

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-087

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA:	22- 087
SUBMISSION DATES:	December 27, 2007
SUBMISSION TYPE	Original NDA
PRODUCT (Generic Name):	Calcitriol Ointment (3 µg/g)
PRODUCT (Trade Name):	Tradename
DOSAGE FORM:	Topical Ointment
PROPOSED INDICATIONS:	Plaque-type psoriasis
SPONSOR:	Galderma Laboratories
OCP DIVISION:	DCP 3
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Lydia Velazquez, Pharm.D.
GENOMICS REVIEWER:	Silvana Borges, M.D.

- 1. Executive Summary**
 - 1.1 Recommendations**
 - 1.2 Phase 4 Commitments**
 - 1.3 Summary of Important Clinical Pharmacology Findings**

- 2. Question Based Review**
 - 2.1 General Attributes of the Drug**
 - 2.2 General Clinical Pharmacology**
 - 2.3 Intrinsic Factors**
 - 2.4 Extrinsic Factors**
 - 2.5 Analytical Section**

- 3. Detailed Labeling Recommendations**

- 4. Appendices**
 - 4.1 Proposed Package Insert**
 - 4.2 Individual Study Reviews**
 - 4.3 Consult Review - Pharmacogenomics**
 - 4.4 Cover Sheet and OCP Filing/Review Form**

1. EXECUTIVE SUMMARY

This 505 (b) (1) original New Drug Application (NDA) provides data in support of Tradename (calcitriol) ointment 3 µg/g, for use in the twice-daily topical treatment of chronic plaque type psoriasis. Psoriasis is one of the most common chronic dermatoses in the world, with chronic plaque psoriasis (Psoriasis vulgaris) accounting for 65 to 85% of cases.

Topical agents are the mostly commonly used therapies for psoriasis and vitamin D analogs are currently used as first line therapy in the treatment of chronic plaque psoriasis. Amongst the vitamin D analogs, calcitriol (1α-25-dihydroxyvitamin D₃) is the naturally occurring and biologically active metabolite of vitamin D₃. 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 was expected to be an effective drug in the topical treatment of psoriasis.

Oral calcitriol has been marketed in Europe since 1979 and in the United States since 1982 for renal osteodystrophy. Topical calcitriol ointment 3 µg/g was initially developed by Solvay and registered in several European countries. In 1996, the product was acquired by Galderma. To date, Tradename ointment 3 µg/g is approved in 39 countries and marketed in 25 countries worldwide.

Clinical pharmacology studies with calcitriol ointment characterized the potential of biological effects secondary to systemic exposure and its bioavailability. The clinical pharmacology of Tradename ointment has been evaluated in eleven studies that include 6 pivotal [1 PK/PD (study RD.03.SRE.40005), 1 genomic (study #2853) and 4 clinical phase 3 (Efficacy and safety studies RD.06.SRE.18053 and RD.06.SRE.18054, long term safety study RD.03.SRE.2663, and Body Surface Area Escalation Study RD.03.SRE.2635)] studies and 5 pilot studies _____ and 3 radio-labeled bioavailability studies (studies H.141.605, H.141.6002, and H.141.6003). The pivotal PK/PD study, genomic study, and the clinical pharmacology aspects of the four Phase 3 clinical studies have been reviewed in detail. The pilot studies were not reviewed in detail as the studies were conducted 15 years ago and not with the final-to-be-marketed formulation. In addition, the information obtained from the three radio-labeled studies did not add any new information over what is already known about the disposition of calcitriol from information in the literature.

The pivotal PK/PD study (RD.03.SRE.40005) conducted under maximal usage condition demonstrated that there was an increase in the mean calcitriol plasma concentrations upon twice-daily application of a maximum dose of calcitriol 3 µg/g ointment (30 g daily) for 21 days in subjects with chronic plaque psoriasis. The geometric mean values of C_{max} increased by approximately 36% and the mean value of AUC_(0-12h) increased by 44% over baseline.

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Based on the data submitted in the maximal usage study just described and the pivotal studies, there was no correlation between PK parameters (AUC, C_{max} , and trough Concentrations) and PD parameters (serum albumin adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus). However, due to the limitations of the study as to when labs were collected, one can not rule out that the pharmacodynamic aspects may have occurred at a later time for patients with high calcitriol levels.

1.1. Recommendation:

The Office of Clinical Pharmacology has reviewed NDA 22-087 dated December 27, 2007. The submission is acceptable from clinical pharmacology perspective provided the sponsor accepts the OCP labeling recommendations.

Primary Reviewer:

Tapash K. Ghosh, Ph.D.
Division of Clinical Pharmacology 3

Team Leader:

Lydia Velazquez, Pharm.D.
Div. of Clinical Pharmacology 3

The OCP briefing was held on August 29, 2008 and the members present were Ritesh Jain, Immo Zdrojewski, Ping Ji, Lucun Bi, Ting-Eng Ong, Michael Pacanowski, Abimbola Adebawale, Patricia Brown, Jill Lindstrom, Milena Lolich, Lydia Velazquez, Hae-Young Ahn, Sylvana Borges, and Tapash Ghosh

CC list: HFD-540: NDA 22-087; HFD-880 (Lydia Velazquez, Hae-Young Ahn, Tapash Ghosh); CDER Central Document Room

1.2. Phase IV commitments: None

1.3. Summary of Important Clinical Pharmacology Findings

Clinical pharmacology studies with calcitriol ointment characterized the potential of biological effects secondary to systemic exposure and its bioavailability. The following section describes the clinical pharmacology findings from different studies submitted under this NDA.

- 1. The pivotal PK/PD study “*Pharmacokinetics and Pharmacodynamics of Calcitriol following twice daily application of Calcitriol 3 µg/g ointment for 3 weeks under conditions of maximal exposure in subjects with psoriasis (RD.03.SRE.40005)*”** was a multi-center, open label study designed to determine the PK and PD of calcitriol 3 µg/g ointment formulation. Twenty-three (23) male and female subjects, 18 years of age or older, suffering from chronic, plaque psoriasis with at least 25% of body surface area (BSA) involvement were enrolled in the study at four study centers. There was an increase in the mean calcitriol plasma concentrations upon twice-daily application of a maximum dose of calcitriol 3 µg/g ointment (30 g daily) for 21 days in subjects with chronic plaque psoriasis. The geometric mean values of C_{max} increased by approximately 36% and the mean value of $AUC_{(0-12h)}$ increased by 44% over baseline.

There was no correlation between PK parameters (AUC and C_{max}) and PD parameters (serum albumin adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus). However, due to the limitations of the study as to when labs were collected, one can not rule out that the pharmacodynamic aspects may have occurred at a different time for patients with high calcitriol levels.

- 2. Additional calcitriol plasma levels were obtained from the following clinical studies conducted by the Sponsor:**

- 2 Pivotal Phase 3 clinical studies RD.06.SRE.18053 and RD.06.SRE.18054,**
- 1 Long term safety study RD.03.SRE.2663, and**
- 1 Body Surface Area Escalation Study RD.03.SRE.2635.**

Calcitriol plasma levels were determined from selected patients in these studies. About 39% (62/158) of these patients from all four above mentioned studies had calcitriol plasma levels > 60 pg/ml (normal range is 15 to 60 pg/ml). Two patients representing 1.3% (2/158) from the two Phase 3 trials (studies 18053 and 18054) who had high plasma calcitriol levels also had higher serum and urinary calcium levels.

Also three out of 28 patients (10.7%) whose calcitriol plasma levels were measured in the long term safety study (study 2663) were diagnosed with kidney stones.

The body surface area (BSA) escalation study (2635) resulted in increases of calcitriol plasma levels with greater BSA drug application involvement.

3. A genomic study (Study Report # 2853 entitled "Analysis of epidermal gene expression after 24, 48 and 72 hours of treatment with calcitriol 3 µg/g applied under occlusion") was conducted with the objective of determining the differential effect on gene expression of calcitriol 3 µg/g ointment in comparison to its vehicle and a non treated site. The pharmacogenomic reviewer recommends that no information from the study results be included in the product label as the failure in the amplification of the CYP24 gene, the inconsistency in the CYP24 gene expression time course shown in the agarose gel electrophoresis and the reported absence of gene expression modulation by calcitriol reflect limitations in the analytical procedures.

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5. The sponsor conducted three radio-labeled bioavailability studies (H.141.605, H.141.6002, and H.141.6003) that were conducted more than 15 years ago and not with the final-to-be-marketed formulation. The information obtained from these radio-labeled studies did not add any new information over what is already known about the disposition of calcitriol.

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2. QBR

2.1. General Attributes

2.1.1. *What are the chemical and physical-chemical properties of the drug substance?*

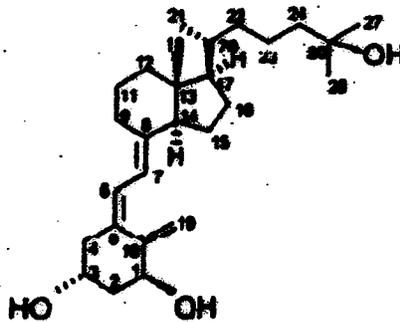
Trade name: Tradename

Generic name: Calcitriol ointment 3 µg /g

Chemical name: (1α, 3β, 5Z, 7E)-9, 10-secocholesta-5,7 10(19)- triene-1, 3, 25-triol

Molecular formula/ molecular weight: C₂₇H₄₄O₃

Chemical Structure.



What is the composition of the to-be-marketed formulation?

Calcitriol ointment 3 µg /g is a translucent ointment containing 3 µg /g (0.0003% w/w) of calcitriol for the topical treatment of psoriasis. It is packaged in aluminum tubes closed with screw caps.

Tube sizes proposed for marketing are 100 g; a 5g size is intended for samples. Table 1 provides a list of all components, their percentage w/w in calcitriol ointment 3 µg /g and their quality standards:

Table 1: Calcitriol Ointment 3 µg/g Formulation

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Names of ingredients	Percent formula (% w/w)	Function	Reference to standards
Active ingredient: Calcitriol	0.0003	Active ingredient	Internal monograph ^a
Other ingredients: White petrolatum Mineral oil Vitamin E			Internal monograph ^b USP 29 USP 29

^a European Pharmacopoeia 5.0 (White Soft Paraffin) + modified test and limits for consistency

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2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Calcitriol interacts with the nuclear vitamin D receptor (VDR) and modulates transcription through binding of VDR to specific vitamin D response elements in the promoter of target genes, resulting in the inhibition of proliferation of keratinocytes and T-cells, the inhibition of the production of inflammatory factors such as interleukins and interferons and the stimulation of differentiation of epidermal keratinocytes.

Tradename ointment is indicated for the topical treatment of plaque-type psoriasis.

2.2. General Clinical Pharmacology

2.2.1. How was the dose/duration selected for Tradename (Calcitriol) Ointment (3 µg/g)?

The sponsor conducted two studies for this purpose. However, they were conducted more than 15 years ago by _____, not using the final-to-be-marketed-formulation. The final-to-be-marketed formulation contains additional ingredients. Topical calcitriol ointment 3 µg/g was initially developed by _____ and registered in several European countries. In 1996, the product was acquired by Galderma. To date, Tradename ointment 3 µg/g is approved in 39 countries and marketed in 25 countries worldwide. According to the sponsor, the selection of the 3 µg/g calcitriol as the final concentration to be applied twice daily was made based on the applicant's objective to _____ and on their experiences with the already marketed product.

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2.2.2. What are the design features and outcomes of the pivotal clinical trials?

