

Clinical Review  
 Patricia C. Brown, M.D.  
 NDA 22-087  
 Tradename (calcitriol 3mcg/g) Ointment

Subject Number Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Serious
297 59/M	Calcitriol ointment 3µg/g	Pruritus due to plaque of psoriasis (pruritus)	Probable	Resolved, no residual effects	Moderate	No
299 61/F	Calcitriol ointment 3µg/g	Breast cancer (Carcinoma breast)	Unlikely	Continuing	Severe	Yes

\*See also discussion section 7.3.5.

Source: Sponsor's NDA Integrated Summary of Safety Table 74, 5.3.5.3.02, p 141.

### 7.3.4 Significant Adverse Events

Please see sections 7.3.5 and 7.4.2.

### 7.3.5 Submission Specific Primary Safety Concerns

#### Hypercalcemia:

Study SRE.40005 involved twice a day application of calcitriol ointment 3µg/g, 30g a day for three weeks. In this maximal use study 15g of calcitriol ointment was applied twice daily to 35% of BSA. According to the clinical pharmacology reviewer there was no significant correlation between the PK parameters (AUC and C<sub>max</sub> for calcitriol) and the PD parameters serum albumin-adjusted calcium, serum phosphorus, urinary calcium, and urinary phosphorus.

Studies SRE.18053 and SRE.18054, the pivotal studies, calcitriol ointment was compared with vehicle in treating subjects with psoriasis. For study 18053, albumin-adjusted serum calcium concentrations were above the upper limit of normal (10.6 mg/dL) in 12 subjects treated with calcitriol ointment 3µg/g and in 10 subjects treated with vehicle ointment. For the 12 subjects exposed to calcitriol the highest albumin-adjusted serum calcium concentration was 11.1 mg/dL or 4.7% above the upper limit of normal (subject 44/site 2102; see also Table 48). For the 10 subjects exposed to vehicle the highest albumin-adjusted serum calcium concentration was 11.1 mg/dL or 4.7% above the upper limit of normal (subject 188/site 2149). For study 18054, albumin-adjusted serum calcium concentrations were above the upper limit of normal in 10 subjects treated with calcitriol ointment 3µg/g and in 7 subjects treated with vehicle ointment. For the 10 subjects exposed to calcitriol the highest albumin-adjusted serum calcium concentration was 11.1 mg/dL or 4.7% above the upper limit of normal (subjects 777/site 438 and 624/site 2036; see also Table 50). For the 10 subjects exposed to vehicle the highest albumin-adjusted serum calcium concentration was 11.1 mg/dL or 4.7% above the upper limit of normal (subject 553/site 2065).

Study SRE.2663 assessed the safety and efficacy of calcitriol 3µg/g applied twice daily for up to 52 weeks in an open label design. A total of 10 subjects (3.1%) had at least one episode of hypercalcemia, albumin-adjusted serum calcium concentration above the upper limit of the reference range, 2.55 mmol/L. For 9 subjects the albumin-adjusted serum calcium concentration was less than 5% above the upper limit of normal. One subject (#250, site 5272) had an albumin-adjusted serum calcium concentration of 2.72 mmol/L (6.7%) above the upper limit of normal (see also Table 58).

**Kidney Stones:**

A total of 5 subjects with psoriasis were reported to have kidney stones or possible renal colic.

Three of the involved subjects were from the long-term safety study, SRE.2663. For this study mean baseline % BSA involvement was approximately 16 ± 8% and mean daily medication use was estimated at 6 ± 5 grams.

1) Subject 169 (site 5265) is a 55 y/o male with no significant medical history and a total body surface area of psoriasis of 4%. Daily medication use was estimated at 2.8 g/d, used for 182 days. The day before entering the treatment phase of the study the subject was noted to have increased urinary calcium levels (8.3 mmol/24 h; normal 2.5-7.5 mmol/24 h). On study day 81, a clinically silent nephrolith was discovered by ultrasound. After workup a diagnosis of silent nephrolithiasis was made. Elevated levels of urine calcium continued for eight months after stopping study treatment.

The investigator considered the high level of urine calcium and the high level of calcitriol in the serum to be possibly related to study drug. The nephrolithiasis was considered by the investigator to be unrelated to study drug. It is noted that during the study some measurements of urine calcium level were higher than that noted at baseline.

Table 38: Subject 169 Laboratory Values

Laboratory measurement & normal values	Albumin adjusted serum total calcium (2.15-2.55 mmol/L)	Phosphate Level (0.87-1.45 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)	Parathormone Level (13-54 ng/L)
Date						
Nov. 26, 2001 (Screening)						
Dec. 2, 01 (Baseline)						
Jan. 14, 02 (Week 6)						
Jan. 21, 02						
Feb. 25, 02						
Apr. 29, 02						
Jun. 3, 02						
Feb. 24, 03						

Source: Sponsor's NDA, 5.3.5.3.02.ISS Appendix 5, p. 85.

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2) Subject 233 (site 5274) is a 43 y/o male with a total body surface area affected by psoriasis of 10%. Daily medication use was estimated at 5.5 g/d, used for 314 days. In week 43 (day 302) of the study painful urinary stone passage was diagnosed. The urine calculus was not analyzed. The subject reported this adverse event to the investigator and discontinued study treatment on study day 313. The subject was discontinued from the study on day 321 and subsequently was lost to follow up. Prior to entry to study and after study treatment was stopped the subject had elevated urinary calcium levels.

The investigator considered the high level of urinary calcium to be possibly related and the renal colic to be unrelated to study drug.

Table 39: Subject 233 Laboratory Values

Laboratory measurement & normal values	Albumin adjusted serum total calcium (2.15-2.55 mmol/L)	Urine Calcium Level (2.5-7.5 mmol/24h)	Calcitriol Level (15-50 ng/L)
Date			
Jan 24, 2002 (Screening)			
Jan 31, 02 (Baseline)			
Mar 14, 02 (Week 6)			
Apr. 25, 02 (Week 12)			
Jun. 6, 02 (Week 18)			
Aug. 1, 02 (Week 26)			
Aug. 13, 02			
Oct. 7, 02 (Week 35)			
Dec. 4, 02			
Dec. 18, 02*			

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\* After study treatment stopped (10/12/02).

Source: Sponsor's NDA, 5.3.5.3.02.ISS Appendix 5, p. 87.

3) Subject 255 (site 5273) is a 35 y/o male with no significant medical history and a total body surface area affected by psoriasis of 18%. Daily medication use was estimated at 3.9 g/d, used for 314 days. On week 42 (study day 300) urinary stone passage was diagnosed by the subject's primary physician based on a 4 hour episode of pain radiating from back to groin. No calculus was found. On study day 308 urinalysis confirmed hypercalciuria (16.8 mmol/24 h; normal range 2.5-7.5 mmol/24 h). Study drug was discontinued study day 313 and the subject was subsequently discontinued from the study on day 342 due to the adverse event. The adverse event was considered to be possibly related to study treatment by the investigator. The

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investigator was later informed that the subject had experienced several episodes of back pain before starting study treatment and that the subject's brother had a history of nephrolithiasis. The subject was noted to have had hypercalciuria before starting study treatment (13.5 mmol/24 h at baseline) and 1 month after study drug discontinuation (9.9 mmol/24 h).

Abnormal urine calcium levels were assessed as possibly related to study drug. The sponsor states that it is highly probable that the subject experienced essential hypercalciuria. The sponsor assessed the adverse event of "renal colic" as unlikely to be related to study treatment.

Table 40: Subject 255 Laboratory Values

Laboratory measurement & normal values	Albumin adjusted serum total calcium (2.15-2.55 mmol/L)	Urine Calcium Level (2.5-7.5 mmol/24h)	Calcitriol Level (15-50 ng/L)
Date			
Jan 24, 2002 (Screening)			
Jan 31, 02 (Baseline)			
Mar 14, 02 (Week 6)			
Apr. 25, 02 (Week 12)			
Jun. 6, 02 (Week 18)			
Aug. 1, 02 (Week 26)			
Oct. 3, 02 (Week 35)			
Dec. 5, 02 (Week 35)			
Dec. 11, 02*			
Jan. 3, 03*			

b(6)

\* After study treatment stopped (10/12/02).  
 Source: Sponsor's NDA, 5.3.5.3.02.ISS Appendix 5, p. 89.

**Study H.141.5012MC**

Subject 11801 is a 51 y/o male who received treatment with calcitriol <3µg/g. Pertinent medical history included kidney stones and coxarthrosis (hip arthritis). The total body surface area affected with psoriasis was 20%. During the study period the subject received non-steroidal anti-inflammatory drugs for psoriatic arthritis. On study day 20 the subject reported experiencing kidney stones of mild severity and lasting for one day. The kidney stones were not confirmed by a physician. Serum total calcium was within the normal range (2.15-2.55 mmol/L) at screening, and at study days 14, 30, 44, and 57. Serum phosphorous was noted to be .9 mmol/L (normal

range: .87-1.45 mmol/L) at screening, .6mmol/L on day 14, .8mmol/L on day 30, 1.5 mmol/L on day 44, and .7 mmol/L on day 57. Twenty four hour urine calcium was above the normal range (2.5-7.5 mmol/24 h) at baseline, and at days 14, 30, 44, and 57.

#### Study SPR.2684

Subject 34 is a 41 y/o male treated with calcitriol 3µg/g and having no significant medical history. The total body surface area affected with psoriasis was 6%. On study day 29 the subject experienced a ureteral stone. Extracorporeal shock wave lithotripsy was performed. Adjusted calcium levels were 2.40 mmol/L and 2.20 mmol/L on study days 0 and 33 (normal range 2.15-2.55 mmol/L). On study day 32, urine calcium level was 2.31 mmol/L (normal range 2.5-7.5 mmol/24 h). The subject discontinued study treatment on study day 28 and was discontinued from the study on day 32 due to the adverse event. The subject later underwent an ultrasound investigation and was found to be free of kidney stones, 89 days after the original event. The investigator considered the event unlikely to be related to study medication. According to sponsor's provided narrative, the investigator stated that it would be impossible to form a urethral stone within 4 weeks.

In the 5 cases of kidney stone/renal colic adverse events, information submitted may suggest a possible role for calcitriol contributing to documented kidney stones in two of the five cases, subjects 169 and 233 from study 2663. The third case, subject 255 from study 2663, the event was reported as renal colic and no stone was found. It is possible this could represent sludge without a kidney stone. In the fourth case, 11801 from study H.141.5012MC, the subject had a history of kidney stones. The fifth case, subject 34 from study SPR.2684, it is unlikely that a ureteral stone could be formed within 4 weeks.

Regarding the two cases where kidney stones were confirmed; for subject 169 the urine 24 hour calcium level was elevated at baseline and for subject 233 urine 24 hour calcium level and serum calcitriol levels were elevated at baseline. These two subjects may have had a preexisting abnormality of calcium metabolism.

For the United States the yearly incidence rate of kidney stones is estimated at .37% or 1/272 persons per year.<sup>4</sup> A roughly similar rate was calculated using tables from Taylor et al.<sup>5</sup> In study 2663 a total of 239 subjects was exposed for at least 6 months and 116 subjects were exposed to calcitriol for one year. This would give a rate of confirmed stones of 2/178 (person years) or 1.1% for those exposed to calcitriol.<sup>6</sup> It is noted that the rates of kidney stones are higher in white men who are middle aged and older when compared with women, other races, and younger age ranges.<sup>7</sup> For study 2663, of the 324 subjects enrolled 195 (60.2%) were males and 129 (39.8%) were females. The mean age was 45.9 years and the majority (98.8%) was Caucasian.

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<sup>4</sup> [www.wrongdiagnosis.com/k/kidney\\_stones/prevalence.htm](http://www.wrongdiagnosis.com/k/kidney_stones/prevalence.htm), accessed 8/27/08.

<sup>5</sup> Taylor EN, Stampfer MJ, and Curhan GC. Obesity, Weight Gain, and the Risk of Kidney Stones. *JAMA* 2005;293(4):455-462.

<sup>6</sup> Person-years was calculated as follows: (239/2) + (116/2) = 119.5 + 58 = 177.5

<sup>7</sup> Hiett RA et al. Frequency of Urolithiasis in a Prepaid Medical Care Program. *American Journal of Epidemiology*, 1982;115(2):255-265.

Of all kidney stones 75 to 85% are calcium stones and the ratio of males to females is 2:1 or 3:1. Of calcium stones 50 to 55% are due to idiopathic hypercalciuria and the male to female ratio is 2:1. This condition is characterized by normocalcemia with unexplained hypercalciuria.<sup>8</sup> It is possible that subjects 169, 233, and 255 had idiopathic hypercalciuria prior to entering study 2663.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Table 41: Adverse Events Occurring in at least 1% of Subjects by COSTART Term (Pivotal Studies SRE.18053 and SRE.18054)

	Calcitriol ointment 3µg/g (n=419)	Calcitriol vehicle ointment (n=420)
Total number of AEs <sup>a</sup>	241	239
Total number of subjects with AEs <sup>b</sup>	147 (35.1%)	141 (33.6%)
Lab test abnormality	19 (4.5%)	19 (4.5%)
Flu syndrome	16 (3.8%)	15 (3.6%)
Discomfort skin	13 (3.1%)	9 (2.1%)
Headache	11 (2.6%)	11 (2.6%)
Injury accident	9 (2.1%)	10 (2.4%)
Pharyngitis	9 (2.1%)	12 (2.9%)
Pruritus	8 (1.9%)	8 (1.9%)
Rhinitis	7 (1.7%)	4 (1.0%)
Myalgia	5 (1.2%)	1 (0.2%)
Sinusitis	5 (1.2%)	12 (2.9%)
Dizziness	4 (1.0%)	1 (0.2%)
Edema peripheral	4 (1.0%)	2 (0.5%)
Infection skin	4 (1.0%)	2 (0.5%)
Psoriasis	4 (1.0%)	12 (2.9%)
Surgical/medical procedure	4 (1.0%)	3 (0.7%)
Gastroenteritis	2 (0.5%)	4 (1.0%)
Nausea	2 (0.5%)	4 (1.0%)
Diarrhea	1 (0.2%)	4 (1.0%)
Pain abdominal	1 (0.2%)	4 (1.0%)

<sup>a</sup> Adverse events are defined as events occurred after first use of medication

<sup>b</sup> A subject was counted once per COSTART term event if more than one occurrence of the event was experienced.

Source: Sponsor's NDA Integrated Summary of Safety Table 49, 5.3.5.3.02, p 69.

<sup>8</sup> Asplin, JR, Coe FL, and Favus MJ. Chapter 281. Nephrolithiasis, Table 281-1 in Harrison's Principles of Internal Medicine, 17<sup>th</sup> Ed.: Fauci AS, et al., McGraw-Hill Companies, Inc. © 2008.

The most common adverse events in the pivotal studies were lab test abnormality and flu syndrome, seen in equal percentages in both active and vehicle groups. Possibly drug related is discomfort of skin 13 (3.1%) in calcitriol active group and 9 (2.1%) in vehicle group.

Table 42: Adverse Events Related to Study Drug by COSTART Term (Pivotal studies 18053, 54)

	Calcitriol oint. 3µg/g (n=419)	Calcitriol vehicle oint. (n=420)
Total No.# of AEs	58	71
Total No.# of Subjects w/ AEs	36 (8.6%)	45 (10.7%)
Lab test abnorm	14 (3.3%)	15 (3.6%)
Discomfort skin	11 (2.6%)	9 (2.1%)
Pruritus	6 (1.4%)	4 (1.0%)
Irritant dermatitis	3 (0.7%)	2 (0.5%)
Erythema	2 (0.5%)	-
Skin dry	2 (0.5%)	2 (0.5%)
Acne	1 (0.2%)	-
Fissures	1 (0.2%)	-
Injury accident	1 (0.2%)	1 (0.2%)
Psoriasis	1 (0.2%)	8 (1.9%)
Diarrhea	-	1 (0.2%)
Edema peripheral	-	1 (0.2%)
Headache	-	1 (0.2%)
Hypertonia	-	1 (0.2%)
Infection skin	-	1 (0.2%)
Nausea	-	1 (0.2%)
Pain	-	1 (0.2%)
Sweat increase	-	1 (0.2%)
Taste pervers	-	1 (0.2%)

Adverse events are defined as events occurring after first use of medication.

