written Informed Consent and Assent, as appropriate. All AEs must be thoroughly documented.

Results of any diagnostic tests conducted during the clinical trial should also be included in the source documentation.

11.5.3 Archives

All pertinent data, samples, photographs, correspondence, and reports, the original or amended clinical trial protocol, and all other material relating to the clinical trial will be maintained securely in Sponsor/CRO/Investigator/Institution archives for the legally required duration for archiving.

The Investigator/Institution should maintain the essential clinical trial documents as specified in Section 8 of ICH-GCP, and according to the applicable regulatory requirements.

The Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

If the Principal Investigator retires, relocates, or withdraws from the responsibility of keeping the clinical trial records for any other reasons, custody must be transferred to a person who will accept the responsibility. The Sponsor/CRO must be notified in writing of the name and address of the new custodian.

11.6 Insurance

A certificate attesting Third Party coverage of CRO/Sponsor will be provided upon request.

11.7 Investigator and Administrative Structure

Designation of a Coordinating Investigator (CI) will be done pursuant to the European Agency for the Evaluation of Medicinal Products (EMA) guidance on "Coordinator Investigator Signature of Clinical Study Reports".

Please refer to the Investigator Site List and completed FDA Form 1572 for each participating site.

12 LITERATURE REFERENCE LIST

Farber EM, Nall L. Childhood psoriasis. *Cutis*. 1999 Nov;64(5):309-14.

Gerritsen MJ, Van De Kerkhof PC, Langner A. Long-term safety of topical calcitriol 3 microg g(-1) ointment. *Br J Dermatol.* 2001; 144(Suppl 58):17-9.

Katz HI, Hien, NT, Prawer SE, et al. Superpotent topical steroid treatment of psoriasis vulgaris – clinical efficacy and adrenal function. *J Am Acad Dermatol.* 1987; 16:804-11.

Lewkowicz D, Gottlieb AB. Pediatric psoriasis and psoriatic arthritis. *Dermatol Ther.* 2004;17(5):364-75.

Nanda A, Al-Hasawi F, Alsaleh QA. A prospective survey of pediatric dermatology clinic patients in Kuwait: an analysis of 10,000 cases. *Pediatr Dermatol.* 1999 Jan-Feb;16(1):6-11.

Schwartz, et al. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics*. 1976; 58(2): 259-263.

Shull B, Haughey D, Koup J, et al. A useful method for predicting creatinine clearance in children. *Clin Chem.* 1978; 24(7): 1167-1169.

Data on file: Evaluation of the efficacy and safety of twice daily application of calcitriol 3 mcg/g ointment and its vehicle, in the treatment of chronic plaque psoriasis. Galderma RD.06.SRE.18053

Data on file: Evaluation of the efficacy and safety of twice daily application of calcitriol 3 mcg/g ointment and its vehicle, in the treatment of chronic plaque psoriasis. Galderma RD.06.SRE.18054

From General Practice Notebook “Rules of Nines - Pediatric subjects”: http://www.gpnotebook.co.uk/simplepage.cfm?ID=-999620530&linkID=30283&cook=yes (accessed 30 March 2009).

Other References

ICH E3 Structure and Contents of Clinical Reports

ICH E6 Good Clinical Practice

ICH E8 General Considerations for Clinical Trials

Investigator’s Brochure

The Declaration of Helsinki (1964) and latest updates

13 APPENDICES

13.1 Appendix 1 Unauthorized Therapy

The list provides examples of treatments known to impact upon calcium homeostasis. If the Investigator becomes aware of a drug used in a particular country that does not appear on the list below, this can be discussed with the Sponsor's Medical Advisor on a case-by-case basis. The trade names used below are the ones most commonly encountered for the drugs listed; there may be some variability in trade names in different countries participating in the study, which is acceptable. The investigator is expected to review all concomitant medications taken by the subjects. Subjects enrolled in this study should not 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:

aminocaproic acid (trade names include Amicar, Cyklokapron)

amiodarone (trade names include Cordarone, Pacerone)

androgen hormones (trade names include Halotestin, Metandren, Deca-Durabolin, Testosterone)

betacarotene (trade names include Lumitene, Max-Caro)

anti-seizure medications (trade names include Apo-Carbamazepine, Gabapentin, Klonopin, Keppra, Lamictal, Tegretol, Trileptal)

chlorthalidone (trade names include Hygroton, Thalitone)

clopamide (trade names include Brinedine)

cyclosporine (trade names include Neoral, Sandimmune)

diltiazem (trade names include Cardizem, Cartia XT, Dilacor XR, Diltia XT, Tiazac)

glucocorticoids (generic names include Betamethasone, Budesonide, Cortisone, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone).