The applicant collected the important efficacy and safety information in the following studies:

Two Phase 3 pivotal multi-center, randomized, double-blind, vehicle-controlled, parallel-group comparisons clinical trials (Studies 18053 and 18054). Efficacy and safety of twice

daily application of calcitriol 3µg/g ointment and its vehicle, in the treatment of chronic plaque psoriasis were evaluated in qualified subjects who were randomized in a 1: 1 ratio to receive calcitriol ointment 3µg/g or its vehicle.

Patients were treated twice daily for 8 weeks with Tradename (calcitriol) Ointment or vehicle ointment. Efficacy was seen as early as two weeks in treating mild to moderate psoriasis. At end of treatment (Week 8) success rate was 34.4% and 33.3% in the Tradename Ointment groups and 22.5% and 12.3% in the vehicle groups in Study 1 and Study 2, respectively (p=0.005 and p=0.001 in Study 1 and Study 2, respectively). There were laboratory test abnormalities that included laboratory values outside reference range in these two vehicle controlled studies. The incidence of out-of-range abnormalities in the Tradename Ointment and vehicle groups were the same (4.5%). *(Please refer to the Clinical and the Biostatistical reviews for details)*

2.2.3. *What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?*

Calcitriol is a naturally occurring Vitamin D analog, the active hormone exerting Vitamin D activity. Endogenous calcitriol facilitates the availability of calcium and phosphate for new bone formation and assists in prevention of hypocalcemia and hypophosphatemia, primarily by increasing bone resorption as well as intestinal and renal tubular calcium absorption of calcium so that calcium homeostasis is maintained. Parathyroid hormone (PTH) mediates calcitriol's effects on bone and kidney. Based on a feedback loop, excess calcitriol would be expected to potentially increase calcium and phosphorus levels and suppress PTH levels and thereby disturb calcium homeostasis. Therefore, serum calcium and phosphorus levels, and urinary calcium and phosphorus levels were used as pharmacodynamic endpoints in the clinical pharmacology studies.

The increase in calcium can combine with phosphate ions, eventually forming deposits of calcium phosphate (stones) in blood vessels and in the kidneys which is a safety concern.

In the pivotal Phase 3 clinical studies, the primary efficacy variable was success rate at Endpoint for the intent-to-treat population. Success was defined as a subject with a Global Severity Score of 0 (clear) or 1 (minimal).

2.2.4. *Were the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?*

Yes. The concentrations of calcitriol were determined in plasma and urine using a validated radioimmunoassay after _____

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2.2.5 Exposure-response evaluations

What is the characteristics of the exposure-response relationship?

In the pivotal Pharmacokinetic and Pharmacodynamic study of Calcitriol following twice daily application (Calcitriol 3 µg/g ointment) for 3 weeks under conditions of maximal exposure in subjects with psoriasis (Study 40005), Spearman's correlation coefficients were calculated to measure the association between the PD parameters (expressed in terms of difference between Treatment and Baseline) and the PK parameters (expressed in terms of ratio Treatment/ Baseline). There was no correlation between calcitriol PK parameters AUC and C_{max} and the PD parameters serum albumin-adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus as shown below:

Pharmacokinetic Parameters	Spearman Correlation Coefficient		
	Pharmacodynamic Parameters		
	Day 0-Baseline ^a	Day 14 - Baseline	Day 21 - Baseline
	Albumin adjusted Calcium (mmol/L)		
AUC (D0)/AUC Baseline ^a	-0.16803	0.18056	0.21354
AUC (D14)/AUC Baseline	-0.20558	0.20678	0.26940
AUC (D21)/AUC Baseline	-0.34198	-0.06777	0.00544
C _{max} (D0)/AUC Baseline	-0.18829	-0.02276	-0.04053
C _{max} (D14)/AUC Baseline	-0.20608	0.03413	0.06426
C _{max} (D21)/AUC Baseline	-0.20361	-0.02276	-0.02966
	Phosphorus (mmol/L)		
AUC (D0)/AUC Baseline	-0.30276	-0.07862	0.04237
AUC (D14)/AUC Baseline	-0.37560	-0.09357	-0.04859
AUC (D21)/AUC Baseline	0.09390	0.06628	-0.03616
C _{max} (D0)/AUC Baseline	0.11847	0.23926	0.20113
C _{max} (D14)/AUC Baseline	-0.21150	0.04224	0.13480
C _{max} (D21)/AUC Baseline	0.03968	0.23782	0.17684
	Urinary Calcium (mmol/D)		
AUC (D0)/AUC Baseline	0.10054	0.32115	0.28458
AUC (D14)/AUC Baseline	-0.17170	0.27866	0.14526
AUC (D21)/AUC Baseline	-0.02768	-0.02273	-0.02075
C _{max} (D0)/AUC Baseline	0.25530	0.23791	0.10568
C _{max} (D14)/AUC Baseline	-0.04349	0.11166	-0.05237
C _{max} (D21)/AUC Baseline	-0.08020	0.00198	-0.02569
	Urinary Phosphorus (mmol/D)		
AUC (D0)/AUC Baseline	0.19699	0.04970	0.07397
AUC (D14)/AUC Baseline	0.27368	-0.23779	-0.44325
AUC (D21)/AUC Baseline	0.03714	0.07738	-0.27930
C _{max} (D0)/AUC Baseline	0.09173	0.34736	0.21174
C _{max} (D14)/AUC Baseline	0.34436	-0.04801	-0.19255
C _{max} (D21)/AUC Baseline	0.06316	0.11861	-0.04912

Does this drug prolong the QTc interval?

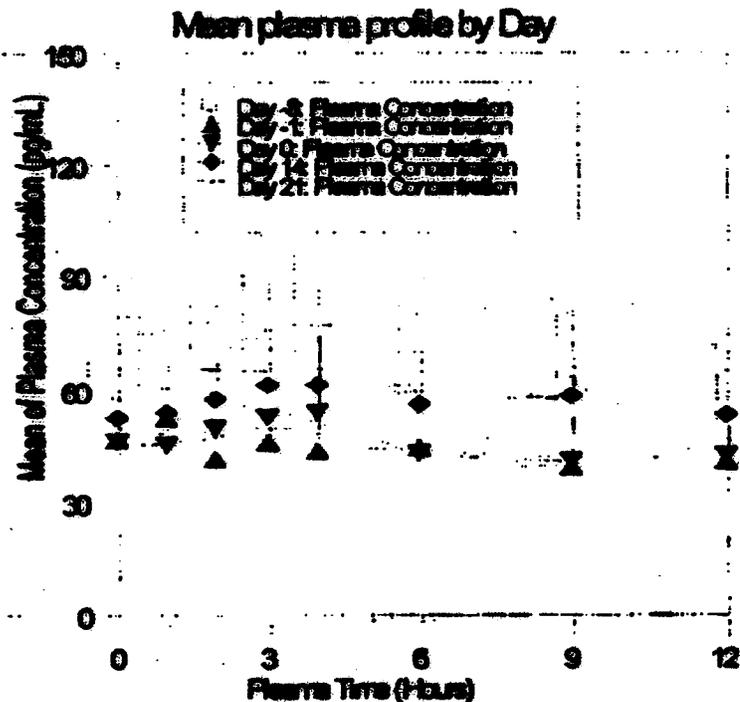
The effect of calcitriol on QTc prolongation has not been studied.

What are the Pharmacokinetic and Systemic Exposure characteristics of Calcitriol Ointment 3 µg/g applied Topically?

Clinical pharmacology studies conducted with calcitriol ointment were carried out to determine its pharmacokinetics and pharmacodynamics and the potential of biological effects secondary to systemic exposure. The studies conducted are:

The pivotal PK/PD study "*Pharmacokinetics and Pharmacodynamics of Calcitriol following twice daily application of Calcitriol 3 µg/g ointment for 3 weeks under conditions of maximal exposure in subjects with psoriasis (RD.03.SRE.40005)*" was a multi-center, open label study designed to determine the PK and PD of calcitriol 3 µg/g ointment formulation. Twenty-three (23) male and female subjects, 18 years of age or older, suffering from chronic, plaque psoriasis with at least 25% of body surface area (BSA) involvement were enrolled in the study at four study centers. The test product was applied on 35% of the BSA. The treated area included all skin lesions (at least 25%) and if necessary additional normal skin to reach 35% BSA. Each subject received 15g twice daily application of calcitriol 3 µg/g ointment for three weeks.

The calcitriol plasma profiles of all subjects was relatively flat, with no terminal log-linear segment corresponding to a marked concentration decrease appearing on the concentration-time curves. Therefore, no terminal half-life was determined (see Figure below). PK parameters (AUC, Cmax, Tmax) was evaluated using baseline unadjusted non-compartmental analysis.



Geometric Mean Calcitriol Values at C_{max} AUC_(0-12h) and Arithmetic Mean Values of T_{max}

Calcitriol 3 µg/g ointment (N = 23)							
PK Parameters	Mean Baseline^a	Day 0	Day 0/Baseline	Day 14	Day 14/Baseline	Day 21	Day 21/Baseline
C_{max} (pg/mL)							
Mean	51.59	53.98	1.05	67.96	1.32	70.23	1.36
p-value ^b	NA	NA	0.4413	NA	0.0009	NA	0.0007
90% CI	NA	NA	0.947, 1.156	NA	1.164, 1.491	NA	1.191, 1.556
AUC_(0-12h) (pg[*]h/ml)							
Mean	471.65	498.57	1.06	635.99	1.35	677.21	1.44
p-value	NA	NA	0.2908	NA	0.0004	NA	<0.0001
90% CI	NA	NA	0.968, 1.154	NA	1.193, 1.524	NA	1.267, 1.627
T_{max} (h:min)							
Mean ± SD	3.07±2.15	4.31±3.33	NA	5.26±4.18	NA	2.36±2.01	NA
Min, Max	0.30, 9.00	0.00, 12.0	NA	0.00, 12.0	NA	0.00, 9.00	NA

There was an increase in the mean calcitriol plasma concentrations upon twice-daily application of a maximum dose of calcitriol 3 µg/g ointment (30 g daily) for 21 days in subjects with chronic plaque psoriasis. The geometric mean values of C_{max} increased by approximately 36% (70.23 pg/mL /51.59pg/mL) over baseline and the mean value of AUC_(0-12h) increased by 44% (677.21pg^{*}h/ml /471.65 pg^{*}h/ml).

Additional calcitriol plasma levels were obtained from the following studies conducted by the Sponsor:

- 2 Pivotal Phase 3 clinical studies RD.06.SRE.18053 and RD.06.SRE.18054,
- 1 Long term safety study RD.03.SRE.2663, and
- 1 Body Surface Area Escalation Study RD.03.SRE.2635.

Calcitriol plasma levels were determined from selected patients in these studies. About 39% (62/158) of these patients had higher than normal range of endogenous (> 60 pg/ml) plasma levels of calcitriol. Two patients representing 1.3% (2/158) from the two Phase 3 trials (studies 18053 and 18054) who had high plasma calcitriol levels also had higher than reference range of serum and urinary calcium levels.

Also three out of 28 patients (10.7%) whose calcitriol plasma levels were measured in the long term safety study (study 2663) were diagnosed with kidney stones. The body surface area (BSA) escalation study (2635) resulted in increases of calcitriol plasma levels with greater BSA drug application involvement.