A subject was counted once per COSTART term even if more than one occurrence of the event was experienced.

Related to study drug means that the relationship to study drug was categorized by the investigator as Possible,

Probable, or Definitely Related

Source: Sponsor's NDA Integrated Summary of Safety Table ISS4.5, 5.3.5.3.02, ISS Appendix 2, p. 40.

Of adverse events considered related to study drug by the sponsor, lab test abnormality, discomfort of skin, pruritus, and irritant dermatitis were most common.

Table 43: Adverse Events Occurring in at least 1% of Subjects in Any Period, by COSTART Term and Period (Long-term Study SRE.2663)

	Periods				Total N <sup>a</sup> =324
	(1-89) days	(90-179) days	(180-269) days	≥ 270 days	
	N <sup>a</sup> =324	N <sup>a</sup> =285	N <sup>a</sup> =239	N <sup>a</sup> =140	
Total number of AEs	116	59	43	46	264
Total no. # of subjects with AEs	82 (25.3%)	47 (16.5%)	32 (13.4%)	33 (23.6%)	130 (40.1%)
Hypercalciuria	9 (2.8%)	0	6(2.5%)	3(2.1%)	11(3.4%)
Lab test abnormality	7 (2.2%)	4(1.4%)	10 (4.2%)	7 (5.0%)	25 (7.7%)
Pruritus	7(2.2%)	2 (0.7%)	1 (0.4%)	0	10 (3.1%)
Bronchitis	6 (1.9%)	1 (0.4%)	0	3 (2.1%)	9 (2.8%)
Pharyngitis	6 (1.9%)	3 (1.1%)	2 (0.8%)	3 (2.1%)	12 (3.7%)
Flu syndrome	5 (1.5%)	2 (0.7%)	1 (0.4%)	4 (2.9%)	12 (3.7%)
Irritant dermatitis	5 (1.5%)	0	0	0	5 (1.5%)
Psoriasis	5 (1.5%)	5 (1.8%)	2 (0.8%)	2 (1.4%)	13(4.0%)
Urine abnormality	5 (1.5%)	4 (1.4%)	4 (1.7%)	2 (1.4%)	14 (4.3%)
Infection skin	4 (1.2%)	4 (1.4%)	1 (0.4%)	2 (1.4%)	10 (3.1%)
Worse treated disease	4 (1.2%)	2(0.7%)	1 (0.4%)	0	7 (2.2%)
Arthralgia	3 (0.9%)	2 (0.7%)	0	0	4 (1.2%)
Eczema	3(0.9%)	0	1 (0.4%)	0	4 (1.2%)
Hyperlipemia	2 (0.6%)	0	1 (0.4%)	1 (0.7%)	4 (1.2%)
Pain back	2 (0.6%)	1 (0.4%)	3 (1.3%)	2 (1.4%)	7 (2.2%)
Rhinitis	2 (0.6%)	1 (0.4%)	1 (0.4%)	0	4 (1.2%)
Tooth disease	2 (0.6%)	2 (0.7%)	0	0	4 (1.2%)
Allergic reaction	1 (0.3%)	1 (0.4%)	1 (0.4%)	1 (0.7%)	4 (1.2%)
Gastroenteritis	1 (0.3%)	2 (0.7%)	1 (0.4%)	0	4(1.2%)
Conjunctivitis	0	0	0	2(1.4%)	2(0.6%)
Pain kidney	0	0	0	2 (1.4%)	2 (0.6%)

<sup>a</sup> Number of subjects at risk

<sup>b</sup> Adverse events are defined as events occurred after first use of medication

<sup>c</sup> A subject was counted once per COSTART term event if more than one occurrence of the event was experienced.

Source: Sponsor's NDA Integrated Summary of Safety Table 49, 5.3.5.3.02, p 86.

Among adverse events, hypercalciuria is an adverse event of interest in the long term safety study. Although this event is the highest by percentage in the first quarter of the study, the percentages do not increase across the remaining quarters of the study. Through all the quarters of the study, lab test abnormality is the most common adverse event.

Laboratory test abnormality included 23 subjects (7%) with high blood calcitriol levels, one subject (0.3%) with high PTH and calcitriol blood levels, and one subject (.3%) with high PTH levels. Urine abnormality included 9 subjects with 10 episodes of increased phosphorus in 24 hour urine samples. Urine abnormality also included a subject with decreased urinary calcium

and a subject with increased urine creatinine and urine phosphorus. Please see section 7.4.2 for further discussion of laboratory findings.

Table 44: Adverse Events Related to study Drug by COSTART Term and Period  
 (Long-term Study SRE.2663)

	Periods				Total
	(1-89) days	(90-179) days	(180-269) days	≥ 270 days	
	N <sup>a</sup> =324	N <sup>a</sup> =285	N <sup>a</sup> =239	N <sup>a</sup> =140	N <sup>a</sup> =324
Total number of AEs <sup>b</sup>	29	14	21	15	79
Total number of subjects with Related <sup>c</sup> AEs <sup>d</sup>	23 (7.1%)	13 (4.6%)	16 (6.7%)	12 (8.6%)	45 (13.9%)
Hypercalciuria	9 (2.8%)	0	6 (2.5%)	3 (2.1%)	11 (3.4%)
Lab test abnormality	7 (2.2%)	4 (1.4%)	10 (4.2%)	7 (5.0%)	25 (7.7%)
Pruritus	4 (1.2%)	2(0.7%)	1 (0.4%)	0	7 (2.2%)
Irritant dermatitis	3(0.9%)	0	0	0	3 (0.9%)
Urinary abnormality	2 (0.6%)	4 (1.4%)	4 (1.7%)	2 (1.4%)	11 (3.4%)
Allergic reaction local	1 (0.3%)	0	0	0	1 (0.3%)
Eczema	1 (0.3%)	0	0	0	1 (0.3%)
Erythema	1 (0.3%)	0	0	0	1 (0.3%)
Nail disease	1 (0.3%)	0	0	0	1 (0.3%)
Worse treated disease	0	2(0.7%)	0	0	2 (0.6%)
Diarrhea	0	1 (0.4%)	0	0	1 (0.3%)
Infection skin	0	1 (0.4%)	0	0	1 (0.3%)
Pain kidney	0	0	0	2 (1.4%)	2 (0.6%)
Menstrual disease	0	0	0	1 (0.7%)	1 (0.3%)

<sup>a</sup> Number of subjects at risk

<sup>b</sup> Adverse events are defined as events occurred after the first use of medication

<sup>c</sup> Related to study drug means that the relationship to study drug is categorized Possible, Probable, or Definitely Related

<sup>d</sup> A subject was counted once per COSTART term even if more than one occurrence of the event was experienced

Source: Sponsor's NDA Integrated Summary of Safety Table 50, 5.3.5.3.02, (ISS) p 88.

Of adverse events considered related to study drug by the sponsor, hypercalcemia was most common in the first quarter of study 2663. In the second quarter lab test abnormality and urine abnormality were most common. (As noted previously urine abnormality consisted mostly of elevated 42 hour urine phosphorus.) In the third and fourth quarters lab test abnormality was most common.

## 7.4.2 Laboratory Findings

### Routine Laboratory Findings:

#### Pivotal Studies

In the pivotal studies routine laboratory tests included clinical chemistry and hematology.

Clinical chemistry consisted of alkaline phosphatase, ALT (SGPT), AST (SGOT), Bilirubin, BUN, Chloride (serum), Cholesterol (total), creatinine (serum), glucose (serum), lactic acid dehydrogenase, potassium (serum), protein (total, serum), sodium (serum), triglycerides, and uric acid (serum). Shift tables for subjects having these values measured have been constructed by the sponsor. Reference ranges used are consistent with those generally accepted. The shift tables have been examined, generally insignificant changes in these values are observed comparing active to vehicle arms. (Approximately 79 subjects in active arm and 81 subjects in vehicle arm had values measured. These numbers are stated as approximate because not all subjects had all laboratory studies performed.)

One value showed a possible difference, uric acid. Of 61 subject within normal range in active arm 5 (7.6%) changed to above normal range in final reading as compared with vehicle arm where of 67 subjects starting in normal range 2 (2.9%) shifted to above normal in final reading. However, descriptive statistics for uric acid did not support a significant difference. (Active showed a mean change of 9.2  $\mu\text{MOL/L}$  with a standard deviation of 49.5 versus vehicle with a mean change of -1.2 and standard deviation of 50.1.)

Descriptive statistics have also been performed by the sponsor for the other laboratory values listed above. Changes pre-treatment to post treatment appear to be mostly due to random variation without significant differences between active and vehicle arms. (Note: no pre-treatment values for creatinine clearance, 24 hour urine creatinine.)

Hematology consisted of basophils (absolute), eosinophils (absolute), hematocrit, hemoglobin, lymphocytes (absolute), monocytes (absolute), neutrophils (absolute), platelets, red blood cell count, and whit blood cell count. With respect to shift tables and descriptive statistics hematology values appear to show changes pre and post treatment and active versus control that correspond to random variation.

Open Label Study:

Routine laboratory findings:

In the open label study routine laboratory tests included clinical chemistry and hematology. Laboratory values were measured on approximately 283 subjects.

Clinical chemistry consisted of alkaline phosphatase, ALT (SGPT), AST (SGOT), Bilirubin, BUN, Chloride (serum), cholesterol (total), creatinine (serum), creatinine (urine 24 hr), glucose (serum), lactic acid dehydrogenase, potassium (serum), protein (total, serum), sodium (serum), triglycerides, and uric acid (serum). Shift tables have been constructed by the sponsor for subjects who had these values measured. Reference ranges are consistent with those generally accepted. These have been examined, generally insignificant changes in these values are observed comparing values pre-treatment to various points later in the study.

Descriptive statistics have also been performed for clinical chemistry values. These were examined and changes were generally insignificant pre-treatment to various points later in the study.

Serum alkaline phosphatase is discussed as a value that sometimes can be a signal for changes in calcium homeostasis. A fall in alkaline phosphatase can precede hypercalcemia. Examination of the shift tables for alkaline phosphatase does not reveal a pattern indicating general shifts either up or down in values measured comparing pre-treatment with measurements at months 6, 12, or final. Examination of descriptive statistics for alkaline phosphatase reveals a pre-treatment mean of  $85 \pm \text{SD } 29$  (U/L). At month 6 the mean is  $74 \pm 24$ , at month 12 the mean is  $73 \pm 27$ , and at final the mean is  $75 \pm 25$ . From pre-treatment to final the change of the mean value is  $-11 \pm 14$  (U/L). The reference range used for this study was 39 – 117 U/L. Although descriptive statistics suggest a possible trend downward in mean alkaline phosphatase values the final mean remains well within the normal reference range.

Hematology consisted of basophils (absolute), eosinophils (absolute), hematocrit, hemoglobin, lymphocytes (absolute), monocytes (absolute), neutrophils (absolute), platelets, red blood cell count, and white blood cell count. With respect to shift tables and descriptive statistics hematology values appear to show changes that are generally insignificant comparing values pre-treatment to various points later in the study.

#### Calcium Homeostasis:

According to ACP PIER & AHFS DI Essentials<sup>9</sup>, therapy with calcitriol (1,25-dihydroxy vitamin D3) has a higher risk of hypercalcemia than with therapy with other forms of vitamin D. However, because calcitriol has a relatively short half life, the related hypercalcemia may reverse more rapidly than with other forms of vitamin D therapy.

In adults serum calcium includes three forms of  $\text{Ca}^{2+}$ ; ionized (50%), protein-bound (40%), and complexed (10%). The ionized  $\text{Ca}^{2+}$  is the biologically active form. Albumin-adjusted calcium takes into account the effect of binding of calcium to serum albumin. The sponsor has used the following formula, similar to that seen in reference texts, to adjust serum total calcium concentrations for changes in serum albumin concentrations:

$$\text{Albumin adjusted serum total calcium (mmol/l)} = \text{serum total calcium measured (mg/dL)} + (4.5 - \text{serum albumin g/dL}) \times 0.8$$

The sponsor notes that 4.5 is the middle of the normal range for albumin (3.5-5.5 g/dL)

If albumin is high the measured calcium will be artificially high and the formula corrects this downward. If albumin is low, the correction will be upward.

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<sup>9</sup> ACP PIER & AHFS DI Essentials™. Hypocalcemia 10.2 Monitor the complications of therapy in patients who are being treated for hypocalcemia. 2008-08-26 accessed via STAT!Ref, 8/27/2008.

Mild hypercalcemia (11-11.5 mg/dl) is usually asymptomatic. Some patients may complain of vague neuropsychiatric symptoms such as trouble concentrating, personality changes, or depression.<sup>10</sup> Presenting symptoms may also include peptic ulcer disease or nephrolithiasis. Higher calcium levels (>12-13mg/dl) may lead to lethargy, stupor, coma, and gastrointestinal symptoms (nausea, anorexia, constipation, or pancreatitis). Polyuria and polydipsia may also be seen. Hypercalcemia can also result in electrocardiographic abnormalities such as bradycardia, AV block, and short QT interval.

According to ACP PIER & AHFS DIO Essentials™ the reference interval of 8.8 mg/dl to 10.2 mg/dL or 2.20 mmol/L to 2.50 mmol/L varies slightly among laboratories and does not generally reflect an albumin-corrected value.<sup>11</sup> In Goodman and Gilman 11<sup>th</sup> Edition it is stated that normal serum calcium concentration ranges from 8.5 to 10.4 mg/dl (4.25 to 5.2 mEq/L, 2.1 to 2.6 mM)<sup>12</sup>. LabCorp (a commercial lab) uses a reference range of 8.5 to 10.6 mg/dL for ages 7 months to adults.<sup>13</sup> For pivotal studies 18053 and 18054, the sponsor has listed the reference range for adjusted calcium as 8.5 to 10.6 mg/dl. For the open label safety study 2663, the sponsor has listed the albumin adjusted calcium reference range as 2.15 to 2.55 mmol/L.

Other important lab parameters for monitoring calcium homeostasis include 24 hour urine calcium. In the setting of increased calcitriol this may be elevated. It is noted that hypercalciuria is the most sensitive indicator of over treatment with calcium and vitamin D.<sup>14</sup> Serum phosphorous and urinary phosphorus may also be elevated. Serum parathyroid hormone PTH (intact) would be at risk for being decreased.

In the pivotal studies, approximately 79 subjects in active arm and 81 subjects in vehicle arm had values measured. These numbers are stated as approximate because not all subjects had all laboratory studies performed. It is possible that with this number of subjects being tested that less frequent adverse events may not be detected.

#### Calcium Homeostasis Mean Values

Laboratory reference intervals employed by the sponsor for studies 18053, 18054, and 2663 for total calcium, adjusted calcium, phosphorus, calcitriol, urine 24 hour calcium, and urine 24 hour phosphorus generally correspond to those in clinical use.<sup>15,16</sup> The only reference range that appears to differ somewhat is that employed by the sponsor for PTH (8-97 pg/mL) in studies

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<sup>10</sup> Khosla S. Chapter 47. Hypercalcemia and Hypocalcemia in Harrison's Principles of Internal Medicine, 17<sup>th</sup> Ed.: Fauci AS, et al. McGraw-Hill Companies, Inc. © 2008.