lithium carbonate (trade names include Lithobid, Eskalith)

nifedipine (trade names include Adalat CC, Procardia, Procardia XL)

tamoxifene citrate (trade names include Nolvadex)

tazarotene (trade names include Tazorac, Avage)

triamterene (trade names include Dyrenium)

thiazide diuretics (trade names include Diucardin, Esidrix, Hydro-chlor, Microzide, Apo-Hydro, Urozide)

Vitamin D and Vitamin D analogs:

Alphacalcidol (trade names include One-Alpha)

calcipotriol (trade names include Dovonex)

calcitriol (trade names include Rocaltrol, Calcijex)

dihydrotachysterol (trade names include DHT, Hytakerol)

Vit. D analogs approved for renal osteodystrophy including Hectoral and Paricalcitol (trade names include Zemplar)

13.2 Appendix 2 Total Blood Sample Volumes and Number of Blood Sampling

18131	Standard analyses sampling volumes	Standard analyses sampling volumes (for subjects included in the PK assessment)	Total number of blood draws Per visit
Screening			1
1, 25(OH)2D	2.5 mL	2.5 mL	
25(OH)D	2.5 mL	2.5 mL	
Pharmacodynamic serum	5 mL	5 mL	
Routine hematology	2 mL	2 mL	
Routine biochemistry	3 mL	3 mL	
PK blood sampling	---	5 mL	
Baseline			1
Pharmacodynamic serum	---	5 mL	
PK blood sampling	---	5 mL	
Week 4			1
Pharmacodynamic serum	5 mL	5 mL	
Routine hematology	2 mL	2 mL	
Routine biochemistry	3 mL	3 mL	
PK blood sampling	---	5 mL	
Week 12			1
1, 25(OH)2D	2.5 mL	2.5 mL	
25(OH)D	2.5 mL	2.5 mL	
Pharmacodynamic serum	5 mL	5 mL	
Routine hematology	2 mL	2 mL	
Routine biochemistry	3 mL	3 mL	
PK blood sampling	----	5 mL	
Weeks 26/ET			1
1, 25(OH)2D	2.5 mL	2.5 mL	
25(OH)D	2.5 mL	2.5 mL	
Pharmacodynamic serum	5 mL	5 mL	
Routine hematology	2 mL	2 mL	
Routine biochemistry	3 mL	3 mL	
PK blood sampling	---	5 mL	
Week 30 Follow-up [1]			1
1, 25(OH)2D	2.5 mL	2.5 mL	
25(OH)D	2.5 mL	2.5 mL	
Pharmacodynamic serum	5 mL	5 mL	
Routine hematology	2 mL	2 mL	
Routine biochemistry	3 mL	3 mL	
PK blood sampling	---	5 mL	
Total	70 mL	105 mL	6
Total volume of blood sampling	70 mL over 30+ weeks	105 mL over 30+ weeks	

[1] Laboratory testing (full panel) will be completed at Week 30 for subjects in the PK group. For all other subjects, laboratory testing at Week 30 will be completed at the Investigator's discretion.

13.3 Appendix 3 Calculation of Percent Body Surface Area Involved

Modified Rules of Nines (Pediatric subjects)*

- The "Rules of Nines" are inaccurate due to the relative disproportion of body parts:
  - Hips and legs are smaller
  - Head, neck, and shoulders are larger

- Hence, a pediatric subjects version is available in chart form that estimates burn area as it changes with age. Alternatively, as estimate can be made from the following for a child up to the age of one (1) year:
  - Head and neck total for front and back: 18%
  - Thorax and abdomen - front: 18%
  - Thorax and abdomen - back: 18%
  - Each upper limb total for front and back: 9%
  - Each lower limb total for front and back: 14%