The sponsor conducted three radio-labeled bioavailability studies (H.141.605, H.141.6002, H.141.6003). The studies were conducted more than 15 years ago and not with the final to be marketed formulations. The formulation used in these studies were calcitriol in petrolatum whereas the final to be marketed formulation contains two other components, namely, mineral oil and vitamin E; which may influence the absorption of all active moieties in the drug product. Release of any active ingredient from any topical formulation and its subsequent percutaneous absorption are dependent on the formulation components. Therefore, the utility of the results from these studies is limited as the information obtained from these radio-labeled studies did not add any new information over what is already known about the disposition of calcitriol from prior approved oral calcitriol product. As a result, the studies were reviewed as supportive studies only. The only observation that can be made deals with the drug moiety (calcitriol) itself. Namely that upon systemic exposure, calcitriol is eliminated fecally and renally

2.3 Intrinsic Factor:

What are the pharmacogenetic characteristics of Calcitriol?

A genomic study (Study Report # 2853 entitled "Analysis of epidermal gene expression after 24, 48 and 72 hours of treatment with calcitriol 3 µg/g applied under occlusion") was conducted with the objective of determining the differential effect on gene expression of calcitriol 3 µg/g ointment in comparison to its vehicle and a non treated site. Twelve healthy Caucasian volunteers (6 females, 6 males) ranging in age from 20 to 53 years were recruited, completed the study and included in the analysis. Specific amplification of the cDNA encoding for 24-OH was not achieved and a detailed gene expression profiling that was performed in two subjects failed to find genes for which transcription was modulated by calcitriol treatment in the conditions of the experiment. According to the genomic reviewer, the failure in the amplification of the CYP24 gene, the inconsistency in the CYP24 gene expression time course shown in the agarose gel electrophoresis and the reported absence of gene expression modulation by calcitriol reflect limitations in the analytical procedures. Therefore, it is recommended that no information based on this study be included in the product label.

2.4. Extrinsic Factors

The sponsor conducted a bioavailability study with the concomitant application of calcitriol ointment 3mcg/g with betamethasone dipropionate cream or betamethasone dipropionate and salicylic acid ointment and concluded that concomitant application of calcitriol ointment 3mcg/g with betamethasone dipropionate cream or betamethasone dipropionate and salicylic acid ointment did not result in increased calcitriol levels compared to treatment with calcitriol ointment 3mcg/g alone. However, as the study was not conducted with the to-be-marketed formulation, no information based on this study will be included in the product label.

2.5 Analytical

Yes. The concentrations of calcitriol were determined in plasma using a validated radioimmunoassay after sample _____ This method involves a _____ of calcitriol from serum or plasma using _____ Following _____ the treated sample is then assayed using a competitive Radio Immuno Assay (RIA) procedure, based on a _____

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The assay parameters are as follows:

Parameters	Data
Analyte	Calcitriol
Method description	Radio Immuno Assay (RIA) based on a _____
Lower Limit of quantitation	5.0 pg/mL
Standard curve concentration range (ng/mL)	_____
Variation in Accuracy (%)	_____
Correlation coefficient	0.9947

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3. Detailed Labeling Recommendation:

The Office of Clinical Pharmacology has the following recommendations for the proposed label to be addressed:

The following labeling recommendations in the "Drug Interactions" and "Pharmacokinetics" section of the proposed label should be addressed by the sponsor.

~~ABC~~ (Strikeout) suggests deletion of text and **ABC** (Bold, italics and underline) suggests insertion of new text.

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10 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

✓ Draft Labeling (b5)

 Deliberative Process (b5)

4.2. Individual Clinical Studies

NDA: 22-087/Study RD.03.SRE.40005

Study Dates: Mar, 04 – Jul, 04

Pharmacokinetics and Pharmacodynamics of Calcitriol following twice daily application of Calcitriol 3 µg/g ointment for 3 weeks under conditions of maximal exposure in subjects with psoriasis

Objectives: The objectives of this study were to

- To assess the systemic exposure (C_{max} , T_{max} and AUC) of calcitriol in psoriatic subjects upon repeated applications of calcitriol 3 µg/g ointment under conditions of maximal exposure.
- To assess the effect of calcitriol 3 µg/g ointment on calcium and phosphorus homeostasis.

Study Design: This was a multi-center, open label study designed to determine the Pharmacokinetics (PK) and Pharmacodynamics (PD) of calcitriol 3 µg/g ointment formulation (Formulation # 730.001).

Twenty-three (23) male and female subjects, 18 years of age or older, suffering from chronic, plaque psoriasis with at least 25% of body surface area (BSA) involvement were enrolled in the study at four study centers.

Table 40005.1: Demographics and Other Baseline Characteristics (Safety Population)

Demographic Parameters	Calcitriol 3 µg/g ointment (N = 23)	
	n	%
Gender		
Male	15	65.2
Female	8	34.8
Race		
Caucasian	23	100
Age (years)		
Mean ± SD		46.4 ± 13.5
Min. Max		22.1, 70.2

The test product was applied on 35% of the BSA. The BSA-treated area included all skin lesions (at least 25%) and if necessary additional normal skin to reach 35% BSA in order

to maximize penetration potential of calcitriol from surrounding normal skin. The subject received 15g twice daily application of calcitriol 3 µg/g ointment for three weeks.

Blood samples were drawn for PK and PD measurements on Days -8, -1, 0, and 21 at the following hourly time points: 0, 1, 2, 3, 4, 6, 9, 12, 16 and 24. Then on Day 14, samples were collected at 0, 1, 2, 3, 4, 6, 9 and 12 hours.

Twenty-four-hour (24-h) urine samples were obtained for PD measurements (serum albumin adjusted calcium level, serum phosphorus level, urinary calcium level and urinary phosphorus level) on Days -8, -1, 0, 14 and 21.

Pharmacokinetics: The maximum calcitriol plasma concentration (C_{max}) and the area under the plasma concentration-time curve over 12 hours (AUC_{0-12h}) at baseline and during the repeated treatment with calcitriol ointment during a 12-hour dosing interval were compared. Baseline measurements were performed on two occasions (Days -8 and -1) in order to assess the intra-subject variability.

AUC_{0-12h} and C_{max} values were used for the assessment of any effects of the application of calcitriol 3 µg/g ointment on the endogenous levels of calcitriol. They were transformed into their natural logarithms prior to analysis. Each time point (Day 0, 14 and 21) were compared to the mean of the two baseline values obtained on Days -8 and -1. The 90% confidence interval for the mean difference (Treatment - Baseline) was calculated using the Student's t distribution. The limits of the interval were back-transformed into exponential to obtain a 90% confidence interval of the ratio (Treatment / Baseline) of geometric means for AUC_{0-12h} and C_{max} respectively. For indicative purpose, the Student's t tests for paired data (treatment phase vs. Baseline) were also performed and significance was declared at 5% two-sided threshold.

Pharmacodynamics: Four mL blood samples for measurement of the serum levels of calcium, phosphorus, albumin and creatinine were collected at Day -8, -1, 0, 14, and 21. Each time point (Day 0, 14 and 21) was compared to baseline (the mean of the two values obtained on Days -8 and -1). A statistical analysis using the Student's t statistic for paired data, similar to that described for the pharmacokinetic parameters was applied.

PK/PD relationship: Spearman's correlation coefficients were calculated to measure the association between the PD parameters (expressed in terms of difference Treatment-Baseline) and the PK parameters (expressed in terms of ratio Treatment/ Baseline).

Assay Validation: The concentrations of calcitriol were determined in plasma using a validated radioimmunoassay after samples _____ This method involves a _____ from serum or plasma using _____ Following _____ the treated sample is then assayed using a competitive Radio Immuno Assay (RIA) procedure, based _____

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The assay parameters are as follows:

Parameters	Data
Analyte	Calcitriol
Method description	Radio Immuno Assay (RIA) based
Lower Limit of quantitation	5.0 pg/mL
Standard curve concentration range (ng/mL)	
Variation in Accuracy (%)	
Variation in Precision (%)	
Correlation coefficient	0.9947

Results:

Pharmacokinetics: The calcitriol plasma profiles of all subjects was relatively flat, with no terminal log-linear segment corresponding to a marked concentration decrease appearing on the concentration-time curves. Therefore, no terminal half-life was determined (see Figure 40005.1 below).

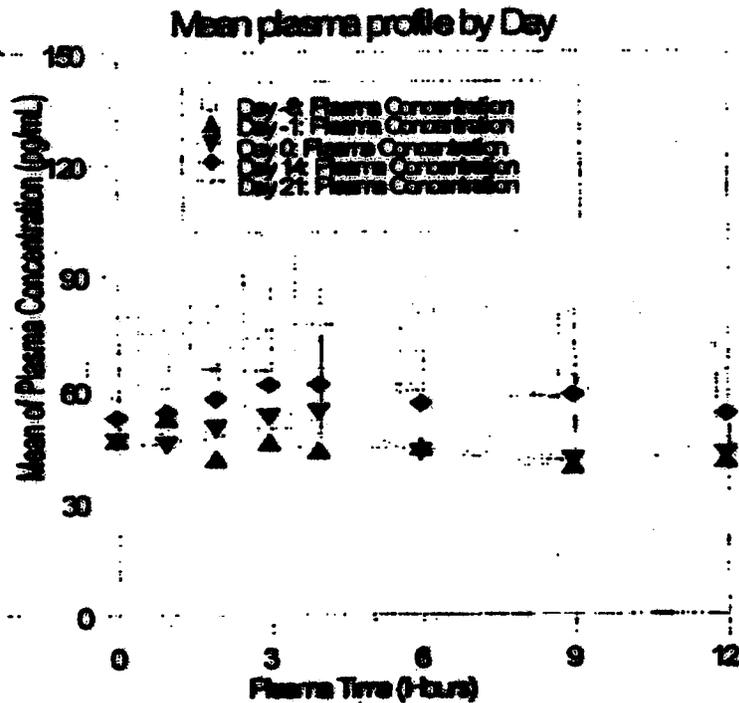


Figure 40005.1: Mean Calcitriol plasma concentrations

The intra-individual calcitriol plasma endogenous levels determined on Days -1 and -8 did not display marked fluctuations during the day. The maximum endogenous calcitriol plasma levels (C_{max}) varied from 20 to 121 pg/mL. Arithmetic mean $C_{max} \pm SD$ was 56.1 ± 26.3 pg/ml on Day -8 and 58.2 ± 28.6 pg/ml on Day -1. The mean plasma concentrations after the first administration (Day 0) were similar to the baseline values (Days -1 and -8). The mean maximum plasma concentrations upon twice daily application of calcitriol 3 μ g/g ointment on Days 14 and 21 were slightly higher (72.3 ± 25.6 pg/ml and 75.3 ± 27.3 pg/ml respectively). The mean values of C_{12h} (trough concentration), C_{max} and $AUC_{0-12h} \pm SD$ on all sampling days evaluated using baseline unadjusted non-compartmental analysis are given in Table 40005.2.