<sup>11</sup> ACP PIER & AHFS DIO Essentials™. Hypercalcemia 2.1 Screen patients with medical conditions in which hypercalcemia is known to occur. 2008-08-28 accessed via STAT!Ref, 8/29/2008.

<sup>12</sup> Freidman PA. Chapter 61: Agents Affecting Mineral Ion Homeostasis and Bone Turnover in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11<sup>th</sup> Ed.: Brunton LL Editor. McGraw-Hill Companies, Inc. © 2006.

<sup>13</sup> LabCorp: [www.labcorp.com/](http://www.labcorp.com/) searched for calcium, accessed via internet 9/8/2008.

<sup>14</sup> ACP PIER & AHFS DIO Essentials™. Hypocalcemia 10.2 Monitor the complications of therapy in patients who are being treated for hypocalcemia. 2008-08-26 accessed via STAT!Ref, 8/27/2008.

<sup>15</sup> LabCorp: [www.labcorp.com/](http://www.labcorp.com/) searched for test names, accessed via internet 9/8/2008.

<sup>16</sup> Kratz a, Pezce MA, Fink DJ. Appendix: Laboratory Values of Clinical Importance in Harrison's Principles of Internal Medicine, 17<sup>th</sup> Ed.: Fauci AS et al. McGraw-Hill Companies, Inc. © 2008.

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18053 and 18054. The test may have been standardized to a different interval. This does not appear to have materially affected the interpretation of lab results for these studies. For study 2663 the sponsor has employed a reference range of 13-54 ng/L. LabCorp lists a reference interval of 12-65 pg/mL for intact PTH.<sup>17</sup>

**Studies 18053 and 18054**

**Table 45: Calcium Homeostasis Values Study 18053**

Laboratory Parameters and Expanded Normal Ranges <sup>1</sup>	Calcitriol Ointment 3µg/g		Vehicle Ointment		
	Screening	Week 8/Final <sup>2</sup>	Screening	Week 8/Final <sup>2</sup>	
<b>Total Calcium</b> (8.5-10.6 mg/dL) Age 14-75, M or F	N	39	38	40	39
	Mean	9.93	9.66	9.86	9.73
	SD	0.403	0.372	0.424	0.398
<b>Adjusted Calcium</b> (8.5-10.6 mg/dL) Age 14-75, M or F	N	39	38	40	39
	Mean	10.2	10.03	10.11	10.07
	SD	0.385	0.357	0.347	0.428
<b>Phosphorus</b> (2.5-5.6 mg/dL) Age 14-19, F (2.5-5.3) Age 14-19, M (2.5-5.6) Age 23-75, All (2.5-4.5)	N	39	38	40	39
	Mean	3.54	3.61	3.53	3.52
	SD	0.565	0.668	0.543	0.562
<b>PTH</b> (8-97 pg/mL) Age 14-75, M or F	N	30	28	33	31
	Mean	63.50	60.89	60.88	60.97
	SD	37.379	37.117	19.631	24.957
<b>Calcitriol</b> (15.9-55.6 pg/mL) Age 14-75, M or F	N	29	28	31	32
	Mean	56.08	52.72	48.97	51.73
	SD	27.182	13.808	17.038	15.355
<b>Calcium, Urine 24 HR</b> (100-300 mg/24 HR) Age 14-75, M or F	N	<sup>3</sup>	37	<sup>3</sup>	39
	Mean		167.81		178.28
	SD		131.932		105.510

<sup>1</sup> Expanded normal ranges indicate lowest value of the normal range and the highest value of the normal range for any age (14 to 75) and gender.

<sup>2</sup> Week 8 or last available post-baseline data if the subject discontinued prematurely

<sup>3</sup> According to the sponsor, the collection of 24 hour urine at Screening was not planned in the two protocols.

Source: Sponsor's NDA, Module 5, 5.3.5.1.1.01, Study Report RD.06.SRE.18053, pp. 92 and 331.

Use of calcitriol 3µg/g ointment in study 18053 did not cause clinically significant changes in mean values for total calcium, adjusted calcium, phosphorus, PTH, or calcitriol. The 24 hour

<sup>17</sup> LabCorp: [www.labcorp.com/](http://www.labcorp.com/) searched for parathyroid hormone intact, accessed via internet 9/8/2008.

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urine calcium can only compared active to vehicle arm at week 8 and the difference seen appears to be clinically insignificant.

Table 46: Calcium Homeostasis Values Study 18054

Laboratory Parameters and Expanded Normal Ranges <sup>1</sup>	Calcitriol Ointment 3µg/g		Vehicle Ointment	
	Screening	Week 8/Final <sup>2</sup>	Screening	Week 8/Final <sup>2</sup>
<b>Total Calcium</b> (8.5-10.6 mg/dL) Age 14-75, M or F	N	38	39	40
	Mean	9.90	9.85	9.66
	SD	0.424	0.345	0.409
<b>Adjusted Calcium</b> (8.5-10.6 mg/dL) Age 14-75, M or F	N	38	39	40
	Mean	10.2	10.14	10.06
	SD	0.402	0.312	0.307
<b>Phosphorus</b> (2.5-5.6 mg/dL) Age 14-19, F (2.5-5.3) Age 14-19, M (2.5-5.6) Age 23-75, All (2.5-4.5)	N	38	39	40
	Mean	3.50	3.50	3.53
	SD	0.549	0.557	0.469
<b>PTH</b> (8-97 pg/mL) Age 14-75, M or F	N	37	36	39
	Mean	67.78	59.47	59.59
	SD	37.379	37.117	24.957
<b>Calcitriol</b> (15.9-55.6 pg/mL) Age 14-75, M or F	N	33	35	38
	Mean	52.56	48.03	47.39
	SD	20.993	19.450	20.518
<b>Calcium, Urine 24 HR</b> (100-300 mg/24 HR) Age 14-75, M or F	N	- <sup>3</sup>	- <sup>3</sup>	40
	Mean		133.27	151.16
	SD		95.087	110.119

<sup>1</sup> Expanded normal ranges indicate lowest value of the normal range and the highest value of the normal range for any age (14 to 75) and gender.

<sup>2</sup> Week 8 or last available post-baseline data if the subject discontinued prematurely

<sup>3</sup> According to the sponsor, the collection of 24 hour urine at Screening was not planned in the two protocols.

Source: Sponsor's NDA, Module 5, 5.3.5.1.1.02, Study Report RD.06.SRE.18054, pp. 93 and 341.

Use of calcitriol 3µg/g ointment in study 18054 did not cause clinically significant changes in mean values for total calcium, adjusted calcium, phosphorus, PTH, or calcitriol. Suggestion of a slight shift downward of mean PTH is noted in the active arm. The mean 24 hour urine calcium can only compared active to vehicle arm at week 8 which shows that the mean value for the vehicle arm is slightly higher than that for the active arm. This difference is difficult to interpret without baseline screening values.

**Calcium Homeostasis Mean Values  
 Study 2663**

**Table 47: Calcium Homeostasis Values Study 2663**

Laboratory Parameters		Baseline	Week 26	Week 52
Total Calcium (2.15-2.55mmol/L)	Mean	2.44	2.43	2.43
	SD	0.10	0.10	0.10
Adjusted Calcium (2.15-2.55mmol/L)	Mean	2.34	2.35	2.32
	SD	0.08	0.08	0.09
Phosphorus (.87-1.45mmol/L)	Mean	1.11	1.11	1.12
	SD	0.18	0.19	0.17
PTH (13-54 ng/L)	Mean	29.79	25.27	27.59
	SD	21.37	11.83	12.67
Calcitriol (15-50 ng/L)	Mean	43.29	45.54	47.96
	SD	14.74	20.09	19.29
Urinary Calcium (2.5-7.5 mmol/24h)	Mean	5.35	4.73	5.14
	SD	3.26	2.93	3.17
Urinary Phosphorus (11-42 mmol/24h)	Mean	33.41	28.92	29.38
	SD	19.10	13.76	14.36

Source: Sponsor's NDA, 5.3.5.2.07. Study Report RD.06.SRE.2663, pp. 85-89.

In study 2663, significant changes in mean total calcium, albumin adjusted calcium, phosphorus, PTH, calcitriol, urinary 24 hour calcium, and urinary 24 hour phosphorus were not seen. Suggestion of a slight increase in calcitriol over time is seen, however this is small compared with the standard deviation.

**Examination of Outliers**

**Albumin Adjusted Calcium Outliers and Calcitriol Outliers  
 Pivotal Trial 18053:**

In the calcitriol group 12 subjects had at least one albumin-adjusted calcium value above the normal range, for the vehicle group 8 subjects (9 subjects-one didn't finish study) had at least one albumin-adjusted calcium above the reference range. If subjects who had values above the normal range only at screening are excluded, 8 subjects in the calcitriol group and 7 subjects in the vehicle group had albumin-adjusted calcium values above the normal range.

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For trial 18053, mean medication use (calcitriol) was  $392 \pm 390$  grams with a daily use of  $7.1 \pm 6.9$  grams. At baseline the mean % BSA involved was  $9.6 \pm 7.5$ .

Examining outliers with values for albumin adjusted calcium of  $\geq 11$  mg/dl reveals:

Table 48: Outliers Study 18053 Albumin Adjusted Calcium (Values  $\geq 11$  mg/dl)\*

Treatment	Site/Subject ID	Age/Sex	Study Day	Albumin Adj. Calcium mg/dl
Calcitriol	2102/44	25/M	-4	10.4
	No AEs listed		15	11.1
			29	11.1
			57	10.3
Vehicle	439/33		32	11
	2094/287		21	11
	2149/188		29	11.1

\* This excludes two subjects (270/site 2102 and 355/site 2102) who had albumin adjusted calcium values of 11 mg/dl only at study day -5 and values within the reference range during the study.

Subject 44 (site 2102) is a 25 year old male. Other laboratory values, PTH and alkaline phosphatase were within normal limits. For this subject 24 hour urine calcium (except one on day 15 just below normal range) and phosphorus values were within normal limits. For this subject baseline BSA involvement was 12%. Total medication used was 31g with daily use of .55g.

Examining outliers for calcitriol levels, subject 477 (site 439) had the highest level (96.5 pg/mL ref range 15.9-55.6). This subject is a 56 year old female. This subject had a 10% BSA involvement at baseline. Total medication use was 326g with a daily use of 6.5g.

Table 49: Outlier Calcitriol: Study 18053

	Lab parameter	Lab day	Lab result	Flag	Ref range
439/477	Calcitriol	-3			15.9-55.6
Site/subject		15		H	
		50		H	
	Adjusted Calcium, serum	-3	10.4 mg/dL		8.5-10.6
		15	10.7	H	
		37	10.8	H	
		43	10.6		
		50	10.8	H	
	Phosphorus, serum	-3			2.5-4.5
		15			
		37			

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	Lab parameter	Lab day	Lab result	Flag	Ref range
	Phosphorus, serum	43		H	
		50		H	
	Calcium, 24 hr	15			100-300
		37		H	
		43			
	Calcium/creatinine ratio	15			
		37			
		43			

b(4)

The above subject (477, site 439) discontinued from the study at day 50 by subject request due to severe knee pain. Adverse events for this subject were listed as right knee pain (joint effusion), left knee pain, hip pain and back pain. The investigator considered these unlikely to be related to study medication.

For study 18053 at some point in the study 24/31 subjects in the active arm had calcitriol levels above the reference range. For the vehicle arm 19/31 subjects had calcitriol levels above the reference range.

**Pivotal Trial 18054:**

For albumin adjusted calcium, 10 subjects in the calcitriol group and 7 subjects in the vehicle group had at least one albumin adjusted calcium value that was above normal range. If one value in the vehicle group above reference range only at screening, 6 subjects in the vehicle group had at least one albumin adjusted calcium that was above the normal range.

For trial 18054, mean medication use (calcitriol) was  $414 \pm 461$  grams with a daily use of  $8.2 \pm 19$  grams. At baseline the mean % BSA involved was  $11 \pm 8.5$ .

Examining outliers with values for albumin adjusted calcium of  $\geq 11$  mg/dl reveals:

**Table 50: Outliers Study 18054 Albumin Adjusted Calcium (Values  $\geq 11$  mg/dl)**

Treatment	Site/Subject ID	Age/Sex	Study Day	Albumin Adj. Calcium mg/dl
Calcitriol	438/777	58/M	15	11.1
	2036/624	60/F	23	11.1
			24	11.3
Vehicle	438/854		50	11
	2064/533		45	11.1
			57	11

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Subject 777 (site 438) is a 58 year old male with 23% BSA involvement at baseline. Total medication use was 1385 g with a daily use of 24.3g. Additional laboratory information for this subject is presented below.

Subject 624 (site 2036) is a 60 year old female with 6% BSA involvement at baseline. Total medication use was 87g with daily use of 1.7g. For albumin-adjusted calcium, the highest observed value was 2.83 mmol/L (reference range 2.13 to 2.65 mmol/L) which was subject 624 in study 18054, calcitriol arm. Additional laboratory information for this subject is presented below.

Table 51: Outliers Study 18054 Albumin Adjusted Calcium Additional Lab Data

Site/subj	Lab Day	Adj Ca (mg/dl)	Serum Ca (mg/dl)	Phos (mg/dl)	Calcitriol (pg/mL)	Urine Ca (mg/24h)
438/777	-5	10.4	9.9	3.7	75.7 H	
	15	11.1 H	10.7 H	3.5	52.6	192.0
	29	10.7 H	10.1	4.4		264.0
	48	10.2	9.7	2.2 L		110.2
	57	10.1	9.5	3.7	51.4	108.0
2036/624	-3	10.5	10.2	4.2	Not done	-
	13	10.5	10.2	3.7	17.8	205.8
	23	11.1 H	10.7	3.5		265.5
	34	11.3 H	10.8 H	4.3		58.5 L
	51	10.3	9.9	3.3	34.9	50.4 L

Examining outliers for calcitriol levels, subject 556 had the highest calcitriol level (106.1 pg/ml; reference range 15.9-55.6). This subject is a 30 year old male with a baseline BSA involvement of 30%. Total medicine use was 1401 g with a daily use of 25g.

Table 52: Outlier Calcitriol Level Study 18054

	Lab parameter	Lab day	Lab result	Flag	Ref range
2065/556	Calcitriol	-5			15.9-55.6
Site/subject		17		H	
		57		H	
	Adjusted Calcium	-5	10.9	H	8.5-10.6
		17	10.0		
		29	10.6		
		43	10.8	H	
		57	10.6		

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	Lab parameter	Lab day	Lab result	Flag	Ref range
	Calcium, urine 24 hr	17	[REDACTED]		100-300
		29		H	
		43		H	
		57			
	Calcium/creatinine ratio	17			
		29			
		43			
		57			

b(4)

In study 18054, at some point in the study 25/39 subjects exposed to calcitriol ointment had plasma calcitriol levels above the reference range (15.9-55.6 pg/mL). For subjects exposed to vehicle 26/40 had plasma calcitriol levels above the reference range.

**24 Hour Urine Calcium Outliers:**

**Pivotal Trial 18053:**

For 24-hour urine calcium, 10 subjects in the calcitriol group and 11 subjects in the vehicle group had values above the normal range. Examining outliers with values 400mg/24 hour and above reveals:

**Table 53: Outliers Study 18053: 24 Hour Urine Calcium (Values > 400mg/24 hr)**

Treatment	Site/Subject ID	Age/Sex	Study Day	24 Hour Urine Calcium mg/24 hr
Calcitriol	2094/378	45/F	15	[REDACTED]
	2102/263	51/M	11	
	2102/355	34/M	44	
	2129/327	37/M	14	
			27	
			41	
			55	
Vehicle	31		9	
	289		29	
	145		15	
	185		15	
	188		15	

b(4)

Subject 378 (site 2094) is a 45 year old female with 5% baseline BSA involvement. Total medication used was 1149g with a daily use of 20.5g.