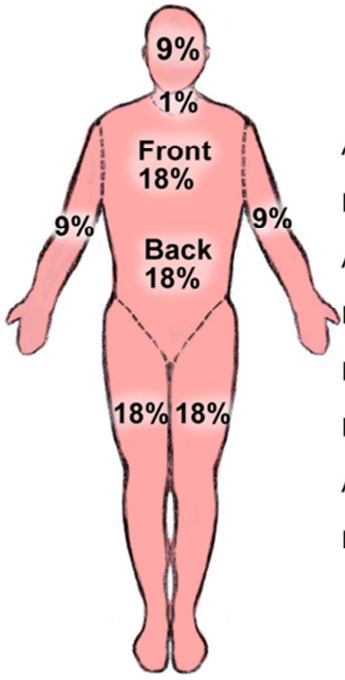
- Over the age of one (1) year, the relative percentage of BSA changes:
  - The head decreases by 1% per year
  - The lower limbs increase by 0.5% per year

- Hence, by the age of ten (10) years, the relative proportions assume the values for adult BSA:
  - Perineum becomes 1%
  - Each lower limb becomes a total of 18% front and back
  - Head and neck become 9% total for front and back.

*From General Practice Notebook "Rules of Nines - Pediatric subjects": http://www.gpnotebook.co.uk/simplepage.cfm?ID=-999620530&linkID=30283&cook=yes (accessed 30 March 2009).

Subject's palm can also be used to estimate BSA and should be considered as a 1% surface area.

Child body	% of total
Part	BSA
Arm	9%
Head and neck	18%
Leg	14%
Anterior trunk	18%
Posterior trunk	18%



Adult body	% of total
Part	BSA
Arm	9%
Head	9%
Neck	1%
Leg	18%
Anterior trunk	18%
Posterior trunk	18%

13.4 Appendix 4 Maximal daily dose and maximal application dose based on body weight.

Body weight (kg)	Maximal daily dose[a] (g)	Maximal dose per application[b] (g)
11	5.5	2.75
12	6	3
13	6.5	3.25
14	7	3.5
15	7.5	3.75
16	8	4
17	8.5	4.25
18	9	4.5
19	9.5	4.75
20	10	5
21	10.5	5.25
22	11	5.5
23	11.5	5.75
24	12	6
25	12.5	6.25
26	13	6.5
27	13.5	6.75
28	14	7
29	14.5	7.25
30	15	7.5
31	15.5	7.75
32	16	8
33	16.5	8.25
34	17	8.5
35	17.5	8.75
36	18	9
37	18.5	9.25
38	19	9.5
39	19.5	9.75
40	20	10
41	20.5	10.25
42	21	10.5
43	21.5	10.75
44	22	11
45	22.5	11.25
46	23	11.5
47	23.5	11.75
48	24	12

Body weight (kg)	Maximal daily dose[a] (g)	Maximal dose per application[b] (g)
49	24.5	12.25
50	25	12.5
51	25.5	12.75
52	26	13
53	26.5	13.25
54	27	13.5
55	27.5	13.75
56	28	14
57	28	14
58	28	14
59	28	14
≥ 60	28	14

a) Maximal daily dose of Calcitriol 3mcg/g ointment is 0.5g ointment per kg of body weight or 28 g, whichever is the lower.

b) Maximal dose per application of calcitriol 3mcg/g ointment is 0.25 of ointment per kg of body weight of 14 g, whichever is the lower.

13.5 Appendix 5 NIH pediatric blood volume for research guideline

NIH pediatric blood volume	
Body weight (kg)	**Maximum draw in 6 wks (7 mL/kg)**
11	77
12	84
13	91
14	98
15	105
16	112
17	119
18	126
19	133
20	140
21	147
22	154
23	161
24	168
25	175
26	182
27	189
28	196
29	203
30	210
31	217
32	224
33	231
34	238
35	245
36	252
37	259
38	266
39	273
40	280
41	287
42	294
43	301
44	308
45	315
46	322
47	329
48	336
49	343

NIH pediatric blood volume	
Body weight (kg)	**Maximum draw in 6 wks (7 mL/kg)**
50	350
51	357
52	364
53	371
54	378
55	385
56	392
57	399
58	406
59	413
60	420
61	427
62	434
63	441
64	448
65	455
66	462
67	469
68	476
69	483
70	490
71	497
72	504
73	511