Table 40005.2: Mean Calcitriol values at C_{12h} (Trough Concentration), C_{max} , T_{max} and AUC_{0-12h}

PK Parameters	Calcitriol 3 μ g/g ointment (N = 23)				
	D -8	D -1	D 0	D 14	D 21
C_{12h} (pg/ml)					
Mean \pm SD	44.3 \pm 20.5	41.1 \pm 22.5	42.2 \pm 17.6	53.3 \pm 20.8	54.1 \pm 18.9
Min, Max	18.0, 95.5	11.72, 100.1	16.2, 91.1	16.1, 96.3	23.4, 89.5
C_{max} (pg/ml)					
Mean \pm SD	56.1 \pm 26.3	58.2 \pm 26.6	59.8 \pm 29.6	72.3 \pm 25.6	75.3 \pm 27.3
Min, Max	19.7, 115.0	26.3, 121.3	26.7, 147.7	35.9, 136.5	29.1, 142.4
AUC_{0-12h} (pg \cdot h/ml)					
Mean \pm SD	539.9 \pm 270.2	519.7 \pm 271.5	544.5 \pm 231.7	694.9 \pm 262.4	725.6 \pm 261.0
Min, Max	156.1, 1213.9	184.0, 1224.6	227.7, 971.4	303.6, 1206.1	297.9, 1233.9
T_{max} (h)					
Mean \pm SD	3.9 \pm 4.0	2.3 \pm 2.7	4.5 \pm 3.6	5.4 \pm 4.3	2.6 \pm 2.0
Min, Max	0.0, 12.0	0.0, 12.0	0.0, 12.0	0.0, 12.0	0.0, 9.0

At Day 14 the Geometric Mean calcitriol plasma concentration values at C_{max} increased by approximately 32% over Baseline and the Geometric Mean value of $AUC_{(0-12h)}$ increased by 35%. At Day 21 the Geometric Mean plasma concentration values of C_{max} increased by approximately 36% over Baseline and the Geometric Mean value of $AUC_{(0-12h)}$ increased by 44%. The 90% CI of the ratio (Treatment/Baseline) of the Geometric Means for C_{max} and AUC at Days 14 and 21 did not entirely lie within the 0.8 and 1.25 limits. On Day 14 and day 21, the lower limits of these 90% CI were all above one and they were statistically different from baseline (all p-values <0.001) (see Table 40005.3).

Table 40005.3: Geometric Mean Calcitriol Values at C_{max} , $AUC_{(0-12h)}$ and Arithmetic Mean Values of T_{max}

PK Parameters	Mean Baseline ^a	Calcitriol 3 μ g/g ointment (N = 23)				
		Day 0	Day 0/Baseline	Day 14	Day 14/Baseline	Day 21

C _{max} (pg/mL)							
Mean	51.59	53.98	1.05	67.96	1.32	70.23	1.36
p-value ^b	NA	NA	0.4413	NA	0.0009	NA	0.0007
90% CI	NA	NA	0.947, 1.156	NA	1.164, 1.491	NA	1.191, 1.556
AUC _(0-12h) (pg·h/mL)							
Mean	471.65	498.57	1.06	635.99	1.33	677.21	1.44
p-value	NA	NA	0.2908	NA	0.0004	NA	< 0.0001
90% CI	NA	NA	0.968, 1.154	NA	1.193, 1.524	NA	1.267, 1.627
T _{max} (h:min)							
Mean ± SD	3.07±2.15	4.31±3.33	NA	5.26±4.18	NA	2.36±2.01	NA
Min, Max	0.30, 9.00	0.00, 12.0	NA	0.00, 12.0	NA	0.00, 9.00	NA

^a For C_{max} and AUC_(0-12h) Baseline is the Geometric Mean of the two values obtained at Day -1 and Day -8. For T_{max} Baseline is the Arithmetic Mean of the two values obtained at Day -1 and -8.

^b p-values are based on the Student paired t-test.

Pharmacodynamics: A summary of mean serum levels of albumin-adjusted calcium and phosphorus and mean 24-hour urine levels of calcium and phosphorus are presented in Table 40005.4 and the analysis of the summary is in Table 40005.5.

Table 40005.4: Summary of Pharmacodynamic (PD) Parameters in Serum and Urine

Calcectrol 3 µg/g ointment						
PD Parameter	Day -08	Day -01	Mean Baseline ^a	Day 0	Day 14	Day 21
Serum Levels:						
Albumin-adjusted Calcium (mmol/L)						
N	22	23	23	23	23	23
Mean	2.38	2.33	2.37	2.37	2.32	2.33
SEM	0.01	0.02	0.01	0.01	0.02	0.02
Median	2.39	2.33	2.35	2.36	2.31	2.34
Min, Max	2.25, 2.48	2.18, 2.55	2.28, 2.55	2.26, 2.50	2.19, 2.47	2.19, 2.46
Phosphorus (mmol/L)						
N	21	23	23	19	21	22
Mean	1.21	1.19	1.20	1.17	1.13	1.17
SEM	0.04	0.04	0.04	0.04	0.03	0.04
Median	1.20	1.19	1.23	1.21	1.15	1.18
Min, Max	0.79, 1.60	0.81, 1.46	0.82, 1.53	0.83, 1.44	0.79, 1.36	0.89, 1.52
24-hour Urine Levels						
Calcium (mmol/D)						
N	23	23	23	22	23	23
Mean	5.26	5.70	5.73	5.69	5.69	6.03
SEM	0.85	0.61	0.62	0.61	0.63	0.59
Median	4.60	4.60	4.80	5.10	5.05	5.30
Min, Max	0.80, 19.10	1.20, 11.60	1.05, 11.20	2.10, 12.10	0.90, 11.20	1.80, 13.30
Phosphorus (mmol/D)						
N	22	22	23	20	22	22

Mean	24.58	26.68	25.53	23.95	25.48	28.77
SEM	1.75	2.18	1.87	2.21	2.41	2.36
Median	23.40	25.70	24.45	24.05	28.10	27.20
Min, Max	7.50, 37.00	6.30, 47.30	7.50, 42.00	7.60, 40.70	6.40, 42.10	11.30, 56.10

The mean serum levels and 24-hour urine levels for most of the parameters were not statistically significant. Among the parameters that were statistically significant were the following:

The mean serum levels of albumin-adjusted calcium decreased from 2.37 mmol/L at baseline to 2.32 mmol/L at Day 14, this difference was statistically significant ($p=0.0162$). However, at D21, this level was 2.33, not significantly different from baseline value.

The mean serum levels of phosphorus decreased from 1.20 mmol/L at baseline to 1.13 nmol/L at Day 14, this difference was statistically significant ($p=0.0372$). However, at D21, this level was 1.17, not significantly different from baseline value.

The mean 24-hour urinary levels of phosphorus increased from 25.53 mmol/D at baseline to 28.77 mmol/D at Day 21, this difference was statistically significant ($p=0.0064$).

However, the findings are based on mean parameters and clinical significance of the mean changes of these parameters is unknown.

Table 40005.5: Analysis of Pharmacodynamic (PD) Parameters

PD Parameters	Calcitriol 3 µg/d treatment						
	Mean Baseline ^a	Day 0	Day 0 - Baseline	Day 14	Day 14 - Baseline	Day 21	Day 21 - Baseline
Serum Levels:							
Albumin-adjusted Calcium (mmol/L)							
N	23	23	23	23	23	23	23
Mean	2.37	2.37	0.00	2.32	-0.04	2.33	-0.04
Min, Max	2.28, 2.55	2.26, 2.50	-0.25, 0.15	2.19, 2.47	-0.23, 0.17	2.19, 2.46	-0.24, 0.16
p-value	NA	NA	0.9219	NA	0.0162	NA	0.0618
90% CI	NA	NA	-0.03, 0.032	NA	-0.07, -0.02	NA	-0.07, -0.01
Phosphorus (mmol/L)							
N	23	19	19	21	21	22	22
Mean	1.20	1.17	-0.03	1.13	-0.06	1.17	-0.04
Min, Max	0.82, 1.53	0.83, 1.44	-0.46, 0.16	0.79, 1.36	-0.33, 0.23	0.89, 1.52	-0.42, 0.23
p-value	NA	NA	0.4426	NA	0.0372	NA	0.2713
90% CI	NA	NA	-0.10, 0.036	NA	-0.11, -0.01	NA	-0.11, 0.022
24-hour Urine Levels							
Calcium (mmol/D)							

N	23	22	22	23	23	23	23
Mean	5.73	5.69	-0.25	5.69	-0.04	6.03	0.30
Min, Max	1.05, 11.20	2.10, 12.10	-7.90, 2.30	0.90, 11.20	-3.20, 3.30	1.80, 13.30	-5.50, 3.85
p-value	NA	NA	0.5807	NA	0.9019	NA	0.5273
90% CI	NA	NA	-1.03, 0.521	NA	-0.64, 0.555	NA	-0.50, 1.102
Phosphorus (mmol/D)							
N	23	20	20	22	22	22	22
Mean	25.53	23.95	-1.00	25.48	-0.23	28.77	3.87
Min, Max	7.50, 42.00	7.60, 40.70	-13.6, 8.55	6.40, 42.10	-12.6, 10.80	11.30, 56.10	-4.80, 14.10
p-value	NA	NA	0.5159	NA	0.8759	NA	0.0064
90% CI	NA	NA	-3.62, 1.616	NA	-2.78, 2.313	NA	1.67, 6.067

Pharmacokinetic/Pharmacodynamic Relationship. There was no significant correlation between the PK parameters AUC and C_{max} and the PD parameters serum albumin-adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus as evident from the representative profiles on Day 14 (see Figure 40005.2 a-d, and Table 40005.6).

Figure 40005.2a: Relationship between Serum Alb-adj Calcium (mmol/L) and AUC of Calcitriol (pg.h/ml) at Day 14

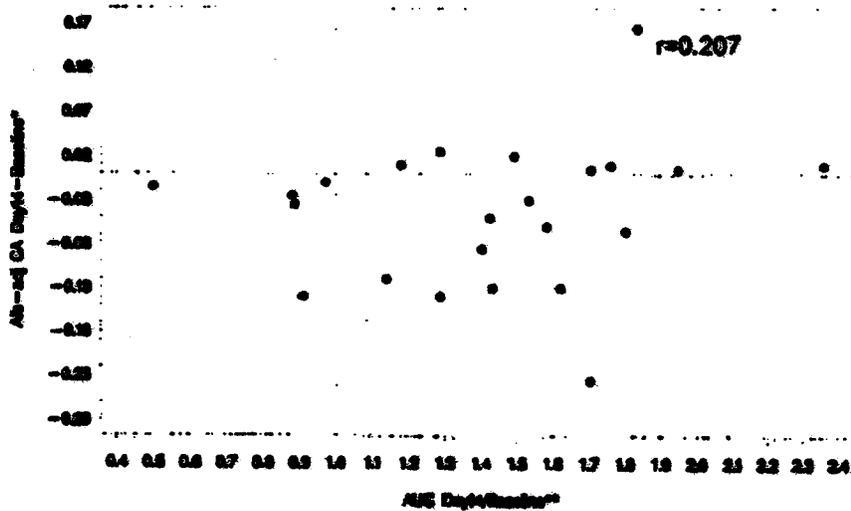


Figure 40005.2b: Relationship between Serum Alb-adj Phosphorus (mmol/L) and AUC of Calcitriol (pg.h/ml) at Day 14

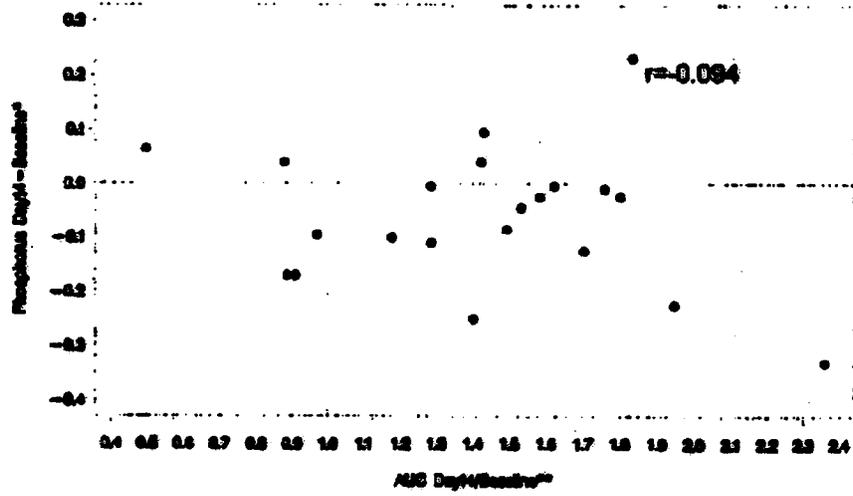


Figure 40005.2c: Relationship between Urinary Calcium 24 h (mmol/L) and AUC of Calcitriol (pg.h/ml) at Day 14