Subject 263 (site 2102) is a 51 year old male with 4% baseline BSA involvement. Total medicine used was 268g with a daily use of 3.8g.

Subject 355 (site 2102) is a 34 year old male with a 4% baseline BSA involvement. Total medicine used was 115g with a daily use of 2g.

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Subject 327 (site 2129) is a 37 year old male with a 5% baseline BSA involvement. Total medicine used was 60g with a daily use of 1.1g.

Table 54: Outliers Study 18053: 24 Hour Urine Calcium Additional Lab Data

Site/subj	Lab Day	Adj Ca (mg/dl)	Serum Ca (mg/dl)	Phos (mg/dl)	Calcitriol (pg/mL)	Urine Ca (mg/24h)	Urine Phos (mg/24 hr)
2094/378	-5	10.2					
	15	10.1					
	29	10.4					
	43	9.7					
	57	10.1					
2102/263	-4	10.8 H					
	11	10.7 H					
	32	10.9 H					
	46	10.1					
	71	9.9					
2102/355	-735*						
	-5	11.0 H					
	15	10.2					
	29	9.7					
	44	10.2					
2129/327	57	10.6					
	-3	10.5					
	14	10.3					
	27	10.3					
	41	10					
	55	9.6					

b(4)

\* As printed in study report

**Pivotal Trial 18054:**

For 24-hour urine calcium, 6 subjects in the calcitriol group and 15 subjects in the vehicle group had values above the normal range. Examining outliers with values 400mg/24 hour and above reveals:

Table 55: Outliers Study 18054: 24 Hour Urine Calcium (Values > 400mg/24 hr)

Treatment	Site/Subject ID	Age/Sex	Study Day	24 Hour Urine Calcium mg/24 hr
Calcitriol	2063/599	29/M	45	
	2065/556*	60/M	29	
	2095/568	74/M	13	
			27	
			41	
			55	
			76	

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			104
Vehicle	565		43
	778		43
			60
	969		33
	562		43
	723		43

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\* Also discussed previously

Subject 559 (site 2063) is a 29 year old male with a 5% baseline BSA involvement. Total medicine used was 115g with a daily use of 2g.

Subject 556 (site 2065) is a 30 year old male with a baseline BSA involvement of 30%. Total medicine use was 1401 g with a daily use of 25g. This subject was discussed earlier in reference to a high outlier calcitriol level.

Subject 868 (site 2095) is a 74 year old male with 5% baseline BSA involvement. Total medicine used was 1570g with a daily use of 26g.

Table 54: Outliers Study 18054: 24 Hour Urine Calcium Additional Lab Data

Site/subj	Lab Day	Adj Ca (mg/dl)	Serum Ca (mg/dl)	Phos (mg/dl)	Calcitriol (pg/mL)	Urine Ca (mg/24h)	Urine Phos (mg/24 hr)
2063/559	-5	9.9					
	17	9.9					
	31	9.8					
	45	9.7					
	59	9.7					
2065/556	-5	10.9 H					
	17	10					
	29	10.6					
	43	10.8 H					
	57	10.6					
2095/868	-3	10.6					
	13	9.7					
	27	10.5					
	41	10.2					
	55	10.7 H					
	76						
	104						

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Table 58: Subjects with Hypercalciuria Reported as Adverse Event (Study 2663)

Site/subj	Lab Day	Adj Ca (mg/dl)	Serum Ca (mg/dl)	Phos (mg/dl)	Calcitriol (pg/mL)	Urine Ca (mg/24h)	Urine Phos (mg/24 hr)
<b>5189/158</b>	SCR						
	Week 6						
26M	Week 12						
BSA 28%	Week 18						
	Week 26						
16.5g	Week 35						
365d	Week 44						
	Week 52						
	Final						
<b>5189/159</b>	SCR						
52 M	Week 6						
BSA 20%	Week 12						
	Week 18						
10.6g	Week 26						
364d	Week 35						
	Week 44						
	Week 52						
	Final						
<b>5189/160</b>	SCR						
	Week 6						
58M	Week 12						
BSA 12%	Week 18						
	Week 26						
16.8g	Week 35						
364	Week 44						
	Week 52						
	Final						
<b>5189/178</b>	SCR						
	Week 6						
66F	Week 12						
BSA 18%	Week 18						
	Week 26						
14.7g	Week 35						
369d	Week 44						
	Week 52						
	Final						
<b>5189/179</b>	SCR						
	Week 6						
46 F	Week 12						

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Site/subj	Lab Day	Adj Ca (mg/dl)	Serum Ca (mg/dl)	Phos (mg/dl)	Calcitriol (pg/mL)	Urine Ca (mg/24h)	Urine Phos (mg/24 hr)
5% BSA	Week 18						
6.1g 365d	Week 26						
	Week 35						
PTH 8 L	Week 44						
	Week 52						
	Final						
<b>5189/195</b>	<b>SCR</b>						
	Week 6						
34 M	Week 12						
16% BSA	Week 18						
4g 364d	Week 26						
	Week 35						
PTH 8 L	Week 44						
	Week 52						
	Final						
<b>5189/381</b>	<b>SCR</b>						
	Week 6						
37 F	Week 12						
11% BSA	Week 18						
	Week 26						
13g 181d	Week 35						
	Week 44						
	Week 52						
	Final						
<b>5189/382</b>	<b>SCR</b>						
PTH 59 H	Week 6						
52 M	Week 12						
27% BSA	Week 18						
	Week 26						
PTH 12 L	Week 35						
PTH 44 L	Week 44						
	Week 52						
15.4g 363d	Final						
<b>5189/383</b>	<b>SCR</b>						
	Week 6						
52 F	Week 12						
BSA 4%	Week 18						
2g 364d	Week 26						
	Week 35						
PTH 5 L	Week 44						

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Site/subj	Lab Day	Adj Ca (mg/dl)	Serum Ca (mg/dl)	Phos (mg/dl)	Calcitriol (pg/mL)	Urine Ca (mg/24h)	Urine Phos (mg/24 hr)
PTH 6 L	Week 52						
PTH 6 L	Final						
<b>5189/384</b>	SCR						
	Week 6						
65 F	Week 12						
BSA 5%	Week 18						
PTH 12 L	Week 26						
PTH 7 L	Week 35						
PTH 6 L	Week 44						
	Week 52						
4.6g 364d	Final						
<b>5262/92</b>	SCR						
	Week 6						
37 M	Week 12						
BSA 25%	Week 18						
	Week 26						
8.8g 361d	Week 35						
	Week 44						
	Week 52						
	Final						
<b>5273/255</b>	SCR						
	Week 6						
35 M	Week 12						
BSA 18%	Week 18						
	Week 26						
3.9g 314d	Week 35						
	Week 44						
	Week 52						
	Final						
<b>5274/233</b>	SCR						
43 M	Week 6						
BSA 10%	Week 12						
	Week 18						
5.5g 314d	Week 26						
	Week 35						
	Week 44						
	Week 52						
	Final						

b(4)

Review of the 13 subjects having hypercalciuria reported as an adverse event for study 2663 reveals the following:

- a) The mean Baseline % BSA involvement for study as a whole was  $16.1 \pm 8.4\%$  and for subjects with hypercalciuria reported as AE the mean Baseline % BSA involvement was 16%.
- b) The adjusted mean daily drug use for the study as a whole was  $5.8 \pm 5$  grams and for subjects with hypercalciuria reported as AE the mean daily drug use (adjusted estimate) was 9.4 grams. Hypercalciuria reported as an adverse event is associated with a trend to increased mean daily drug use.

Table 60: Shift Table – Urinary Calcium (mmol/24H) APT\* Population Study 2663

Shift Baseline vs final test	Final result						
	Clinically low	Low	Normal	High	Clinically High	Missing	Total
Clinically low	-	-	-	-	-	-	-
Low	2 (4.2%)	23 (47.9%)	21 (43.8%)	1 (2.1%)	0	1 (2.1%)	48 (100%)
Normal	0	35 (17.8%)	137 (69.5%)	18 (9.1%)	1 (0.5%)	6 (3.0%)	197 (100%)
High	0	2 (3.4%)	31 (52.5%)	21 (35.6%)	1 (1.7%)	4 (6.8%)	59 (100%)
Clinically High	0	0	2 (66.7%)	1 (33.3%)	0	0	3 (100%)
Missing	0	3 (17.6%)	11 (64.7%)	3 (17.6%)	0	0	17 (100%)
Total	2 (0.6%)	63 (19.4%)	202 (62.3%)	44 (13.6%)	2 (0.6%)	11 (3.4%)	324 (100%)

\*APT = All patients treated population

Source: Sponsor's NDA 5.3.5.2.07.Study Report. RD.03.SRE.2663, Table 25, p. 87.

The shift table for urinary calcium shows that of those subjects having a normal baseline value, 18 (9.1%) shift to high and 1 (.5%) shifts to clinically high at the final result. Of those subjects having a high baseline value, 31 (52.5%) shift to normal, 2 (3.4%) shift to low and 1 (1.7%) shifts to clinically high at the final result. Of those subjects having a clinically high baseline level, 1 (33.3%) shifts to high and 2 (66.7%) shift to normal at the final result.

**General Examination of Shift Tables:**

**Pivotal Trials and Open Label Study (2663)**

The sponsor has constructed shift tables for pre-treatment (the last available data observed during the pre-treatment period) versus maximum (the maximal value observed during the post-baseline period). Values examined include albumin adjusted calcium, albumin (serum), calcitriol, calcium (serum), calcium (24 hr urine), phosphorus (serum), phosphorous (24hr urine), and PTH (intact).

See also next section, data for pre-treatment (the last available data observed during the pre-treatment period) versus minimum (the minimal value observed during the post-baseline period).

**Values of Note:**

1) **Calcitriol:** Examination of shift tables and descriptive statistics reveal changes consistent with random variation in the pivotal trials. Suggestion of an upward shift is seen in the open label study for both the active arm in the pivotal studies and in the open label study.

**Open Label Study**

Starting value within reference range	Maximal value post-baseline above reference range	Mean change NG/L	Standard deviation
Open Label   218 subjects	140 (64%)	19	21

**Pivotal Studies**

Starting value within reference range	Maximal value post-baseline above reference range	Mean change NG/L	Standard deviation
active   29 subjects	14 (48%)	4.3	27
vehicle   41 subjects	20 (49%)	10	20

2) **Calcium (serum):** Examination of shift tables reveals changes consistent with random variation. Descriptive statistics show no definitive trend.

**Open Label Study**

Starting value within reference range	Maximal value post-baseline above reference range	Mean change MMOL/L	Standard deviation
Open Label   269 subjects	70 (26%)	.064	.092

**Pivotal Studies**

Starting value within reference range	Maximal value post-baseline above reference range	Mean change MMOL/L	Standard deviation
active   66 subjects	5 (7%)	.032	.093
vehicle   73 subjects	3 (4%)	.041	.084

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3) Calcium (24 hr urine): Examination of shift tables and descriptive statistics reveal changes consistent with random variation.

**Open Label Study**

Starting value within reference range	Maximal value post-baseline above reference range	Mean change MMOL/24 hr	Standard deviation
Open Label   191 subjects	71 (37%)	2.1	4.2

		Mean value Pre-treatment - MMOL/24 hr	Mean Maximal value post-baseline - MMOL/24 hr
Pivotal studies	active	-	5.6 (SD 3.7)
	vehicle	-	6.3 (SD 5.3)
Open Label		5.4 (SD 3.3)	7.5 (SD 4.7)

4) Phosphorous (serum): Examination of shift tables and descriptive statistics reveal changes consistent with random variation.

**Open Label Study**

Starting value within reference range	Maximal value post-baseline above reference range	Mean change MMOL/L	Standard deviation
Open Label   277 subjects	38 (14%)	.14	.18

**Pivotal Studies**

Starting value within reference range	Maximal value post-baseline above reference range	Mean change MMOL/L	Standard deviation
active   64 subjects	8 (11%)	.15	.15
vehicle   73 subjects	3 (4%)	.10	.16

5) Phosphorous (24hr urine): Examination of shift tables and descriptive statistics reveal changes consistent with random variation in the pivotal studies. Suggestion of a shift upward in the maximal value post-baseline is seen in the open label study.

**Open Label Study**

Starting value within reference range	Maximal value post-baseline above reference range	Mean change MMOL/24 hr	Standard deviation
Open Label   244 subjects	76 (34%)	10	28

		Mean value Pre-treatment - MMOL/24 hr	Mean Maximal value post-baseline - MMOL/24 hr
Pivotal studies	active	-	37 (SD 24)
	vehicle	-	36 (SD 13)
Open Label		33 (SD 19)	44 (SD 24)

The sponsor has constructed shift tables for pre-treatment (the last available data observed during the pre-treatment period) versus minimum (the minimal value observed during the post-baseline period). Values examined include albumin adjusted calcium, albumin (serum), calcitriol, calcium (serum), calcium (24 hr urine), phosphorus (serum), phosphorous (24hr urine), and PTH (intact).

Values of Note:

1) Calcitriol: Examination of shift tables and descriptive statistics reveal a suggestion of an upward shift in the minimal value post-baseline in the active arm of the pivotal studies. At the same time there is a suggestion of a downward shift in the mean minimal value observed post-baseline.

Open Label Study

Starting value within reference range	Minimal value post-baseline below reference range	Minimal value post-baseline above reference range	Mean change NG/L	Standard deviation
Open Label   218 subjects	28 (13%)	6 (3%)	-15	16

Pivotal Studies

Starting value within reference range	Minimal value post-baseline below reference range	Minimal value post-baseline above reference range	Mean change NG/L	Standard deviation
active   29 subjects	0	9 (31%)	-7.3	26
vehicle   41 subjects	0	5 (12%)	-5.1	19

2) Calcium (24 hr urine): Examination of shift tables and descriptive statistics reveal changes consistent with random variation.

Open Label Study

Starting value within reference range	Minimal value post-baseline below reference range	Mean change MMOL/24 hr	Standard deviation
Open Label   191 subjects	70 (37%)	-2.1	2.7

	Mean value Pre-treatment - MMOL/24 hr	Mean Minimal value post-baseline - MMOL/24 hr
Pivotal studies   active	-	2.8 (SD 2.3)
Pivotal studies   vehicle	-	2.7 (SD 2.1)
Open Label	5.3 (SD 3.3)	3.3 (SD 2.2)

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3) Phosphorous (serum): Examination of shift tables and descriptive statistics reveal changes consistent with random variation.

**Open Label Study**

Starting value within reference range		Minimal value post-baseline below reference range	Minimal value post-baseline above reference range	Mean change MMOL/24 hr	Standard deviation
Open Label	277 subjects	59 (21%)	2 (1%)	-.12	.18

**Pivotal Studies**

Starting value within reference range		Minimal value post-baseline below reference range	Minimal value post-baseline above reference range	Mean change NG/L	Standard deviation
active	72 subjects	7 (10%)	0	-.1	.16
vehicle	76 subjects	8 (10%)	0	-.13	.17

4) Phosphorous (24 hr urine): Examination of shift tables and descriptive statistics reveal changes consistent with random variation.