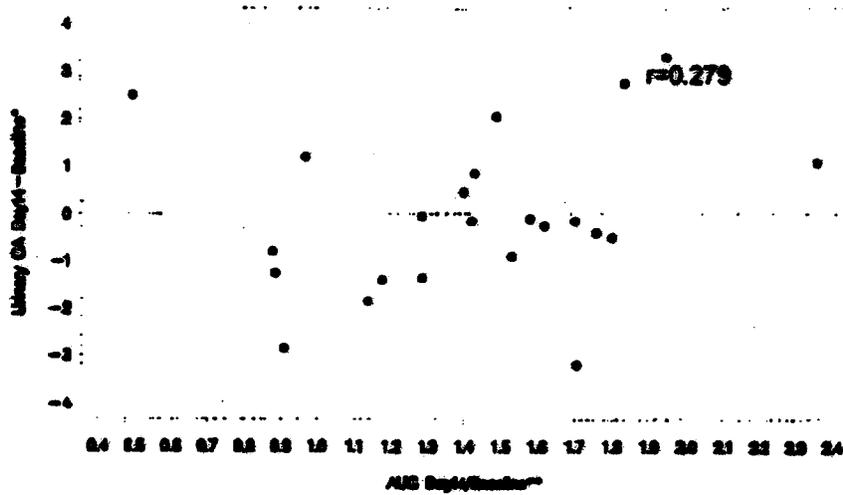


Figure 40005.2d Relationship between Urinary Phosphorus 24 h (mmol/L) and AUC of Calcitriol (pg.h/ml) at Day 14

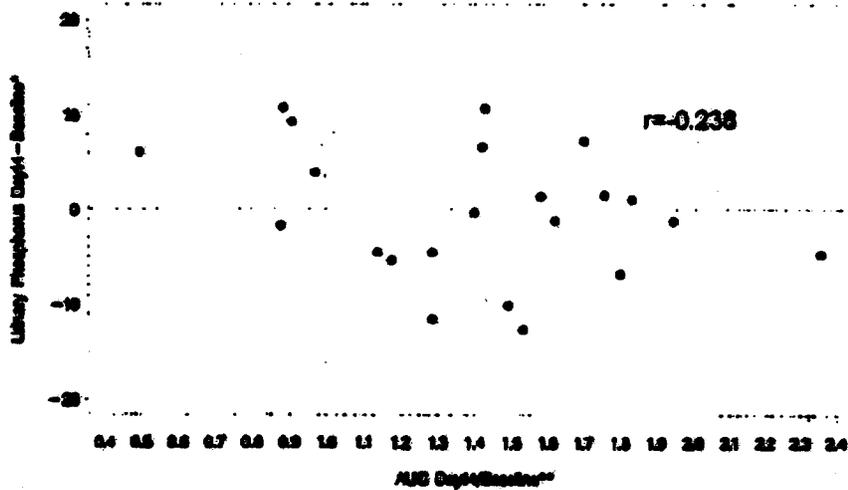


Table 40005.6: PK/PD Relationship (Spearman Correlation Coefficient)

Pharmacokinetic Parameters	Spearman Correlation Coefficient		
	Pharmacodynamic Parameters		
	Day 0-Baseline ^a	Day 14 - Baseline	Day 21 - Baseline
	Albumin adjusted Calcium (mmol/L)		
AUC (D0)/AUC Baseline ^b	-0.16903	0.18056	0.21354
AUC (D14)/AUC Baseline	-0.20558	0.20678	0.26940
AUC (D21)/AUC Baseline	-0.34198	-0.06777	0.00344
C _{max} (D0)/AUC Baseline	-0.18829	-0.02276	-0.04053
C _{max} (D14)/AUC Baseline	-0.20608	0.03413	0.06426
C _{max} (D21)/AUC Baseline	-0.26361	-0.02276	-0.02966
	Phosphorus (mmol/L)		
AUC (D0)/AUC Baseline	-0.30276	-0.07862	0.04237
AUC (D14)/AUC Baseline	-0.37560	-0.09357	-0.04839
AUC (D21)/AUC Baseline	0.09390	0.06628	-0.03616
C _{max} (D0)/AUC Baseline	0.11847	0.25926	0.20113
C _{max} (D14)/AUC Baseline	-0.21150	0.04224	0.15480
C _{max} (D21)/AUC Baseline	0.05968	0.23782	0.17684
	Urinary Calcium (mmol/D)		
AUC (D0)/AUC Baseline	0.10054	0.32115	0.20458
AUC (D14)/AUC Baseline	-0.17170	0.27866	0.14526
AUC (D21)/AUC Baseline	-0.02768	-0.02273	-0.02075
C _{max} (D0)/AUC Baseline	0.25330	0.25791	0.10968
C _{max} (D14)/AUC Baseline	-0.04349	0.11166	-0.05237
C _{max} (D21)/AUC Baseline	-0.08020	0.00198	-0.02569
	Urinary Phosphorus (mmol/D)		
AUC (D0)/AUC Baseline	0.19489	0.04970	0.07397
AUC (D14)/AUC Baseline	0.27361	-0.23779	-0.44325
AUC (D21)/AUC Baseline	0.05714	0.07738	-0.27950
C _{max} (D0)/AUC Baseline	0.09173	0.34726	0.21174
C _{max} (D14)/AUC Baseline	0.34436	-0.04801	-0.19235
C _{max} (D21)/AUC Baseline	0.06316	0.11861	-0.04912

^a Baseline is the Arithmetic Mean of the two values obtained on Day -1 and Day -8.

^b Baseline is the Geometric Mean of the two values obtained on Day -1 and Day -8.

Discussion:

The following section may be important to understand why it is necessary to monitor plasma level of calcitriol and the PD parameters like serum and urinary levels of calcium and phosphorus.

Calcium in serum exists in three fractions: bound to plasma proteins (approximately 40%), chelated to serum anions (13%) and free ionized calcium (47%). It is this last fraction which has biological activity and is under homeostatic control. Total calcium is usually a good reflection of free calcium since the free and bound forms are typically each about half of the total and the total is the sum of all three moieties described above. However, because about half of the calcium in blood is bound to protein, total calcium test results can be affected by high or low levels of protein. Approximately 80% of the protein-bound calcium fraction is associated with albumin. Therefore, a patient with abnormally high serum albumin will have proportionally elevated total serum calcium; and, the reported serum calcium in a patient with low serum albumin will also be reported as less than the true value. That is why total serum calcium is usually reported as albumin adjusted calcium.

Calcium homeostasis refers to the regulation of the concentration of calcium ions in the extracellular fluid $[Ca^{++}]_{ECF}$.

Maintaining normal blood calcium and phosphorus concentrations is managed through the synchronized action of three hormones that control fluxes of calcium in and out of blood and extracellular fluid:

Parathyroid hormone serves to increase blood concentrations of calcium. *Vitamin D* acts to increase blood concentrations of calcium. It is generated through the activity of parathyroid hormone within the kidney. The most important effect of vitamin D is to facilitate absorption of calcium from the small intestine. In concert with parathyroid hormone, vitamin D also enhances fluxes of calcium out of bone.

Calcitonin is a hormone that functions to reduce blood calcium levels.

Calcitriol is a naturally occurring Vitamin D analog, thought to be the active hormone exerting Vitamin D activity. Calcitriol facilitates the availability of calcium and phosphate for new bone formation and assists in prevention of hypocalcemia and hypophosphatemia, primarily by increasing bone resorption as well as intestinal and renal tubular calcium absorption of calcium. Parathyroid hormone (PTH) mediates calcitriol's effects on bone and kidney. Based on the feedback loop, excess calcitriol would be expected to potentially increase calcium and phosphorus levels and suppress PTH levels and that calcium can combine with phosphate ions, forming deposits of calcium phosphate (stones) in blood vessels and in the kidneys.

Calcitriol is an endogenous substance. Its plasma level in normal subjects is low (20-60 pg/mL) and variable from one subject to another. The plasma level of calcitriol was determined in this study both, at baseline before calcitriol ointment application and at specified time points during the repeated treatment with calcitriol ointment in each subject in order to assess increases in calcitriol levels above baseline.

Mean calcitriol plasma concentrations slightly increased upon twice-daily application of a maximized dose of calcitriol 3 µg/g ointment (30 g daily) for 21 days in subjects with chronic plaque psoriasis. At Day 21 the Geometric Mean plasma concentration values of C_{max} increased by approximately 36% over Baseline (59.8±29.6 to 75.3±27.3 pg/ml) and the Geometric Mean value of AUC (0-12h) increased by 44% (544.5±231.7 to 725.6±261.0 pg.h/ml).

In order to evaluate possible implications of higher mean AUC and C_{max} values, individual patient PK and PD data were carefully examined. The following is the summary of those findings:

Analysis of the data by this reviewer lists below patients who had serum calcitriol C_{max} level > 60 pg/ml (normal range between 20 and 60 pg/ml) at any time during the study:

PATNO	INIT	EVENT_ID	C _{MAX}	T _{MAX}	AUC
1		D21	67.82	2	598.60
2		D_01	67.69	3	679.58
2		D00	76.8	2	753.31
2		D14	82.38	3	743.505
2		D21	85.83	6	831.545
3		D_00	107.11	0	1215.81
3		D_01	121.32	3	1224.50
3		D00	147.85	4	971.405
3		D14	71.46	12	806.42
3		D21	93.87	0	874.015
5		D_01	74.11	3	745.53
5		D_00	98.37	3	882.83
5		D00	93.91	3	953.725
5		D14	108.36	3	1048.01
5		D21	88.39	4	908.03
7		D14	78.73	9	888.085
7		D21	88.37	3	742.81
8		D00	78.88	3	482.82
8		D14	87.7	4	881.73
8		D21	74.16	1	788.315
13		D14	61.1	2	634.425
13		D21	88.88	3	874.115
14		D00	88.84	4	583.175
14		D14	98.27	9	1104.13
14		D21	82.85	4	788.345
17		D14	74.28	3	748.58
17		D21	82.98	2	727.88
18		D_00	88.84	3	843.448

b(6)

19	77	D_01	78.38	6	695.76
19		D14	98.34	4	987.295
19		D21	118.88	3	1118.58
20		D_08	92.55	0	888.19
20		D_01	98.71	2	982.785
20		D08	78.19	4	792.62
20		D14	98.3	12	985.885
20		D21	122.88	4	1233.87
21		D14	61.33	12	471.31
21		D21	67.41	1	487.78
22		D_08	115.84	1	1122.88
22		D_01	114.41	0	1048.54
22		D08	117.14	4	928.535
22		D14	95.98	4	957.51
22		D21	88.17	2	922.37
23		D_08	83.88	4	728.28
23		D_01	187.18	1	837.03
23		D08	88.88	6	713.15
23		D21	88.88	3	571.105
34		D14	88.83	12	508.88
34		D21	83.28	9	837.535
38		D14	84.79	1	787.275
38		D21	88.48	2	838.81
37		D_08	74.43	4	688.78
37		D_01	78.23	1	728.63
37		D08	78.84	3	828.54
37		D14	138.47	3	1288.1
37		D21	142.38	4	1214.83

b(6)

Seventeen out of 23 patients (74%) had high calcitriol levels that are considered above the normal range of 15 to 60 pg/ml during screening to end of study period . However, 9 of the 17 patients had high calcitriol levels at baseline leaving a total of 8 patients that developed high calcitriol levels during their therapy (35%).

Analysis of the data by this reviewer lists below patients whose serum calcium (normal range 2.5 – 2.54 mmol/L) and phosphorus (normal range 0.81 – 1.45 mmol/L) levels were flagged as “out of range”:

PATNO	INIT	EVENT_ID	TESTID	VALUE	FLAG
9	77	D14	CA	2.57	H
13		SCREEN	CA	2.58	H
14		SCREEN	CA	2.57	H
14		D_08	CA	2.63	H
14		D_01	CA	2.81	H
14		D08	CA	2.6	H
14		D_08	PHUS	1.8	H
14		D_01	PHUS	1.48	H
16		D08	CA	2.57	H
17		D_08	CA	2.58	H
17		D08	CA	2.84	H

b(6)

17	7	D_08	PHUS	0.79	L
18		D14	PHUS	0.79	L
20		D_01	CA	2.6	H
21		D_01	PHUS	1.46	H
22		D08	CA	2.55	H
34		SCREEN	CA	2.59	H
36		SCREEN	CA	2.63	H
37	3	D21	PHUS	1.52	H

b(6)

None of these eight patients mentioned above with high calcitriol levels had abnormal labs throughout their therapy. Data from some of the patients worth mentioning are as follows:

- *Patient # 13* had slightly above normal calcitriol levels on Days 14 and 21 but did not have high calcium and/or phosphorus levels on those days though the patient had slightly high calcium level at screening that did not remain high during therapy.
- *Patient # 14* had above normal calcitriol levels on Days 0, 14 and 21 but did not have high calcium and/or phosphorus levels on those days though the patient had slightly high calcium and phosphorus levels on Days -8, -1.
- *Patient # 17* had above normal calcitriol levels on Days 14 and 21 but did not have high calcium and/or phosphorus levels on those days though the patient had slightly high calcium levels on Days -8, 0 and slightly low phosphorus level on Day -8.
- *Patient # 22* had persistent above normal calcitriol levels on Days -8, -1, 0, 14 and 21 but had slightly high calcium level only on Day 0.
- *Patient # 37* had persistent above normal calcitriol levels on Days -8, -1, 0, 14 and 21 but had slightly high phosphorus level only on Day 21.

None of the subjects in this study had outside normal range (2.15 – 2.55 mmol/L) of serum albumin adjusted calcium and alkaline phosphatase (36 – 118 U/L) levels (another clinically relevant parameter) throughout the study period on the days that labs were collected (D14 and D21).

There was no correlation between the PK parameters AUC and C_{max} and the PD parameters of serum albumin adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus on the days the labs were collected. However, due to the limitations of the study as to when labs were collected, one can not rule that the pharmacodynamic aspects may have occurred at a later time.

As a result, the clinical significance of increased systemic exposure of calcitriol upon twice-daily application of a maximized dose of calcitriol 3 µg/g ointment (30 g daily) for 21 days in subjects with chronic plaque psoriasis remains unclear.

According to the sponsor, calcitriol 3 µg/g was well tolerated. There were no deaths, serious Adverse Events or discontinuations due to Adverse Events. The most frequently

reported Adverse Event experienced by four subjects was headache, considered to be of moderate intensity, and unrelated to treatment. There were no treatment-related changes observed for laboratory values, vital signs and physical examinations.

Comments:

- *While one of the inclusion criteria for patient recruitment was that the subject had normal serum calcium and phosphorus values at Day -8, there was no restriction in recruiting subjects with above normal calcitriol level at the beginning.*
- *While no apparent PK/PD relationship was observed based on the data, extent of percutaneous absorption of exogenous calcitriol (as they were not radiolabeled) could not be ascertained.*
- *As blood samples were taken at weekly interval, real-time transient effects of exogenous calcitriol on individual organ function could not be ascertained.*
- *There were no calcitriol plasma level measurements beyond Day 21. Therefore, it was not possible to assess the time required for elimination of high plasma calcitriol levels.*
- *The mean 24-hour urinary levels of phosphorus increased from 25.53 mmol/D at baseline to 28.77 mmol/D at Day 21, this difference was statistically significant ($p=0.0064$) though there was no correlation with calcitriol level (except for patient # 37). However, due to the limitations of the study as to when labs were collected, one can not rule that the pharmacodynamic aspects may have occurred at a later time for other patients with high calcitriol levels. Therefore, the clinical significance of this increase is unclear.*

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Clinical Pharmacology Review of the Clinical Studies:

Additional calcitriol plasma levels were obtained from the following studies conducted by the Sponsor:

- Two Pivotal Phase 3 clinical studies RD.06.SRE.18053 and RD.06.SRE.18054,
- One Long term safety study RD.03.SRE.2663, and
- One Body Surface Area Escalation Study RD.03.SRE.2635.

Brief description of the studies along with results are described in the following section:

NDA: 22-087/Study R.06.SRE.18053

Study Dates: Jan, 02 – Jul, 02

Evaluation of the Efficacy and Safety of Twice Daily Application of Calcitriol 3µg/g Ointment and its Vehicle, in the Treatment of Chronic Plaque Psoriasis

It was a multi-center, randomized, double-blind, vehicle-controlled, parallel-group comparison study. Qualified subjects were randomized in a 1: 1 ratio to receive calcitriol ointment 3µg/g or its vehicle for a period of 8 weeks.

A total of 418 subjects (209 in calcitriol ointment 3µg/g group, and 209 in vehicle ointment group) were enrolled. Trough samples for the determination of calcitriol plasma levels were collected at Screening, week 2 and at Week 8, in selected centers.

Calcitriol plasma levels - Mean values (RD.06.SRE.18053)

Laboratory Parameters and Expanded Normal Range ^a		Calcitriol Ointment 3µg/g		Vehicle Ointment	
		Screening ^a	Week 8/Final ^b	Screening ^a	Week 8/Final ^b
Calcitriol (15.9 to 95.6 pg/mL)	N	28	28	31	33
	Mean	56.08	52.72	48.97	51.73
	SD	27.182	13.808	17.038	15.355

^a Week 8 or last available post-baseline data (trough level) if the subject discontinued prematurely.

^b Expanded normal range indicates the lowest value of the normal range and the highest value of the normal

The mean (SD) calcitriol level showed a minimal change from Screening: from 56.08 pg/mL (27.182) at Screening, to 52.72 pg/mL (13.808) at Week 8/Final in calcitriol ointment 3µg/g group, corresponding to a 6.0% decrease; and from 48.97 pg/mL (17.038) at Screening to 51.73 pg/mL (15.355) at Week 8/final in vehicle ointment group, corresponding to a 5.6% increase.

Reviewer's Comment: Review of the calcitriol levels of the subjects in this pivotal Phase 3 studies showed a mean decrease after 8 week. About 38 % (12/32) patients did have a higher than normal range of calcitriol (> 60 pg/ml) during different time points within the 8 weeks. Careful review of the laboratory results of these subjects revealed that one subject who had high calcitriol levels with one subject having abnormal laboratory parameters as well and is described below:

Study 18053:

Site/subject	Lab parameter	Lab day	Lab result	Flag	Ref range
4399477	Calcitriol level	-3	[[
		15		H	
		30		H	
	Adj Calcium	-3			
		15		H	
		37		H	
		43			
		50		H	
	Phos serum	-3			
		15			
		37			
		43		H	
		50		H	
	Calcium, 24 hr	15			
		37			
		43		H	
	Calcium/creat ratio	15			
		37			
		43			

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The clinical significance of the above findings unclear. The safety aspect of this study is being reviewed by the clinical division.

NDA: 22-087/Study R.06.SRE.18054

Study Dates: Jan, 02 – Jul, 02

Evaluation of the Efficacy and Safety of Twice Daily Application of Calcitriol 3µg/g Ointment and its Vehicle, in the Treatment of Chronic Plaque Psoriasis

It was a multi-center, randomized, double-blind, vehicle-controlled, parallel-group comparison study. Qualified subjects were randomized in a 1: 1 ratio to receive calcitriol ointment 3µg/g or its vehicle for a period of 8 weeks.

A total of 421 subjects (210 in calcitriol ointment 3µg/g group, and 211 in vehicle ointment group) were enrolled in the study. Trough samples for the determination of

calcitriol plasma levels were collected at Screening, week 2 and at Week 8, in selected centers.

Calcitriol plasma levels - Mean values (RD.06.SRE.18054)

Laboratory Parameters		Calcitriol Ointment 3µg/g		Vehicle Ointment	
		Screening ^a	Week 8/Final ^b	Screening ^a	Week 8/Final ^b
Calcitriol (13.9-56.6 pg/mL)	N	33	34	35	38
	Mean	52.56	50.91	48.03	47.39
	SD	20.993	18.906	19.450	20.518

^aScreening: The last laboratory value during pre-treatment period.

^bWeek 8 or last available post-baseline data (trough level) if the subject discontinued prematurely.

The mean (SD) calcitriol level showed a minimal change from Screening: from 52.56 pg/mL (20.993) at Screening, to 50.91 pg/mL (18.906) at Week 8/Final in calcitriol ointment 3µg/g group, corresponding to a 3.1% decrease; and from 48.03 pg/mL (19.450) at Screening to 47.39 pg/mL (20.518) at Week 8/final in vehicle ointment group, corresponding to a 1.3% decrease.

Reviewer's Comment: Review of the calcitriol levels of the subjects in this pivotal Phase 3 study showed a mean decrease of calcitriol levels after 8 weeks. However, about 38 % (15/39) of patients did have a higher than normal range of calcitriol level (> 60 pg/ml) during different time points within the 8 weeks of the study. Careful review of the laboratory results of these subjects revealed that 1 subject who had high calcitriol levels also had abnormal laboratory parameters as described below:

Study 18054

Site/subject	Lab parameter	Lab day	Lab result	Flag	Ref range		
2062/336	Calcitriol level	17	[REDACTED]	H	[REDACTED]		
		57		H			
	AdiCa	-3		H			
		17					
		29					
		43		H			
	Calcium, 24 hr	57					
		17					
		29		H			
		43		H			
	Calcium/total calc	57					
		17					
		29					
		43					
				57			

The clinical significance of these findings is unclear.

NDA: 22-087/Study RD.03.SRE.2663

Study Dates: Sep, 01 – Mar, 03

Multi-center, open-label, non-comparative long-term safety study to assess the local and systemic safety of Calcitriol 3µg/g Ointment applied twice daily for up to 52 weeks in subjects suffering from mild to moderate Chronic Plaque Psoriasis

It was a multi-center, open-label, non-comparative long-term safety study, designed to assess the local and systemic safety of calcitriol ointment 3µg/g applied twice daily for up to 52 weeks in subjects suffering from mild to moderate chronic plaque psoriasis. A total of 324 subjects were enrolled. Calcitriol plasma trough levels were determined at Baseline, Week 26 and Week 52. The summary of data obtained is presented below.