**Open Label Study**

Starting value within reference range		Minimal value post-baseline below reference range	Mean change MMOL/24 hr	Standard deviation
Open Label	224 subjects	38 (17%)	-12	20

		Mean value Pre-treatment - MMOL/24 hr	Mean Minimal value post-baseline - MMOL/24 hr
Pivotal studies	active	-	19 (SD 9.5)
	vehicle	-	19 (SD 9)
Open Label		33 (SD 19)	21 (SD 12)

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5) **PTH intact:** Examination of shift tables and descriptive statistics reveals suggestions of a downward shift. In the open label study the minimum value post-baseline was below the reference range for 31% of subjects. Note that the mean change for the minimal value post-baseline shifts downward for both active (-19 ng/L  $\pm$  SD 24) and vehicle arms (-12 ng/L  $\pm$  SD 19) in the pivotal studies.

**Open Label Study**

Starting value within reference range	Minimal value post-baseline below reference range	Minimal value post-baseline above reference range	Mean change NG/L	Standard deviation
Open Label   271 subjects	84 (31%)	1 (.4%)	-11	21

**Pivotal Studies**

Starting value within reference range	Minimal value post-baseline below reference range	Minimal value post-baseline above reference range	Mean change NG/L	Standard deviation
active   50 subjects	3 (6%)	0	-19	24
vehicle   65 subjects	1 (2%)	0	-12	19

**7.4.3 Vital Signs**

During the pivotal clinical studies 18053 and 18054. Vital signs, weight and blood pressure, were performed at screening and at Week 8/Final. No clinically significant vital signs findings were noted.

Vital signs were not performed in the open label safety study, 2663.

**7.4.4 Electrocardiograms (ECGs)**

ECGs were not performed during any of the clinical studies.

An information request was sent to the sponsor regarding the need for data from a thorough QT/QTc study or a rationale for why such a study is not needed. The sponsor responded with an amendment to the NDA received April 30, 2008. This response has been reviewed. Following are the most significant points regarding the necessity of a thorough QT/QTc study:

A) Calcitriol ointment is approved for treatment psoriasis in 39 countries and marketed in 25: Sponsor's cumulative review of 78 adverse events launch (late 80s) until Feb. 28, 2008 showed no cases of arrhythmia or ECG changes including any changes in ventricular repolarization.

B) Oral product (Rocaltrol®, Roche) and intravenous product (Calcijex®, Abbott) are approved and marketed in U.S. Indications for Rocaltrol are for management of hypocalcemia in patients with chronic renal failure and in patients undergoing dialysis. Additionally it is indicated for hypocalcemia in patients with hypoparathyroidism. A search of AERS reports for these products did not detect a signal for torsades, sudden cardiac death, or QT prolongation.

C) Calcitriol is a normal component of plasma and the proposed drug product is topical and has limited absorption. Normal plasma levels are 20 – 60 pg/ml. Calcitriol mean  $C_{max}$  under maximal topical use conditions is not far above normal calcitriol range.

Maximal use was studied as 15g calcitriol ointment 3µg/g applied BID on 35% BSA, psoriasis subjects for 3 weeks. Steady state  $C_{max}$  was  $75.3 \pm 27.3$  pg/ml. Under these conditions laboratory parameters of calcium homeostasis (serum albumin-adjusted calcium, serum phosphorus, urinary calcium, and urinary phosphorus) were not altered.

D) Oral and injected calcitriol, sometimes with calcium carbonate, are reported to shorten prolonged QT intervals. Calcijex-injectable calcitriol (2mcg twice weekly after hemodialysis) for 15 weeks reduced prolonged QT interval in patients with secondary hyperparathyroidism on Hemodialysis<sup>18</sup>. Prolonged QT intervals were shortened significantly when patients with hypocalcemia were treated with Rocaltrol® (.25 to 1 mcg/day) and calcium carbonate (3g/day).<sup>19</sup>

For these reasons this reviewer believes that a thorough QT/QTc study for calcitriol 3µg/g ointment is not needed.

#### 7.4.5 Special Safety Studies

##### Phase 1 Dermal Safety Studies

A total of 5 special safety studies were performed with the to-be-marketed formulation. These included two contact irritancy studies, CG.03.SRE.2598 and RD.03.SRE.2652, contact allergy, CG.03.SRE.2600, contact photoirritancy, CG.03.SRE.2602, and contact photoallergy, CG.SRE.2601.

##### Study CG.03.SRE.2598: "Evaluation of the Cumulative Irritancy Potential of Calcitriol versus Tacalcitol versus Calcipotriol in Healthy Subjects"

This study was performed in compliance with Good Clinical Practice, September 14, 1998 to October 5, 1998.

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<sup>18</sup> Kim HW, Park CW, Shin YS et al. Calcitriol Regresses cardiac Hypertrophy and QT Dispersion in Secondary Hyperparathyroidism on Hemodialysis. *Nephron Clin Pract.* 2006;102:e21-e29.

<sup>19</sup> Eryol NK, Colak R, Ozdogru I et al. Effects of Calcium Treatment on QT Interval and QT Dispersion in Hypocalcemia. *American J. of Cardiol* 2003;91:730-752.

This was a single-center, within subject, randomized, evaluator-blinded trial that enrolled 25 healthy adult volunteers (male 9, female 16). Female subjects were ineligible if they were pregnant, nursing, or planning a pregnancy during the course of the trial. To be included, female subjects were to have undergone a urine pregnancy test with negative results and were to have been using a "reliable" contraceptive method since at least three months before the start of the study. Test articles included; calcitriol 3µg/g ointment 3 µg/g, Daivonex® ointment (calcipotriol 50 µg/g), Curatoderm ® ointment (tacalcitol 4 µg/g) and white petrolatum. Approximately 50 µl of each test article was applied under separate occlusive patches for four 24 applications and one 72-hour application per week for three weeks according to a randomization scheme. Sites were evaluated for response after removal of each patch (timing of reading not specified). Scoring of reactions for each site was performed 24 hours after applications (or 72 hours if application was on a Friday). The following grading system for erythema was used:

- 0 No reaction
- 0.5 Erythema barely visible
- 1 Mild erythema
- 2 Moderate erythema
- 3 Severe erythema

Other signs of skin reactions to the test products such as edema, papules, pustules, hyperpigmentation were given codes listed in the protocol. If a severe reaction (3) was noted, application of the test product was discontinued.

**Results:**

A total of 25 subjects were enrolled, with one subject discontinuing after 18 days (two days before the end of the study). This subject was hospitalized with cholelithiasis (a SAE), considered unrelated to study drugs. The safety analysis was conducted on 25 subjects.

Three subjects exhibited severe erythema at a test site and had to discontinue study application. Subject 1 stopped Tacalcitol at Week 2 Day 7. Subject 3 stopped Calcipotriol at Week 2 Day 7. Subject 25 stopped calcipotriol at Week 3 Day 14.

The sponsor has provided a table listing the frequency of erythema by test product, time in study, and severity. For calcitriol only one episode of moderate erythema was noted early in the study. Most of the reactions were either no reaction or barely visible. The other reaction noted for low numbers of subjects was marked reaction to adhesive patch.

For calcipotriol the majority reactions noted were either mild or moderate. Two subjects experienced severe erythema. Other reactions noted included edema, papules, and weeping for a few subjects as well as marked reaction to adhesive patch for low numbers of subjects.

For Tacalcitol one severe and one moderate reaction were noted. The majority of reactions were either no reaction or barely visible reaction with a few mild reactions. Other reactions included one episode of papules and one episode of weeping. Low numbers of subjects also exhibited marked reaction to adhesive patch.

For white petrolatum, a low number of episodes of moderate erythema was noted. The majority of reactions were either no reaction or barely visible reaction with a few mild reactions. The other reaction noted for low numbers of subjects was marked reaction to adhesive patch.

For each subject and each product a cumulative irritancy index (C.I.I.) was computed as the sum of all erythema scores across all readings (Day 1 to Day 21) divided by the number of readings. A mean cumulative irritancy index (MCII) was calculated for each product by averaging individual CIIs across subjects.

Table 61: Mean of Cumulative Irritation Index (Study 2598)

	Calcitriol	Calcipotriol	Tacalcitol	White Petrolatum
Mean	0.21	1.20	0.35	0.31

Source: Sponsor's NDA, Study Report CG.03.SRE.2598, 5.3.5.4.1.01, Table 5, p 34.

Conclusion: Calcitriol, tacalcitol, and white petrolatum showed roughly equivalent levels of irritation. These test items were less irritating than calcipotriol.

**Study RD.03.SRE.2652: "Evaluation of the Cumulative Irritancy Potential of Calcitriol Ointment versus Calcipotriol Ointment and Calcipotriol Cream in Healthy Subjects"**

This study was performed in compliance with Good Clinical practice, June 19, 2000 to October 7, 2000.

This was a single-center, intra-individual comparison, randomized, evaluator-blinded trial that enrolled 25 healthy adult volunteers (male 9, female 16). Female subjects were ineligible if they were pregnant, nursing, or planning a pregnancy during the course of the trial. To be included, female subjects of childbearing potential were to have undergone pregnancy testing (urine) with negative results and were to use a reliable form of contraception (protocol lists: oral contraceptive pill, intra-uterine device, condom) during the course of the study. Test articles included; calcitriol ointment 3µg/g, Daivonex® ointment (calcipotriol 50 µg/g), Daivonex® cream (calcipotriol 50 µg/g), and white petrolatum. Test article applications were performed at the investigation site by the study nurse not involved in the evaluation of responses.

Approximately 50 µl of each test article was applied under occlusive patches ("large Finn chambers") to the back of each subject according to a randomization scheme. The application schedule was four 24-hour applications per week and a 72 hour application each weekend for a total of three weeks.

Assessment of reactions was done for each site on the day after each application (or on Monday if the previous application was on a Friday), half an hour after removal of the patches, and before the following application. The following grading system for erythema was used:

- 0 No reaction
- 0.5 Erythema barely visible
- 1 Mild erythema
- 2 Moderate erythema
- 3 Severe erythema

Other signs of skin reactions to the test products such as edema, papules, pustules, hyperpigmentation were given codes listed in the protocol. If a severe reaction (3) was noted, application of the test product was discontinued at the affected site.

**Results:**

A total of 25 subjects were enrolled and 24 completed the entire study. One subject discontinued at Day 11 for personal reasons (Found a job on a boat leaving Nice).

A total of 17 adverse events were reported by 13 subjects in the study (10 headache, 3 pain-shoulder pain, tooth ache, painful menses, 1 sore throat, 1 venous insufficiency, 1 diarrhea, and 1 dyspepsia. These were judged to be unrelated to the test articles by the investigator. No serious adverse events were reported.

No severe erythema or scores of "3" were reported during the study. The distribution of erythema scores is shown in the following table.

**Table 62: Distribution of Erythema Scores (Study 2652)**

Scores	Test Products			
	Daivonex 50µg/g ointment	Daivonex 50µg/g cream	Calcitriol 3µg/g ointment	White petrolatum ointment
0	83	221	245	285
0.5	210	125	118	76
1	72	23	6	8
2	4	0	0	0
3	0	0	0	0
<b>Total</b>	<b>369*</b>	<b>369*</b>	<b>368*</b>	<b>369*</b>

\*  $15 \times 25 = 375 - 6 \text{ missing scores} = 369$

Source: Sponsor's NDA, Study Report RD.03.SRE.2652, 5.3.5.4.1.05, p 30.

The frequency of other local reactions is shown in the following table.

**Table 63: Distribution of other Local Reactions (Study 2652)**

Reaction code	Test Products			
	Daivonex 50µg/g ointment	Daivonex 50µg/g cream	Calcitriol 3µg/g ointment	White petrolatum ointment
A	0	0	0	0
B	0	0	0	0
H	0	0	0	0
O	0	0	0	0
P	29	12	5	6
Pa	0	0	0	0
S	0	0	0	0
W	0	0	0	0
V	5	0	0	3

A = Marked reaction to adhesive patch, B = Blisters, H = Hyperpigmentation, O = (O)edema, P = Papules, Pu = Pustules, S = Spreading of reaction beyond patch study site, V = Vesiculation, W = Weeping/oozing.

Source: Sponsor's NDA, Study Report RD.03.SRE.2652, 5.3.5.4.1.05, p 31.

A Cumulative Irritancy Index (C.I.I.) was calculated for each treatment and each subject as follows:

C.I.I = Sum of all erythema scores/Number of readings

A Mean Cumulative Irritancy Index (M.C.I.I.) was calculated for each product by averaging individual C.I.I.s across subjects. The M.C.I.I.s for the tested products are shown in the following table.

Table 64: Mean Cumulative Irritancy Index (M.C.I.I.): Study 2652

Test Products	M.C.I.I. (erythema)
Daivonex 50µg/g ointment	0.50
Daivonex 50µg/g cream	0.23
Calcitriol 3µg/g ointment	0.18
White petrolatum	0.12

Source: Sponsor's NDA, Study Report RD.03.SRE.2652, 5.3.5.4.1.05, p 29.

Conclusion: Daivonex (calcitriol) 50µg/g cream, calcitriol 3µg/g ointment, and white petrolatum showed roughly equivalent levels of irritation. These test items were less irritating than Daivonex (calcitriol) 50µg/g ointment. These results are generally consistent with those of study CG.03.SRE.2598.

**Study CG.03.SRE.2602: "Evaluation of the Phototoxicity Potential of Calcitriol 3µg/g Ointment and its Vehicle on Healthy Subjects"**

The purpose of this study was to determine the phototoxicity potential of Calcitriol 3µg/g ointment and its vehicle versus white petrolatum after a single application to the skin of healthy subjects. This study was performed in compliance with Good Clinical Practice, November 2, 1998 to December 5, 1998.

This was a single-center, intra-individual comparison, randomized, vehicle-controlled, investigator-blinded trial that enrolled 28 healthy adult volunteers (28 female). Subjects were between 18 and 65 years of age and had skin phototypes I, II, or III on the 4-point Fitzpatrick scale. Female subjects were ineligible if they were pregnant, nursing, or planning a pregnancy during the course of the trial. To be included, all female subjects were to have undergone pregnancy testing (urine) with negative results and were to use a reliable form of contraception

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(case report form includes: oral contraceptive pill, intra-uterine device, diaphragm, condom, sponge, spermicides, abstinence, implant, injection) during the course of the study.

Test articles included Silkis® (calcitriol 3 µg/g) ointment, calcitriol ointment vehicle, and white petrolatum.

For each subject, the Minimal Erythema Dose (MED) of UVA/UVB was determined within the 7 days before the baseline visit. The MED was determined to be the smallest dose of energy that produced a perceptible redness reaching the borders of the exposure site at 22 to 24 hours post-exposure for each series of exposures.

The test articles were applied, one test article per patch (approximately 50µl), to two groups of four patch sites according to a randomization scheme. The sites to the left of midline received irradiation and those on the right served as non-irradiated controls. Each product was symmetrically located on each side of the back. Test products were applied under occlusive conditions for 24 hours. All subjects were asked to keep the patch sites dry. Also to be avoided were swimming and vigorous exercise which could result in excessive sweating. Subjects were to avoid sunlight or UV light exposure to the patched areas.

After patch removal, excess test material was removed with a dry gauze pad and one group of 4 patch sites was irradiated with 20 J/cm<sup>2</sup> UVA. After irradiation with UVA the filter was removed from the light source and the irradiated patch sites were then exposed to 0.8 MED of UVA/UVB radiation as previously determined for each subject.

All patch sites were evaluated prior to product application, 15-30 minutes after the irradiation procedure, and 24 and 48 hours after the irradiation procedure.  
The following grading system for erythema was used:

- 0 No reaction
- 0.5 Erythema barely visible
- 1 Mild erythema
- 2 Moderate erythema
- 3 Severe erythema
  
- A Marked reaction to Adhesive patch
- X Not patched (subject absent, marked reaction...)
- PD Patch dislocated
- L Patch lost (came off) during the first 12 hours

Other signs of skin reactions to the test products such as edema, papules, pustules, hyperpigmentation were given codes listed in the protocol.

**Results:**

A total of 30 subjects were screened and 28 were enrolled in the study. A total of 27 subjects completed the study. One serious adverse event was reported for subject 21 who was a 31 year

old female. The subject was hospitalized for two days, tests were carried out, and the diagnosis was a viral infection. This subject was withdrawn from the study. The event occurred after the MED procedure but prior to application of test materials. This was considered unrelated to the test materials. One subject (No. 11) experienced two adverse events (headache and nausea) that were classified by the investigator as mild and unlikely to be study related.

**Table 65: Distribution of Erythema Grades Calcitriol (Study 2602)**

Calcitriol 3µg/g Ointment										
Grade	Irradiated Sites					Non-irradiated sites				
	0	0.5	1	2	3	0	0.5	1	2	3
Baseline (prior to application)	27	0	0	0	0	27	0	0	0	0
0.25 hours after irradiation	11	8	8	0	0	13	10	4	0	0
24 hours after irradiation	5	9	13	0	0	15	12	0	0	0
48 hours after irradiation	13	9	5	0	0	27	0	0	0	0

Source: Sponsor's NDA, Study Report CG.03.SRE.2602, 5.3.5.4.1.04, p 37.

**Table 66: Distribution of Erythema Grades Vehicle Ointment (Study 2602)**

Calcitriol Vehicle Ointment										
Grade	Irradiated Sites					Non-irradiated sites				
	0	0.5	1	2	3	0	0.5	1	2	3
Baseline (prior to application)	27	0	0	0	0	27	0	0	0	0
0.25 hours after irradiation	16	10	1	0	0	18	9	0	0	0
24 hours after irradiation	5	12	10	0	0	16	11	0	0	0
48 hours after irradiation	14	8	5	0	0	27	0	0	0	0

Source: Sponsor's NDA, Study Report CG.03.SRE.2602, 5.3.5.4.1.04, p 37.

**Table 67: Distribution of Erythema Grades White Petrolatum (Study 2602)**

White petrolatum										
Grade	Irradiated Sites					Non-irradiated sites				
	0	0.5	1	2	3	0	0.5	1	2	3
Baseline (prior to application)	27	0	0	0	0	27	0	0	0	0
0.25 hours after irradiation	13	10	4	0	0	14	12	1	0	0
24 hours after irradiation	4	11	10	2	0	16	10	1	0	0
48 hours after irradiation	13	5	9	0	0	27	0	0	0	0

Source: Sponsor's NDA, Study Report CG.03.SRE.2602, 5.3.5.4.1.04, p 38.

**Table 68: Distribution of Erythema Grades No Topical Study Treatment (Study 2602)**

Untreated										
Grade	Irradiated Sites					Non-irradiated sites				
	0	0.5	1	2	3	0	0.5	1	2	3
Baseline (prior to application)	27	0	0	0	0	27	0	0	0	0
0.25 hours after irradiation	12	9	6	0	0	9	14	3	1	0
24 hours after irradiation	3	12	10	2	0	14	12	1	0	0
48 hours after irradiation	12	10	5	0	0	27	0	0	0	0

Source: Sponsor's NDA, Study Report CG.03.SRE.2602, 5.3.5.4.1.04, p 38.

At the irradiated sites, for calcitriol 3µg/g ointment and calcitriol vehicle ointment the highest ratings were 1, mild erythema. The erythema peaked at 24 hours after irradiation and means were .65 and .59 for calcitriol 3µg/g ointment and calcitriol vehicle ointment respectively. For white petrolatum and untreated irradiated sites, ratings up to 2, moderate erythema were seen at 24 hours (means .72 and .74 respectively).

At the non-irradiated sites the highest ratings were 1, mild erythema, for both calcitriol 3µg/g ointment and white petrolatum. For calcitriol vehicle ointment the highest rating was .5, barely visible erythema. For the untreated site the highest rating was 2, moderate erythema.

Other local reactions seen during the study consisted only of hyperpigmentation, both irradiated and non-irradiated sites and for all four test conditions, and reactions to the adhesive patch.

**Conclusion:** This reviewer agrees with the investigator that under the conditions of the study calcitriol 3µg/g ointment did not show evidence of phototoxicity. It is noted that with 27 subjects completing the study and no evidence of phototoxicity, it can be stated that phototoxicity does not occur at a rate greater than 3/27 or 11% with 95% confidence.<sup>20</sup>

**Study CG.03SRE.2601: "Evaluation of the Photoallergic Contact Sensitization Potential of Calcitriol 3µg/g Ointment and its Vehicle Following Repeated Applications to the Skin of Human Subjects"**

The purpose of this study was to determine the photoallergic contact sensitization potential of calcitriol 3µg/g ointment compared to its vehicle using a standard photoallergenicity testing

<sup>20</sup> "rule of three" Hanley JA and Lippman-Hand A. If Nothing Goes Wrong, Everything All Right? JAMA, April 1, 1983;249(13); 1743-1745.

methodology in healthy human subjects. This study was performed in compliance with Good Clinical Practice, November 9, 1998 to December 18, 1998.

This was a single-center, intra-individual comparison, randomized, vehicle-controlled, investigator-blinded trial that enrolled 25 healthy adult volunteers (18 females and 7 males). Subjects were 21 and 48 years old and had skin phototypes of II and III on the 4-point Fitzpatrick scale. Female subjects were ineligible if they were pregnant, nursing, or planning a pregnancy during the course of the trial. All female subjects were to undergo pregnancy testing (urine) before enrollment into the study with negative results. An additional pregnancy test was also performed upon completion (challenge). During the study female subjects of childbearing potential were to use a reliable method of contraception (contraceptive pills, intra-uterine device, tubal ligation) during the study.

Test articles included Calcitriol 3 $\mu$ g/g ointment, calcitriol ointment vehicle, and white petrolatum.

For each subject, the Minimal Erythema Dose (MED) of UVA/UVB was determined during the baseline visit. The MED was determined to be the smallest dose of energy that produced a perceptible redness reaching the borders of the exposure site at 22 to 24 hours post-exposure for each series of exposures.

During the induction phase, 50  $\mu$ l of the test articles were applied twice a week on a 1.1cm<sup>2</sup> area of the left side, lumbar area of the back, for 24 hours under occlusion. Test articles were applied according to a randomization scheme. The control was an untreated occluded site. During the first week of the induction phase, the 4 test sites were irradiated immediately after patch removal with 2 times the MED of UVA/UVB light specific for that subject. During the second and third weeks of induction the test sites were irradiated with 3 times the MED. Evaluation of sites occurred 15 to 30 minutes after irradiation. The sequence of patching, removal, irradiation, and evaluation was repeated twice a week for 3 weeks during the induction phase.

After a two week rest period, the challenge period started. During this period, duplicate sets of 4 patches (3 test articles and one untreated site) were applied to naïve sites on the lower back of each subject. After 24 hours the patches were removed and the 4 sites on one side of the back were exposed to 0.5 MED of UVA/UVB light. Following this, the irradiated sites were also exposed to 10 J/cm<sup>2</sup> of UVA light. The 4 non-irradiated sites on the opposite side of the back served as control for single sensitization.

Site evaluation was performed after removal of any excess test material with a dry gauze pad or tissue.

**Induction Phase:** Patch sites were evaluated at baseline. Skin reactions were also evaluated before application of test products (15 to 30 minutes after patch removal and prior to irradiation of the sites). Skin reactions were also evaluated 24 hours after each irradiation session.

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**Challenge Phase:** Responses were evaluated 15 to 30 minutes after patch removal and prior to site irradiation and then 48 to 72 hours later. If a photosensitization reaction occurred this could be scored 96 hours after irradiation.

The following grading system for erythema was used:

- 0 No reaction
- 0.5 Erythema barely visible
- 1 Mild erythema
- 2 Moderate erythema
- 3 Severe erythema
  
- A Marked reaction to Adhesive patch
- X Not patched (subject absent, marked reaction...)
- PD Patch dislocated
- L Patch lost (came off) during the first 12 hours

Other signs of skin reactions to the test products such as edema, papules, pustules, hyperpigmentation were given codes listed in the protocol.

**Photosensitization reaction:**

After the challenge phase, the investigator rendered an opinion whether a photosensitization reaction had occurred by evaluation of each site in comparison to the associated non-irradiated challenge site and the untreated irradiated site. The following categories were used:

- 0 Negative
- 1 Equivocal
- 2 Positive

**Results:**

A total of 25 subjects were enrolled in the study and 24 completed the study. One subject (No. 24) left the study at the end of week 1 of the induction phase due to mononucleosis. This was considered unrelated to the test articles. No serious adverse events occurred during the study. A total of 8 other adverse events were reported in this study (subjects; 5, 8, 13, 14, 17, 19, and 21) and included fever, pain on toes, cold, three subjects with headache, painful menses, and sore throat. All of the adverse events were considered by the investigator as unlikely to be related to study medication.

Table 69: Distribution of Scores for the Four Types of Test Site

Product	scores	Week 1				Week 2				Week 3				Total
		D <sup>1</sup>	D2	D4	D5	D1	D2	D4	D5	D1	D2	D4	D5	
Calcitriol ointment	0	25	24	0	0	19	22	13	17	6	16	12	17	171
	0.5		0	0	3	2	2	7	4	12	7	7	6	50
	1		1	23	22	3	0	4	3	5	1	5	1	68
	2		0	2	0	0	0	0	0	1	0	0	0	3
	3		0	0	0	0	0	0	0	0	0	0	0	0
Calcitriol Vehicle ointment	0	25	25	0	0	18	21	11	16	6	16	10	17	165
	0.5	0	0	0	3	2	3	11	7	11	6	9	6	58
	1	0	0	24	22	4	0	1	1	6	2	5	1	66
	2	0	0	1	0	0	0	1	0	1	0	0	0	3
	3	0	0	0	0	0	0	0	0	0	0	0	0	0
White petrolatum	0	25	25	0	0	19	22	8	14	7	17	11	19	167
	0.5	0	0	0	3	2	2	13	9	10	5	9	5	58
	1	0	0	24	22	3	0	2	1	6	2	4	0	64
	2	0	0	1	0	0	0	1	0	1	0	0	0	3
	3	0	0	0	0	0	0	0	0	0	0	0	0	0
Untreated	0	25	25	0	0	18	21	11	20	7	17	11	18	173
	0.5	0	0	0	3	3	3	12	4	11	6	8	5	55
	1	0	0	24	22	3	0	1	0	5	1	5	1	62
	2	0	0	1	0	0	0	0	0	1	0	0	0	2
	3	0	0	0	0	0	0	0	0	0	0	0	0	0

D = Day

Source: Sponsor's NDA, Study Report CG.03.SRE.2601, 5.3.5.4.1.03, p 40.

As shown by the table above reactions were similar for the three test articles and the untreated sites.

Table 70: Distribution of Scores - Challenge Phase

Product	Scores	15 to 30 min. after patch removal, before irradiation		48 hours post-irradiation		72 hours post-irradiation	
		Day 2 Left side	Day 2 Right side	Day 4 Irrad. Left side	Day 4 Non-irrad. Right side	Day 5 Irrad. Left side	Day 5 Non-irrad. Right side
Calcitriol ointment	0	24	24	24	23	24	24
	0.5	0	0	0	1	0	0
Calcitriol Vehicle ointment	0	24	24	24	23	24	24
	0.5	0	0	0	1	0	0
White petrolatum	0	24	24	24	23	24	24
	0.5	0	0	0	1	0	0
Untreated	0	24	24	24	23	24	24
	0.5	0	0	0	1	0	0

Source: Sponsor's NDA, Study Report CG.03.SRE.2601, 5.3.5.4.1.03, p 41.

As shown above the only non-zero reactions (scores of 0.5) were seen on one subject (no. 9) on the non-irradiated test sites at Day 4.

Examination of test sites 48 and 72 hours post-irradiation showed no skin reactions either on irradiated or non-irradiated sites. No subject needed a rechallenge.

**Conclusion:** This reviewer agrees with the conclusion of the investigator that under the conditions of this study, calcitriol 3µg/g ointment compared to its vehicle and to white petrolatum using photoallergenicity testing in healthy human subjects did not show evidence of photosensitization. It is noted that with 25 subjects completing the study and no evidence of phototoxicity, it can be stated that phototoxicity does not occur at a rate greater than 3/25 or 12% with 95% confidence.<sup>21</sup>

**Study CG.03.SRE.2600: "Evaluation of the Cutaneous Contact Sensitization and Cumulative Irritancy Potential of Calcitriol 3µg/g Ointment and its Vehicle following Repeated applications to the Skin of Humans."**

The purpose of this study was to determine the irritation and the contact sensitization potential of repeated applications of calcitriol 3µointment and its vehicle versus white petrolatum in healthy human subjects. This study was performed in compliance with Good Clinical Practice, October 15, 1998 to February 1, 1999.

This was a single-center, intra-individual comparison, randomized, vehicle-controlled, investigator-blinded trial that enrolled 225 healthy adult volunteers (193 females and 32 males). Subjects were 18 to 65 years old. Female subjects were ineligible if they were pregnant, nursing, or planning a pregnancy during the course of the trial. All female subjects were to undergo pregnancy testing (urine) before enrollment into the study with negative results. An additional pregnancy test was also performed upon completion (both for normal and for premature study completion). During the study female subjects of childbearing potential were to use a reliable method of contraception (case report form includes: oral contraceptive pill, intra-uterine device, diaphragm, condom, sponge, spermicides, abstinence, implant, injection) during the study.

Test articles included calcitriol 3µg/g ointment, calcitriol ointment vehicle, and white petrolatum.

During the induction phase, approximately 50 µl of the test products were applied under occlusive patches / \_\_\_\_\_ to the back of the subject according to a randomization scheme. Marking with crystal violet was used to ensure that successive patches were located on the same place on the subject's back. Duration of occlusion was 48 hours twice

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<sup>21</sup> "rule of three" Hanley JA and Lippman-Hand A. If Nothing Goes Wrong, Everything All Right? JAMA, April 1, 1983;249(13): 1743-1745.

a week and 72 hours once a week for a total of three weeks. Skin reactions were assessed 15 to 30 minutes after removal of patches.

The challenge period followed a two week rest phase. During the challenge phase the test items were applied once for 48 hours, under occlusion to naïve sites. Skin reactions were assessed prior to test article application, 15 to 30 minutes after patch removal, and 72 hours after patch removal. If a sensitization reaction occurred this would be scored 120 hours after patch removal.

The following grading system for erythema was used:

- 0 No reaction
- 0.5 Erythema barely visible
- 1 Mild erythema
- 2 Moderate erythema
- 3 Severe erythema
  
- A Marked reaction to Adhesive patch
- X Not patched (subject absent, marked reaction...)
- PD Patch dislocated
- L Patch lost (came off) during the first 12 hours

Other signs of skin reactions to the test products such as edema, papules, pustules, hyperpigmentation were given codes listed in the protocol.

**Sensitization reaction:**

A consultant dermatologist was present at the 48 and 72 hour assessments (and 120 hours if necessary) to provide an evaluation regarding potential sensitization reactions. The following categories were used:

- 0 Negative
- 1 Equivocal
- 2 Positive

If a subject had a sensitization reaction that was assessed as equivocal at challenge, that subject was re-challenged after at least a two week rest period under the same conditions as those of the challenge.

**Results:**

A total of 240 subjects were screened into the study. A total of 15 subjects withdrew prior to any study procedures, thus 225 were enrolled and patch tested. A total of 15 subjects did not complete the patch testing; 3 did not wish to continue, 5 could not continue due to work commitments, one did not continue because of personal reasons, one forgot to attend on challenge day, and 5 were withdrawn (3 protocol violations, 2 for non-serious adverse events).