Calcitriol plasma levels - Mean values (RD.03.SRE.2663)

Calcitriol plasma level determination (pg/mL)	Normal Range	Baseline	Week 26	Week 52
Mean (SD)	15 to 90 pg/mL	43.29 (14.74)	45.54 (20.09)	47.96 (19.29)

The mean (SD) calcitriol level showed a minimal change from Baseline: 43.29 pg/mL (14.74) at Baseline; 45.54 pg/mL (20.09) at Week 26; 47.96 pg/mL (19.29) at Week 52.

Reviewer's Comment: Calcitriol plasma levels were measured randomly in 28 subjects in this trial with 27 of them (96%) having high levels at various times during the 52-week study.

The highest calcitriol level (118 pg/ml) was observed in a 46 year old female (Patient # 179) at week 26. Notably, three subjects in this study (#s 169, 233 and 255) were diagnosed with kidney stones. These patients had high calcitriol levels most of the time, which may have correlated with the development of kidney stones. The clinical review will describe more about the findings. Their profiles are as follows:

Table 1 Corrected calcium, phosphorus, urine calcium and calcitriol levels for Subject 100

Laboratory measurement and normal values.	Albumin adjusted serum total calcium (2.15-2.55 mmol/L)	Phosphate Level (0.87-1.48 mmol/L)	Urine Calcium Level (2.5-7.5 mmol/24h)	Urine Phosphate Level (11-42 mmol/24 h)	Calcitriol Level (15-50 ng/L)	Parathyroid hormone Level (13-54 ng/L)
Date (dd/mm/yyyy)						
20Nov01* (Screening)	2.35	0.98	-	-	73	52
02Dec01* (Baseline)	-	-	8.3	25.5	-	-
14Jan02 (Week 8)	2.31	1.11	10.2	38.3	70	36
21Jan02	-	-	9.9	25.2	-	-
25Feb02 (Week 12)	2.3	0.99	6.5	27.3	66	22
28Apr02	2.28	1.11	10.2	30.4	67	25
03Jun02 (Week 20)	2.19	0.99	15.9	31.6	91	23
24Feb03	-	-	8.9	-	-	31.6

* Before study treatment commenced. Bold text = values out of normal range.

Table 2 Calcium, calcium urinary and calcitriol levels for Subject 233

	Albumin adjusted serum total calcium (2.15-2.55 mmol/L)	Urinary Calcium Level (2.5-7.5 mmol/24 h)	Calcitriol Level (15-50 ng/L)
Date (dd/mm/yyyy)			
24Jan02 (screening)	2.28	-	54
31Jan02 (baseline)	-	10.2	-
14Mar02 (Week 6)	2.35	9.4	31
25Apr02 (Week 12)	2.31	10.7	27
08Jun02 (Week 18)	2.38	8.5	30
01Aug02 (Week 26)	2.41	15.6	51
13Aug02	2.34	8.8	38
07Oct02 (Week 33)	2.32	9	48
04Dec02 (Week 40)	2.41	15.6	52
18Dec02**	2.39	8.7	37

* Before study treatment commenced; ** After study treatment stopped (10/12/02); bold values = out of normal range.

Table 3: Calcium, calcium urinary and calcitriol levels for Subject 268

	Albumin adjusted serum total calcium (2.15-2.55 mmol/L)	Urinary Calcium Level (2.5-7.5 mmol/24 h)	Calcitriol Level (15-68 ng/L)
Date (dd/mm/yy)			
24Jan02* (screening)	2.18	-	40
31Jan02* (baseline)	-	13.5	
14Mar02 (Week 6)	2.32	7.5	97
25Apr02 (Week 12)	2.38	6	72
08Jun02 (Week 18)	2.28	11.6	88
01Aug02 (Week 26)	2.24	3.2	38
03Oct02 (Week 36)	2.28	3.7	88
08Dec02 (Week 44)	2.27	16.8	38
11Dec02**	2.21	-	78
03Jan03**	2.24	6.8	74

*Before study treatment commenced. **After study treatment stopped (10/12/02). Bold text = values out of normal range

NDA: 22-087/Study RD.03.SRE.2635

Study Dates: Dec, 99 – Aug, 00

Evaluation of systemic safety during and after 12 weeks of treatment with Calcitriol 3µg/g Ointment in subjects suffering chronic Plaque Psoriasis in three parallel groups involving various body surface areas

This was an open label, multi-center, safety study with 3 parallel groups of equal sizes depending on the body surface area involved (5 to < 15%; 15 to < 25%; 25 to 35% BSA). Calcitriol ointment 3 µg/g was applied twice daily for 12 weeks. A total of 59 subjects were enrolled. Calcitriol plasma levels were determined at Inclusion and at Week 2, Week 6, Week 9 and Week 12 and albumin-adjusted serum calcium levels were determined at each sampling point. The data obtained are presented below.

Calcitriol plasma levels - Mean values - APT Safety Population (RD.03.SRE.2635)

(Normal range 48 to 110 pmol/L *)				
Time-point	BSA 5 to <15% (0-23)	BSA 15 to <25% (0-18)	BSA 25 to 35% (0-18)	Total (0-59)
Inclusion visit				
Number of subjects	21	18	18	57
Mean (SD)	91.8 (28.8)	110.2 (38.3)	86.7 (28.7)	96.0 (33.2)
Geometric mean	87.4	104.6	82.6	90.9
CV	33.0	33.4	33.6	34.3
Range	48 to 168	58 to 228	48 to 138	48 to 228
Week 2				
Number of subjects	20	18	18	56
Mean (SD)	103.2 (23.4)	108.3 (28.4)	107.7 (33.6)	108.2 (28.1)
Geometric mean	100.5	104.5	102.9	102.5
CV	24.9	28.6	32.4	28.1
Range	58 to 138	58 to 156	51 to 186	51 to 186
Week 6				
Number of subjects	19	13	18	48
Mean (SD)	98.9 (21.1)	114.4 (24.8)	114.6 (31.8)	107.1 (27.0)
Geometric mean	93.4	112.0	110.4	103.7
CV	24.9	21.7	28.9	28.5
Range	48 to 138	71 to 173	85 to 165	48 to 186
Week 9				
Number of subjects	18	12	14	44
Mean (SD)	96.0 (25.9)	118.1 (31.3)	101.4 (18.7)	108.8 (31.9)
Geometric mean	92.8	108.8	98.8	99.3
CV	28.1	41.0	19.1	36.2
Range	48 to 145	48 to 201	72 to 138	48 to 201
Week 12				
Number of subjects	18	12	14	44
Mean (SD)	98.6 (31.4)	116.3 (25.8)	114.6 (40.0)	108.6 (33.4)
Geometric mean	94.2	113.4	108.7	104.0
CV	31.2	24.8	28.8	28.7
Range	55 to 168	64 to 156	64 to 228	55 to 228

48 to 110 pmol/L correspond to: 20 to 46 pg/mL

Mean trough serum calcitriol levels at the end of the treatment period were slightly higher than those at inclusion in all three groups. Overall, mean serum calcitriol levels increased from 96.0 pmol/L at baseline to 108.5 pmol/L at Week 12.

Time-Point	BSA 5 to <15%	BSA 15 to <25%	BSA 25 to 35%
Inclusion visit	91.8	110.2	86.7
Week 12	98.6	116.3	114.6
% Change	7.4	3.3	32.2

Reviewer's comment: While few subjects (8/59) enrolled in the study had marginal increase in calcitriol level (maximum 180 pmol/l corresponding to 75 pg/ml), none of the subjects had increase in albumin adjusted serum calcium at any point during the study. As previously observed, the increase in calcitriol levels was greater in the BSA 25 to 35%

group (+32.2%), compared to the BSA 5 to < 15% and to the BSA 15 to < 25% groups (+7.4% and +5.5%, respectively).

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4.3 Consult Genomic Review

Executive Summary

The sponsor is seeking approval for calcitriol ointment 3 µg/g for the treatment of plaque-type psoriasis. Psoriasis is characterized by hyperproliferation and abnormal differentiation of keratinocytes, and inflammation. Calcitriol stimulates differentiation and inhibits epidermal keratinocytes and T-cell proliferation and the production of essential inflammatory factors such as interleukins and interferons through interaction with the vitamin D receptor (VDR). One of the VDR target genes is CYP24 which encodes 24-hydroxylase (24-OH), a mitochondrial cytochrome P450 that converts calcitriol into an inactive metabolite that is subsequently excreted in the urine. The sponsor conducted a study to determine the effect on CYP24 and other markers gene expression of topical application of calcitriol 3 µg/g ointment. Specific amplification of the cDNA encoding for 24-OH was not achieved and a detailed gene expression profiling performed in two subjects failed to find genes for which transcription was modulated by calcitriol treatment in the conditions of the experiment. Although there are no labeling recommendations from the sponsor based on these studies, it is important to note some aspects for future investigations the sponsor may choose to pursue.

RECOMMENDATIONS

- Given the proposed indication for calcitriol 3 µg/g ointment, the effect of the treatment on gene induction/inhibition should be also studied in patients with psoriasis.
- VDR and other ligands genetic variants could be explored as factors influencing the effects of calcitriol 3 µg/g ointment on target genes expression.
- Any findings in this kind of experiments should be followed by an appropriate replication study.
- The procedures for collection, handling and storage of biological specimens, RNA and DNA isolation, handling and characterization, analytical methods including quality control and quality assurance procedures should be included in the submission of the studies.
- Given the methodological shortcomings and the results of the study, it is recommended that no information based on this study be included in the product label.

General Clinical Pharmacology related to Genomics

Calcitriol is the biologically active metabolite of vitamin D3. In keratinocytes and other cell types, it regulates growth and differentiation. Consequently, vitamin D analogues have been introduced for the treatment of the hyperproliferative skin disease psoriasis. Calcitriol interacts with the nuclear vitamin D receptor (VDR) and modulates transcription through binding of VDR to specific vitamin D response elements in the promoter of target genes, resulting in the inhibition of proliferation of keratinocytes and

T-cells, the inhibition of the production of inflammatory factors such as interleukins and interferons and the stimulation of differentiation of epidermal keratinocytes. Expression profiling using microarray technology indicates that comparable numbers of genes are downregulated as they are upregulated by calcitriol. One of the VDR target genes is CYP24 which encodes 24-hydroxylase (24-OH), a mitochondrial cytochrome P450 that converts calcitriol into an inactive metabolite that is subsequently excreted in the urine. The mRNA expression levels of the CYP24 gene have been shown to be very low in the absence of ligand, but it can be up to 1000-fold induced by stimulation with calcitriol. The sponsor conducted a study (Study Report # 2853 entitled "Analysis of epidermal gene expression after 24, 48 and 72 hours of treatment with calcitriol 3 µg/g applied under occlusion") with the objective of determining the differential effect on gene expression of calcitriol 3 µg/g ointment in comparison to its vehicle and a non treated site. The goals of the study are in concert with the current knowledge in the field. Twelve healthy Caucasian volunteers (6 females, 6 males) aged from 20 to 53 years were recruited, completed the study and were included in the analysis. Calcitriol 3 µg/g ointment was applied under occlusion on three sites of the lower back/buttocks during 24, 48 or 72 hours, respectively. Calcitriol vehicle was also applied under occlusion during 24 and 72 hours. In addition, an empty patch was incorporated as a negative control and left in place during 72 hours. Erythema was evaluated 1 hour after the removal of patches. Following this, a 4mm punch biopsy of the occluded site was taken by the investigator and sent for molecular biology investigations. RNA was extracted from the biopsies and retro-transcribed into cDNA for subsequent amplification by RT-PCR of CYP24 and glyceraldehyde 3-phosphate dehydrogenase (GAPDH), used as control. RNA from two subjects was selected for a detailed gene expression profiling using high density arrays. Although the study design appears in general appropriate, only two subjects were selected for further analysis and there is no information on the criteria used to select these two individuals. In addition, all the subjects included in the study were healthy volunteers and it is expected that the pattern of gene expression induction/inhibition could be different in patients with psoriasis. In terms of the selection of the markers, CYP24 has been previously shown to be a VDR target gene and GAPDH is an appropriate control.

Analytical Section

The procedures for collection, handling and storage of the biological specimens are adequate. RNA isolation, handling and characterization are also appropriate. RNA was extracted from the biopsies and retro-transcribed into cDNA for subsequent amplification by RT-PCR of CYP24 and GAPDH, used as control. There is not enough information on the amplification procedures and the assay proficiency testing to avoid procedural failures. The primers utilized in the PCR reactions are not presented; therefore, it is not possible to evaluate the specificity of the primers for the selected target genes. RNA from two subjects was selected for a detailed gene expression profiling (i.e. expression for different biological markers, e.g. 24 hydroxylase, interleukins and growth factors) using high density arrays. The microarrays and reader used are commercially available and are adequate technologies for the study of the expression of a large number of target genes. However, there is no information on the quality control of the samples, the runs and the hybridization procedures.

Interpretation of results

The sponsor states that specific amplification of the cDNA encoding for 24-OH was not achieved even after several combinations of primers as well as several conditions of PCR reactions were tested. This failure in the amplification of the CYP24 gene contrasts with the findings by many researchers who have been able to achieve the gene amplification and to show successfully the effect of different compounds on the CYP24 gene expression in different tissues. As an alternate method to identify the effect of calcitriol ointment treatment on the expression of CYP24, the sponsor presents the visualization of CYP24 cDNA by agarose gel electrophoresis in the skin of the 12 subjects (Fig. 1, page 18 of the Study Report #2853). In that figure it is possible to identify the absence of CYP24 cDNA in the vehicle and non-treated samples and its presence in the active treatment samples. However, the agarose gel electrophoresis is not a good method for the quantification of gene expression. In fact, in Fig. 1, the cDNA at 24 h appears to be quantitatively similar to that at 72 h and higher than the samples taken at 48 h. This apparent difference in gene expression between samples at different time points reflects more likely the limitations of the procedure to quantify the cDNA rather than a particular time course in the induction of CYP24 gene expression by calcitriol. In the microarray assays of the samples from two subjects, the sponsor reports it was not possible to find genes for which transcription was modulated after 24, 48 and 72 hours of calcitriol treatment in the epidermis of these two subjects. Again, given that calcitriol and other vitamin D analogues have shown to induce the expression of different genes, a possible explanation for these negative findings could be the failure in the microarray procedures. Another aspect worth considering is that studies involving assessment of VDR mRNA in psoriatic lesional biopsies taken from calcitriol and vehicle treated plaques reported that it was upregulated 2.4-fold in calcitriol-treated plaques, relative to vehicle treatment in responders. Conversely, no upregulation of VDR mRNA was observed in calcitriol-treated plaques from patients who displayed no significant improvement, suggesting that response to vitamin D therapy in psoriasis is determined by the ability to upregulate transcription or stability of this gene and that some individuals lack this ability. Alleles of polymorphic regions within the VDR gene may contribute to the observed phenomenon of nonresponsiveness to calcitriol therapy. For instance, the A-1012G, FokI and TaqI VDR polymorphisms have been associated with response to calcitriol. Similar associations could be found with calcitriol. The genetic variation in VDR and other ligands is another possible explanation for the negative findings of this study. Finally, it is of note that, given the proposed indication for calcitriol, the effect of the treatment on gene induction/inhibition should be studied in patients with psoriasis and that any findings in this kind of experiments should be followed by an appropriate replication study that supports the results as a real rather than a random event.

Labeling Recommendations

Given the methodological shortcomings and the results of the study, it is recommended that no information based on this study be included in the product label.

4.4. Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information about the Submission				
	Information		Information	
NDA Number	22-087	Brand Name	Tradename Ointment	
OCPB Division (I, II, III)	DCP3	Generic Name	Calcitriol Ointment (3mcg/g)	
Medical Division	HFD-540	Drug Class	Immunomodulator	
OCPB Reviewer	Tapash Ghosh	Indication(s)	Treatment of plaque-type psoriasis	
OCPB Team Leader	Lydia Velazquez	Dosage Form	Ointment	
Letter Date	December 27th, 2007	Dosing Regimen	To be applied to the areas affected with psoriasis twice daily, morning and evening	
Application Receipt Date	December 27th, 2007	Route of Administration	Topical	
Estimated Due Date of OCPB Review	August 27th, 2008	Sponsor	Galderma Laboratories, Texas, USA	
FDUFA Due Date	October 27th, 2008	Priority Classification	3S	
		IND Number	62,151	
Clin. Pharm. and Biopharm. Information				
	X if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Table of Contents of All Human Studies	X			
IRIS Summary	X			
Labels	X			
Reference Biophysical and Analytical Methods	X	1	1	CLIN4627 (Radioimmunoassay)
I. Clinical Pharmacology				
Pharmacokinetics				
Pharmacodynamics				
Toxicology				
Pharmacovigilance				
Pharmacoeconomics (e.g., Phase I) -				
Healthy Volunteers				
single dose	X	2	2	N.141.603 (15 mcg/g ointment), N.141.602
multiple dose				
Patients				
single dose	X	1	1	N.141.603

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multiple dose:	X	6	6	SRE.18033 and SRE.18054 (pivotal Phase 3 studies), SRE.2663 (long term safety study), SRE.2635 (BSA escalation) Dose ranging studies (H.141.5004., H.141.5013)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
in-vivo effects on primary drug:				
in-vivo effects of primary drug:	X	1	1	H.141.6003
in-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	SRE.4005 (maximal exposure study)
Phase 3 clinical trial:				
Formulation Analyses -				
Data rich:				
Data sparse:				
II. Bioequivalency				
Absolute Bioavailability:				
Relative Bioavailability -				
solution as reference:				
alternate formulation as reference (IR):				
Bioequivalence studies -				
traditional design: single / multi dose:				
modified design: single / multi dose:				
Food/Drug Interaction studies:				
Dissolution:				
IV/VC:				
Bio-equivalency based on BCS:				
ECI data:				
III. Other CVD Studies				
Genotoxicity studies:	X	1	1	SRE.2853 (Molecular pharmacology study)
Other (in vitro percutaneous absorption study):				
Circulation pharmacokinetics:				
Exposure Assessment plan:				
Literature References:				
Total Number of Studies		11	11	
Fitability and QBR comments: Total 11 studies were included in this NDA . 6 studies were reviewed in detail and 5 were reviewed briefly)				

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Types and #'s of studies and supplementary information (Literature review) are adequate to conduct a review	"X" if yes X	Comments IR sent to the applicant to provide module 5, volumes 1.005 (including the missing pages 630 to 904 for the clinical study report No. 40005). This was received on 2/24/08.
Application fileable?	X	Reasons if the application is <u>not</u> fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	No	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		Was the formulation used in the maximal use PK study the same as that used in the clinical trials/TBMP? Yes Do we need a PM consult? No Do we need a Pharmacogenetics consult? Pharmacogenomics consult was sent on 2/11/08. Silvana Borges is the designated reviewer.
Other comments or information not included above		
Primary reviewer Signature and Date		Abi Adobowan 02/03/2008. Transferred to Tapash Ghosh on 3/17/08 by Lydia Velazquez.
Secondary reviewer Signature and Date		Lydia Velazquez

CC: NDA 22-087, HFD-540 (M. Owens), DCP 3 (D. Bashaw, L. Velazquez, T. Ghosh)

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Tapash Ghosh
8/29/2008 04:32:31 PM
BIOPHARMACEUTICS

Lydia Velazquez
8/29/2008 06:16:24 PM
BIOPHARMACEUTICS

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**Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form**

General Information about the Submission

	Information		Information
NDA Number	22-087	Brand Name	Silkis Ointment
OCPB Division (I, II, III)	DCP3	Generic Name	Calcitriol Ointment (3mcg/g)
Medical Division	HFD-540	Drug Class	Immunomodulator
OCPB Reviewer	Abi Adebawale	Indication(s)	Treatment of plaque-type psoriasis
OCPB Acting Team Leader	Sue-Chih Lee	Dosage Form	Ointment
Letter Date	September 25th, 2006	Dosing Regimen	To be applied to the areas affected with psoriasis twice daily, morning and evening
Application Receipt Date	December 27th, 2007	Route of Administration	Topical
Estimated Due Date of OCPB Review	August 27th, 2008	Sponsor	Galderna Laboratories, Texas, USA
PDUFA Due Date	October 27th, 2008	Priority Classification	3S
		IND Number	62,151

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Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Table of Contents of All Human Studies	X			
RFI Summary	X			
Labels	X			
Reference Bioanalytical and Analytical Methods	X	1		CLIN4827 (Radioimmunoassay)
I. Clinical Pharmacology				
Mass balance:				
In-vivo characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I):				
Healthy Volunteers:				
single dose:	X	2		H.141.603 (15 mcg/g ointment), H.141.602
multiple dose:				
Patients:				
single dose:	X	1A		H.141.603
multiple dose:	X	3		SRE.13033 and SRE.13034 (pivotal Phase 3 studies), SRE.2463 (long term safety study), H.141.5010/K, H.141.5012/K
Dose proportionality:				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies:				
in-vitro effect on primary drug:				
in-vitro effect of primary drug:	X	1A		H.141.603
in-vitro:				
Substitution studies:				
chemistry:				
pharmacology:				
pharmacokinetics:				
toxicology:				

renal impairment:			
hepatic impairment:			
FD:	X	1	SRE 2635
Phase 2:			
Phase 3:			
PK/PD:			
Phase 1 and/or 2, proof of concept:	X	1	SRE 40063 (maximal exposure study)
Phase 3 clinical trial:			
Population Analysis -			
Data risk:			
Data source:			
II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference (IR):			
Bioequivalence studies -			
traditional design: single / multi dose:			
replicate design: single / multi dose:			
Food-drug interaction studies:		2	
Dissolution:			
(IVIVC):			
Bi-waiver request based on MCS:			
BCS class:			
III. Other CYP Studies			
Genotype/phenotype studies:	1		SRE 2851 (Molecular phenotyping study)
Other (in vitro permeation absorption study):			
Chromatopharmaceutics:			
Pediatric development plan:			
Literature References:			
Total Number of Studies:		16	
Feasibility and ORR comments			
Types and #s of studies and supplementary information (literature review) are adequate to conduct a review	X X		Comments PM sent an IR to the applicant to provide module 5, volumes 1.005 (including the missing pages 630 to 904 for the clinical study report No. 40005)
Application fileable?	X		Reasons if the application is not fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	No		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QIR questions (key issues to be considered)			Was the formulation used in the maximal use PK study the same as that used in the clinical trials/TBMF? Yes Do we need a PM consult? No Do we need a Pharmacogenetics consult?
Other comments or information not included above			
Primary reviewer Signature and Date		AM Adabowale 02/03/2008	
Secondary reviewer Signature and Date		Lydia Velazquez	

CC: NDA 22-087, HFD-856 (F. Lee), HFD-540 (M. Owens, M. Bernstein), DCF 3 (D. Baskin, L. Velazquez)

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/s/

Abi Adebawale
2/15/2008 04:42:31 PM
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