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Subject 237 was withdrawn due to probable viral illness. Subject 193 experienced flushing, giddiness, and generally feeling unwell; these reactions were assessed by the investigator as probably related to the patch.

A total of 92 non-serious adverse events were recorded in 71 subjects during the study. Most of these events were assessed as mild, some (23) were moderate and two were severe. Subject No. 1 experienced a headache that was rated as severe and unlikely related to study medication. Subject No. 114 experienced a hematoma rated as severe and definitely unrelated to study medication. The majority of the non-serious adverse events were either headache or variants of rhinitis/influenza/influenza.

A total of 9 adverse events were reported as possibly (8) or probably (1-see subject 193 above) related to test articles. For sites patched with white petrolatum subjects 10 and 13 reported burning and subjects 98 and 109 reported itching. For sites patched with Calcitriol vehicle ointment, subject 43 and 104 reported itching. For sites patched with Calcitriol 3µg/g ointment, subject 6 reported burning and subject 104 reported itching.

Subject 43 had marked reactions to adhesive patch for the calcitriol vehicle ointment sites on days 15 and 17. Subject 104 was noted to have marked reaction to adhesive patch from days 5 through 22 for all test article patch sites. During induction subject 6 was noted to have barely visible erythema (grade 0.5) reactions to calcitriol vehicle ointment over a span from day 3 to day 22. This subject also showed barely visible erythema to calcitriol ointment on day 22 and to white petrolatum on day 40.

Table 71: Distribution of Erythema Grade Frequencies Calcitriol (Study 2600)  
 Calcitriol 3µg/g Ointment

Time Point	Grade				
	0	0.5	1	2	3
<b>Induction Phase</b>					
Day 3	204	16	1	-	-
Day 5	203	15	-	1	-
Day 8	203	12	-	-	-
Day 10	195	17	-	-	-
Day 12	206	8	-	-	-
Day 15	202	7	-	-	-
Day 17	201	8	-	-	-
Day 19	199	9	-	1	-
Day 22	199	11	1	-	-
MU					
<b>Challenge Phase</b>					
Day 3	181	29	-	-	-
Day 5	205	5	-	-	-
Day 6	209	1	-	-	-
Day 8	1	-	-	-	-

Source: Sponsor's NDA, Study Report CG.03.SRE.2600, 5.3.5.4.1.02, p 37.

**Table 72: Distribution of Erythema Grade Frequencies Vehicle (Study 2600)**  
**Calcitriol Vehicle Ointment**

Time Point	Grade				
Induction Phase	0	0.5	1	2	3
Day 3	215	6	-	-	-
Day 5	215	4	-	-	-
Day 8	210	5	-	-	-
Day 10	208	4	-	-	-
Day 12	211	3	-	-	-
Day 15	205	4	-	-	-
Day 17	207	2	-	-	-
Day 19	206	2	1	-	-
Day 22	209	3	-	-	-
MU	30	1	-	-	-
Challenge Phase					
Day 3	202	8	-	-	-
Day 5	208	2	-	-	-
Day 6	210	-	-	-	-
Day 8	1	-	-	-	-

Source: Sponsor's NDA, Study Report CG.03.SRE.2600, 5.3.5.4.1.02, p 38.

**Table 73: Distribution of Erythema Grade Frequencies White Petrolatum (Study 2600)**

White Petrolatum					
Time Point	Grade				
Induction Phase	0	0.5	1	2	3
Day 3	216	5	-	-	-
Day 5	209	9	-	-	-
Day 8	203	8	2	2	-
Day 10	206	11	3	-	-
Day 12	199	12	3	-	-
Day 15	197	12	-	-	-
Day 17	199	9	-	-	-
Day 19	201	5	3	-	-
Day 22	203	8	1	-	-
MU	29	-	2	-	-
Challenge Phase					
Day 3	202	8	-	-	-
Day 5	204	5	1	-	-
Day 6	208	1	1	-	-
Day 8	-	1	-	-	-

Source: Sponsor's NDA, Study Report CG.03.SRE.2600, 5.3.5.4.1.02, p 38.

A Cumulative Irritancy Index (C.I.I.) was calculated for each treatment and each subject as follows:

$C.I.I. = \text{Sum of all erythema scores} / \text{Number of readings}$

A Mean Cumulative Irritancy Index (M.C.I.I.) was calculated for each product by averaging individual C.I.I.s across subjects. The M.C.I.I.s for the tested products are shown in the following table.

Table 74: Mean Cumulative Irritancy Index (M.C.I.I.) Study 2600

Test Article	M.C.I.I.
Calcitriol 3 µg/g ointment	0.03
Calcitriol vehicle ointment	0.01
White petrolatum	0.03

**Conclusion induction phase:** Calcitriol 3 µg/g ointment, Calcitriol vehicle ointment, and white petrolatum showed roughly equivalent levels of irritation. These results are generally consistent with those of studies CG.03.SRE.2598 and RD.03.SRE.2652.

**Challenge phase:**

For white petrolatum, the dermatologist assessed a positive sensitization reaction for one subject, No. 110.

Also for white petrolatum, subject No. 233, at 48 hours after removal of the challenge patch, mild erythema (grade 1) was recorded. By 72 hours after challenge patch removal this had decreased to barely visible erythema (grade 0.5). This was assessed as an equivocal sensitization reaction and subject 233 was re-challenged approximately one month later. For this subject mild erythema (grade 1) was seen at .25 and 48 hours after rechallenge patch removal. Barely visible erythema (grade 0.5) was seen at 72 hours after rechallenge patch removal. No erythema was seen at 120 hours after rechallenge patch removal. This subject was finally assessed as having a positive sensitization to white petrolatum.

For calcitriol 3µg/g ointment, subject 173 showed barely visible erythema (grade 0.5) 72 hours after challenge patch removal. This was assessed as an equivocal sensitization reaction and the subject was rechallenged approximately one month later. At rechallenge this subject did not show any reaction to any of the three test articles.

**Conclusion challenge phase:** Calcitriol 3µg/g ointment under the conditions of this study does not show evidence of sensitization.

#### 7.4.6 Immunogenicity

This is not applicable since the drug is not a therapeutic protein.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

A) Please see also section 7.2.2. In the pivotal trials and in the long-term safety study only the 3µg/g dose was evaluated. Evidence for dose dependency was seen in study H.141.5012/M in the group of subjects treated with calcitriol ointment 9µg/g BID for 8 weeks. This took the form of a small increase in urinary calcium excretion.

B) The adverse event profile was examined for subjects in the pivotal studies using more than 30 grams of calcitriol 3µg/g ointment per day. No obvious associated adverse events were noted.

Table 75: Subjects with Daily Medication (Calcitriol) Use > 30 grams/day: Pivotal Trials

Site/subj							
<b>Study 18053</b>							
1)2019/171	43/F	%BSA 13	33g/d	1843g tot	56d	No AEs No gen corn	completed
<b>Study 18054</b>							
2)2036/623	16/F	%BSA 14	255g/d	255g tot	1d	No AEs Upset about blood draw-lab work, busy schedule	d/c subject's request
3) 2038/639	71/M	%BSA 20	30g/d	1756g tot	58d	No AEs Missed 2 applications 2/27/02	completed
4) 2091/885	38/M	%BSA 11	32g/d	1803g tot	56d	Abscess on finger URI resolved 4/16/02	completed
5) 2184/684	44M	%BSA 25	30g/d	1735g tot	57d	No AEs One visit out of window	completed
6) 2185/598	74M	%BSA 30	32g/d	1866g tot	58d	No AEs Pt instructed not to apply so much study medicine	completed
7) 2188/933	62M	%BSA 32	33g/d	1847g tot	56d	No AEs 5 tubes returned	completed

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8) 2189/658	45F	%BSA 21	31g/d	1788g tot	57d	No AEs	completed
						Missed one dose 4/16, 4/17, 4/23/02	

The above subjects were not included among those who had laboratory parameter evaluation.

### 7.5.2 Time Dependency for Adverse Events

In general clinical evaluations and laboratory evaluations for systemic effects were performed so that end of treatment results could be compared with baseline results. The open label study included interval assessments.

### 7.5.3 Drug-Demographic Interactions

The sponsor performed sub-group analysis by race, age, and sex for studies SRE.18053, SRE.18054, and SRE.2663. The majority of subjects were Caucasian and no clear differences were seen across racial categories. In the pivotal studies, the subset of subjects 65 years and older showed a trend to higher incidence of adverse events compared with those 18 to <65 years of age. This trend was seen in both active and vehicle arms. In study 2663 the frequency of adverse events was similar in subjects 65 and older and subjects less than 65 years of age. In general the overall incidence for adverse events was higher for female subjects than male subjects.

Table 76: Adverse Events by Gender (Pivotal Studies and Long-term Study)

		Pivotal Studies SRE.18053 and SRE.18054				Long-term Study SRE.2663	
		Calcitriol ointment 3µg/g		Calcitriol vehicle ointment		Calcitriol ointment 3µg/g	
		Female	Male	Female	Male	Female	Male
Subjects with AEs <sup>a</sup>	N <sup>b</sup>	135	284	172	248	129	195
	Any type of AEs	55 (41%)	92 (32%)	68 (40%)	73 (29%)	56(43%)	74 (38%)
	Dermatological AEs	18 (13%)	23 (8%)	21 (12%)	22 (9%)	23 (18%)	33 (17%)
	Non-dermatological AEs	46 (34%)	77 (27%)	55 (32%)	55 (22%)	47 (36%)	60 (31%)
Subjects with related <sup>c</sup> AEs	Any type of AE	11 (8%)	25 (9%)	18 (10%)	27 (11%)	22 (17%)	23 (12%)
Subjects with serious AEs	Any type of AE	1 (0.7%)	1 (0.4%)	-	3 (1%)	6 (5%)	2 (1.0%)
Subjects with AE leading to DC	Any type of AE	5 (4%)	2 (.7%)	6 (4%)	5 (2%)	3 (2%)	5 (3%)

<sup>a</sup> Adverse events are defined as events occurring after the first use of medication

<sup>b</sup> Subjects may be counted twice, once in Dermatological AE and once in Non-dermatological AE categories for those having more than one AE.

<sup>c</sup> Related to study drug means that the relationship to study drug is categorized as Possible, Probable or Definitely Related.

Source: Sponsor's NDA Integrated Summary of Safety, adapted from Table 56, 5.3.5.3.02, (ISS) p 104.

**Table 77: Adverse Events by Race (Pivotal Studies and Long-term Study)**

		Pivotal Studies SRE.18953 and SRE.18954				Long-term Study SRE.2663	
		Calcitriol ointment 3µg/g		Calcitriol vehicle ointment		Calcitriol ointment 3µg/g	
		Caucasian	Non-Caucasian	Caucasian	Non-Caucasian	Caucasian	Non-Caucasian
Subjects with AEs <sup>a</sup>	N <sup>b</sup>	372	47	376	44	320	4
	Any type of AEs	132 (36%)	15 (32%)	132 (35%)	9 (20%)	129 (40%)	1 (25%)
	Dermatological AEs	38 (10%)	3 (6%)	39 (10%)	4 (9%)	56 (18%)	0
	Non-dermatological AEs	110 (30%)	13 (28%)	103 (27%)	7 (16%)	106 (33%)	1 (25%)
Subjects with related <sup>c</sup> AEs	Any type of AE	32 (9%)	4 (8%)	40 (11%)	5 (11%)	45 (14%)	0
Subjects with serious AEs	Any type of AE	2 (0.5%)	0	3 (0.8%)	0	8(2%)	0
Subjects with AE leading to DC	Any type of AE	6 (2%)	1 (2%)	9 (2%)	2 (4%)	8 (2%)	0

<sup>a</sup> Adverse events are defined as events occurring after the first use of medication

<sup>b</sup> Subjects may be counted twice, once in Dermatological AE and once in Non-dermatological AE categories for those having more than one AE.

<sup>c</sup> Related to study drug means that the relationship to study drug is categorized as Possible, Probable or Definitely Related.

Source: Sponsor's NDA Integrated Summary of Safety, adapted from Table 57, 5.3.5.3.02, (ISS) p 106.

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**Table 78: Adverse Events by Age (Pivotal Studies and Long-term Study)**

		Pivotal Studies SRE.18053 and SRE.18054						Long-term Study SRE.2663		
		Calcitriol ointment 3µg/g			Calcitriol vehicle ointment			Calcitriol ointment 3µg/g		
		12 to<18	18 to<65	≥65	12 to<18	18 to<65	≥65	12 to<18	18 to<65	≥65
Subject with AEs <sup>a</sup>	N <sup>b</sup>	4	356	59	6	352	62	4	278	42
	Any type of AEs	3 (75%)	120 (34%)	24 (41%)	3 (50%)	113 (32%)	25 (40%)	2 (50%)	112 (40%)	16 (38%)
	Non-dermatological AEs	3 (75%)	100 (28%)	20 (34%)	3 (50%)	90(26%)	17 (27%)	2 (50%)	93 (34%)	12 (29%)
	Dermatological AEs	0	33 (9%)	8 (14%)	1(17%)	31(9%)	11 (18%)	1 (25%)	49 (18%)	6 (14%)
Subjects with related <sup>c</sup> AEs	Any type of AE	1(25%)	26 (7%)	9 (15%)	2 (33%)	37 (10%)	6 (10%)	1(25%)	41 (15%)	3 (7%)
Subjects with serious AEs	Any type of AE	0	0	2(3%)	0	2 (0.6%)	1 (1.6%)	0	7 (2%)	1 (2%)
Subjects with AE leading to DC	Any type of AE	0	5 (1%)	2 (3%)	1 (17%)	6 (2%)	4 (6%)	0	7 (2%)	1 (2%)

<sup>a</sup> Adverse events are defined as events occurring after the first use of medication

<sup>b</sup> Subjects may be counted twice, once in Dermatological AE and once in Non-dermatological AE categories for those having more than one AE.

<sup>c</sup> Related to study drug means that the relationship to study drug is categorized as Possible, Probable or Definitely Related.

Source: Sponsor's NDA Integrated Summary of Safety, adapted from Table 59, 5.3.5.3.02, (ISS) p 109.

#### 7.5.4 Drug-Disease Interactions

No formal analyses were performed for drug-disease interactions with this topical drug product.

#### 7.5.5 Drug-Drug Interactions

Formal analyses for drug-drug interactions were not performed with this topical drug product.

Under concomitant drug therapy, the sponsor proposes the following labeling:

T  
C

T  
C

b(4)

b(4)

According to the clinical pharmacology reviewer, the study above was not conducted with the to-be-marketed formulation, and no information based on this study will be included in product labeling.

The sponsor states that the safety of calcitriol ointment 3µg/g was assessed in studies wherein it was administered concomitantly with other treatments including psoralen plus ultraviolet light A, clobetasol, ultraviolet B, and betamethasone. The sponsor proposes the following language be included under concomitant drug therapy:

b(4)

The concomitant therapy studies included CG.03.SRE.2599, a pilot clinical comparison of calcitriol (BID) and calcipotriol (Daivonex®) in combination with PUVA therapy (3 times a week) in the treatment of moderate to severe chronic plaque psoriasis for a total of 6 weeks. This study only involved 24 randomized subjects with no calcitriol arm without PUVA therapy for comparison. This study is inadequate to assess the effects of calcitriol in combination with PUVA therapy.

Study RD.03.SRE.2647 was a comparison of efficacy and safety of calcitriol ointment with calcipotriol ointment as maintenance therapy, following 2 or 4 weeks of initial treatment by calcitriol or calcipotriol with clobetasol propionate cream in subjects suffering from mild to moderate chronic plaque-type psoriasis. This study design is inadequate to assess the effects of calcitriol in combination with clobetasol propionate. Initial use of calcitriol was only once a day for only 2 to 4 weeks when used with clobetasol propionate. A better design would have involved twice a day use of calcitriol plus daily use of clobetasol propionate for 8 weeks and the addition of an arm with only calcitriol use twice a day.

Study H141.904 was a prospective, randomized, double-blind, parallel-group trial of calcitriol and vehicle ointment in combination with UV-B phototherapy in the treatment of chronic plaque psoriasis. The study was not conducted with the final-to-be-marketed formulation.

Study H141.907 was a prospectively randomized, double-blind, parallel group study of once daily application of betamethasone valerate 0.1% ointment in the morning and once daily application of 3 µg/g calcitriol ointment in the evening versus twice daily application of betamethasone valerate 0.1% ointment in the treatment of chronic plaque psoriasis. This study was not conducted with the final-to-be-marketed formulation.

Because these studies are inadequate in various ways, as noted above, no information based on these studies will be included in product labeling.

## 7.6 Additional Safety Explorations

### 7.6.1 Human Carcinogenicity

Human carcinogenicity was not assessed as part of the clinical development program. Based on the drug class this was not needed.

### 7.6.2 Human Reproduction and Pregnancy Data

No studies in pregnant women were performed as part of the development program.

There are no adequate and well-controlled studies in pregnant women. Silkis should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During the clinical development program a total of seven cases of pregnancy were reported and four of these were during calcitriol exposure. More information regarding those subjects exposed to calcitriol follows:

- 1) Subject 1157 (study H.141.5003; Phase 1) was a 26 year old who entered the double-blind vehicle-controlled study to evaluate the photosensitization potential of calcitriol and dihydrotachysterol in white petrolatum. On Day 1 an irritant reaction developed. On Day 7 the subject was found to be pregnant and was withdrawn from the study. According to the sponsor no further information was available and the outcome of the pregnancy was not reported.
- 2) Subject 12487 (study H.141.908; active controlled) was a 23 year old who entered the double-blind, parallel comparison of calcitriol ointment 3µg/g versus calcipotriol ointment 50µg/g twice daily. After 43 days of treatment with calcitriol ointment the subject was found to be pregnant and was withdrawn from the study. This case was reported as a protocol violation because the subject was pregnant at time of inclusion in the study. According to the sponsor, no further information was available and the outcome of the pregnancy was not reported.
- 3) Subject 390 (study SRE.2663; open label safety study) was a 23 year old who entered the open label safety study of calcitriol ointment 3µg/g twice daily and was discontinued on Day 35 because a pregnancy test was positive. According to the sponsor, the pregnancy date was estimated as 8 days before entry to the study. Delivery occurred at normal term and no malformation or neonatal abnormality was observed.
- 4) Subject 10759 (study H.141.5010/M; open label safety study) was a 20 year old who entered a long-term safety study of calcitriol ointment 3µg/g (not in final-to-be-marketed formulation). The subject had a negative urine pregnancy test at study entry and was taking an oral contraceptive during the course of the study. On Day 121 pregnancy was diagnosed and study medication was discontinued. According to the sponsor, no further information was available on the outcome.

### 7.6.3 Pediatrics and Effect on Growth

Assessment of effect on growth was not performed as part of the clinical development program. The pivotal phase 3 studies were of 8 weeks duration.

The sponsor's plans for pediatric development were discussed at the pre-NDA meeting (November 15, 1999). \_\_\_\_\_

b(4)

On June 5, 2007 the sponsor submitted a request to the FDA \_\_\_\_\_

b(4)

In the NDA submission, the sponsor has requested \_\_\_\_\_

b(4)

Also in the NDA submission, the sponsor has requested \_\_\_\_\_

b(4)

In the NDA submission, the sponsor indicated that \_\_\_\_\_

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

#### Overdose:

The accidental ingestion of calcitriol 3µg/g ointment could produce symptoms that are consistent with Vitamin D toxicity and hypercalcemia. Hypercalcemia can produce the clinical signs of depression, lethargy, stupor, coma, nausea, anorexia, constipation, polyuria, and polydipsia.<sup>22</sup>

The sponsor cites a reference (Beer et al 2005)<sup>23</sup>, detailing a pharmacokinetic study of a single dose of a new formulation of calcitriol. In this study ingestion of 165 µg of calcitriol (equivalent to an oral dose of 55 grams of calcitriol 3µg/g ointment) was not associated with hypercalcemia.

If signs of hypercalcemia occur during prescribed use of calcitriol 3µg/g ointment, calcium serum levels should be checked and treatment should be discontinued until serum calcium levels return to normal.

**Drug Abuse:**

No instances of abuse have been reported in the studies in this development program and calcitriol ointment is not known to possess drug abuse potential

**Withdrawal and Rebound:**

No instances of withdrawal or rebound were reported in the safety database.

**7.7 Additional Submissions**

The 120 day safety update was submitted on April 22, 2008. No new clinical information was reported.

**8 Post-marketing Experience**

The sponsor has provided information regarding non-US adverse events between August 2000 and April 2007. All adverse events and SAE's evaluated as possibly, probably, or definitely related to treatment with calcitriol are included by the sponsor.

Spontaneously reported adverse events (up to April 26, 2007):

Two SAEs that were skin related were reported spontaneously and their narratives follow.

**CH-GD-0310501**

Subject was a 14 year old boy applied calcitriol 3µg/g ointment daily and Dermovate (topical clobetasol propionate) one time weekly for weeks under occlusive gloves for treatment of psoriasis palmaris. When the patient presented, after 6 weeks of treatment, atrophy of the subcutaneous tissue and of a small area of skin was noted. The individual reporting the event, a Swiss dermatologist, classified it as 'maybe' related to the use of calcitriol 3µg/g ointment /Dermovate ointments.

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<sup>22</sup> Khosla S. Chapter 47. Hypercalcemia and Hypocalcemia in Harrison's Principles of Internal Medicine, 17<sup>th</sup> Ed.: Fauci AS, et al. McGraw-Hill Companies, Inc. © 2008.

<sup>23</sup> Beer TM, Javie M, Lam GN et al. Pharmacokinetics and Tolerability of a Single Dose of DN-101, a New Formulation of calcitriol, in Patients with Cancer. Clin Cancer Res 2005;11(21):7794-7799.

The atrophy noted could be explained based on use of Dermovate under occlusion.

**GB-GDP-0714104**

Subject was a 74 year old female patient who applied calcitriol ointment 3 µg/g for 2 days starting \_\_\_\_\_ The patient presented with blisters over the body, burning sensation and extensive flare-up of weepy eczema. The patient was hospitalized \_\_\_\_\_ and subsequently fully recovered on 1/1/2007. Concomitant medications included methotrexate (20mg/week) for psoriasis, folic acid (5mg/day), and hydroxyzine as needed. This case was reported by a health professional to Medicines and Healthcare Regulatory Agency.

b(6)

The above event could be consistent with an acute contact dermatitis reaction. It is uncertain whether the possible causative agent was the calcitriol or a component of the vehicle.

**Spontaneously reported non-serious AEs:**

Up to April 26, 2007 a total of 62 adverse events were reported spontaneously or during post-marketing surveillance. The most common (more than one case reported) events that also appear related include erythema (5 cases), pruritus (5 cases), skin burning sensation (4 cases), skin inflammation (3 cases), skin discomfort (2 cases), skin irritation (2 cases), condition aggravated (2 cases), face edema (2 cases), and eyelid edema (2 cases).

**Adverse events reported in post-marketing and post-approval studies:**

Through April 26, 2007 a total of eight studies have been performed with safety data available. One SAE was reported which was a traumatic injury that led to a hospitalization. A total of 50 non-US adverse events were reported that were considered to be related by the investigator. The most common adverse events, more than one case, included; skin irritation (16 cases), pruritus (12 cases), rash erythematous (6 cases), skin exfoliation (5 cases), and erythema (4 cases).

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## 9 Appendices

### 9.1 Literature Review and other Relevant Materials

- A) Literature references are cited in the body of the review.
- B) Regarding IGA scale with the category "clear" not being clear for erythema; references sections 5.3 and 6.1.7:

Secondary analysis by FDA biostatistician, Mat Soukup, Ph.D.

#### Study 18053:

	patno	invgrp	bpelev4	nbpelev4	bery4†	nbery4*	bscal4	nbscal4	prurit4	sever†	treat	bsever#
37	037	04	0	0	0	0	0	0	0	0	Calcitriol	3
43	043	08	0	0	0	0	1	0	1	0	Vehicle	3
64	064	03	0	0	0	0	0	0	0	0	Calcitriol	3
153	153	13	0	0	1	1	0	0	0	0	Calcitriol	3
181	181	03	0	0	0	0	0	0	0	0	Calcitriol	3
194	194	04	0	0	0	1	0	0	2	0	Vehicle	3
210	210	11	NA	NA	NA	NA	NA	NA	NA	NA	Calcitriol	3
243	247	09	0	0	1	1	0	1	0	0	Calcitriol	2
263	271	08	0	0	0	0	0	0	1	0	Vehicle	3
291	301	02	0	0	0	0	0	0	0	0	Calcitriol	3
381	425	10	0	0	1	0	0	0	0	0	Calcitriol	3

#### Study 18054:

	patno	invgrp	bpelev4	nbpelev4	bery4	nbery4	bscal4	nbscal4	prurit4	sever	treat	bsever
28	528	13	0	0	0	0	0	0	0	0	Calcitriol	2
162	666	14	NA	NA	NA	NA	NA	NA	NA	NA	Vehicle	2
185	689	14	0	0	0	0	0	0	0	0	Vehicle	3
197	701	06	0	0	1	0	0	0	0	0	Calcitriol	3
207	712	01	0	0	0	0	0	0	0	0	Vehicle	3
234	739	09	0	0	0	0	0	0	0	0	Vehicle	2
278	783	01	0	0	0	0	0	0	0	0	Calcitriol	3
324	838	08	NA	NA	NA	NA	NA	NA	NA	NA	Calcitriol	2
367	891	13	0	0	0	0	0	0	1	0	Calcitriol	2

†erythema bony area end of treatment

\*erythema non-bony area end of treatment

†severity at end of treatment

# baseline severity

### 9.2 Labeling Recommendations

The label was reviewed. Major changes to the sponsor proposed labeling include:

b(4)

Clinical Review  
Patricia C. Brown, M.D.  
NDA 22-087  
Tradename (calcitriol 3mcg/g) Ointment

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b(4)

### **9.3 Advisory Committee Meeting**

No Advisory Committee was convened in response to this application.

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/s/

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Patricia Brown  
9/22/2008 12:38:26 PM  
MEDICAL OFFICER

Jill Lindstrom  
9/29/2008 06:34:33 PM  
MEDICAL OFFICER

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### DDDP CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Yes	No	N/A	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>				
1. Identify the general format that has been used for this application, e.g. electronic CTD.				paper CTD
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	x			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?			x	
5. Are all documents submitted in English, or are English translations provided when necessary?	x			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	x			
<b>LABELING</b>				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56 <sup>1</sup> and 201.57, current divisional and Center policies, and the design of the development package?	x			
<b>SUMMARIES</b>				
8. Has the applicant submitted all the required discipline summaries (i.e. Module 2 summaries)?	x			
9. Has the applicant submitted the integrated summary of safety (ISS)?	x			
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11. Has the applicant submitted a benefit-risk analysis for the product?				not found
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
<b>DOSE</b>				
<b>EFFICACY</b>				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1 RD.03.SRE.18053 Indication: mild to moderate plaque psoriasis Pivotal Study #2 RD.03.SRE.18054 Indication: same	x			

b(4)

<sup>1</sup> [http://www.access.gpo.gov/nara/cfr/waisidx\\_01/21cfr201\\_01.html](http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html)

15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				not found; pivots conducted in U.S.; topical and long-term safety studies were not
<b>SAFETY</b>				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	x			
<b>OTHER STUDIES</b>				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	x			
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (e.g., labeling comprehension)?			x	
<b>PEDIATRIC USE</b>				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			formal waiver request for not found
<b>ABUSE LIABILITY</b>				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				not found
<b>DATASETS</b>				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				
27. Has the applicant submitted datasets in the format agreed to previously by the Division?				
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
29. Are all datasets to support the critical safety analyses available and complete?				
30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?				
<b>CASE REPORT FORMS</b>				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs)?			x	

b(4)

as previously requested by the Division?				
<b>FINANCIAL DISCLOSURE</b>				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	x			
<b>GOOD CLINICAL PRACTICE</b>				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			
<b>CONCLUSION</b>				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	x			

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

- index for case report forms (by patient number and page number)
- benefit-risk analysis for the product (or its location in the submission)
- a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission (or its location in the submission)
- pediatric waiver request for \_\_\_\_\_ (or its location in the submission)

b(4)

Brenda Carr, M.D.  
 Reviewing Medical Officer

Jill Lindstrom, M.D.  
 Clinical Team Leader

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/s/

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Brenda Carr  
11/15/2006 02:08:41 PM  
MEDICAL OFFICER

Jill Lindstrom  
11/22/2006 11:38:30 AM  
MEDICAL OFFICER

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## CLINICAL FILING CHECKLIST FOR A NEW NDA

NDA Number: 22-087

Applicant: Galderma Labs., LP Stamp Date: 12/27/07

Drug Name: Silkis(calcitriol) Oint. NDA Type: standard

On initial overview of the NDA application for RTF:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	Paper CTD			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?			X	
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	X			SPL in XML
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Mod 2 vol 1.1, pp. 42-44
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(1)			
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: H.141.5004/M and H.141.5012/M Study Title: Sample Size: enrolled 104, 247 Arms: 3, 7, 15µg/g .3, 1, 3, 9µg/g Location in submission: Mod. 5, vols. 1.029 & 1.030				Calcitriol in white petrolatum – not conducted with to-be-marketed formulation
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1RD.03.SRE.18053 Indication: mild to moderate chronic plaque psoriasis	X			

## CLINICAL FILING CHECKLIST FOR A NEW NDA

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 RD.06.SRE.18054 Indication: mild to moderate chronic plaque psoriasis				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				Not found. (See next page)
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?		X		
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			Mod.2, vol 1.4, pp. 98, 99
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Endocrine consult
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR A NEW NDA

	Content Parameter	Yes	No	NA	Comment
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Formal waiver request not found
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?				Not found. Short and long-term safety conducted in Europe
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?				Incomplete- details of disclosable financial interests for 5 investigators not found
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				Found for 2 pivotal studies and studies SRE 40005 & 2663

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

## CLINICAL FILING CHECKLIST FOR A NEW NDA

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

**A) Filing review issue:**

Insufficient information has been provided to assess the effect of the product on cardiac repolarization.

**B) The following information request should be included in the 74 day letter.**

The sponsor is asked to provide the following:

- a) information to assess the effect of the product on cardiac repolarization
- b) a rationale for assuming the applicability of foreign data in the submission to the U.S. population (or its location in the submission)
- c) pediatric assessment wherein the prevalence of psoriasis in the pediatric population is not based on projected data
- d) details of disclosable financial arrangements and interests for 5 investigators; Martha Ann McCarty, Julie Jurgensmeyer, Allan B. Fleischer, Steven Feldman, and Debbie Dalgleisch (or location in the submission)
- e) a statement of Good Clinical Practice for all of the clinical studies
- f) an English translation for foreign labeling 1.14.5.3 (Columbia) and 1.14.5.4 (China)

Patricia Brown, M.D.  
Reviewing Medical Officer

1/30/2008, revised 3/5/08  
Date

Jill Lindstrom, M.D.  
Clinical Team Leader

see sign off date  
Date

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/s/

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Patricia Brown  
3/5/2008 01:05:42 PM  
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Jill Lindstrom  
3/7/2008 12:06:13 PM  
MEDICAL OFFICER

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