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APPLICATION NUMBER:
22-087

MEDICAL REVIEW

CLINICAL REVIEW

Addendum

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Reviewer Name Patricia Brown, MD
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Established Name Calcitriol Ointment, 3mcg/g
Trade Name Vectical Ointment
Therapeutic Class Psoriasis Product
Applicant Galderma Laboratories, L.P.

Priority Designation S

Formulation Ointment
Dosing Regimen Twice Daily
Indication Plaque psoriasis
Intended Population Adults

Addendum Review NDA 22-087 Including Major Amendment

This addendum discusses issues related to bioavailability with emphasis on the maximal use study and clinical implications. The consult genomic review is discussed. This addendum also revisits the clinical safety issue of kidney stones and reviews safety laboratory data provided in response to Division information requests

Clinical Pharmacology:

The following three sections, radio-label studies, and pharmacodynamic parameters in the pivotal trials and open-label safety study, constitute a discussion of issues related to systemic bioavailability.

Radio-labeled studies:

The sponsor conducted three radio-labeled bioavailability studies H.141.605, H.141.6002, and H.141.6003, March 1991, November 1991, and March–May 1992, respectively. The formulation was calcitriol 15µg/g, 3µg/g, and 3µg/g in white petrolatum, which is not the final-to-be marketed formulation. As stated by the clinical pharmacology reviewer, release of any active ingredient from a topical formulation and its subsequent percutaneous absorption are dependent on formulation components. Because systemic absorption is influenced by formulation, I agree with the recommendation that information from these studies not be included in current labeling.

Maximal use study:

The sponsor conducted a pivotal PK/PD study, RD.03.SRE.4005, under maximal use conditions. The subjects for this study had chronic, plaque psoriasis involving at least 25% of body surface area (BSA). The test product was applied on 35% of BSA, which included all skin lesions and if necessary additional normal skin to reach 35% BSA. Subjects applied calcitriol 3µg/g ointment, 15g twice daily for 21 days. For C_{max} the arithmetic mean value at day -1 was 58.2 ± 26.6 (pg/ml) and the day 21 value was 75.3 ± 27.3 . For $AUC_{(0-12h)}$ the arithmetic mean value at day -1 was 519.7 ± 271.5 and the day 21 value was 725.6 ± 261.0 . Although both C_{max} and AUC increase from day -1 to day 21, the data do show variability.

Geometric means, which are better for dealing with data with wide variability, were also analyzed. From baseline to day 21, the geometric mean values of C_{max} increased by approximately 36% and the mean value of $AUC_{(0-12h)}$ increased by 44% over baseline. To compare with the already approved oral calcitriol drug product, Rocaltrol®, examination of Rocaltrol ® labeling reveals for single oral doses, mean serum concentrations achieved a 50% increase over baseline¹ Note however that Rocaltrol ® data are based on other studies in different populations at different times.

¹ Rocaltrol package insert, CLINICAL PHARMACOLOGY: Pharmacokinetics section; labeling approved 7/27/2004.

In the maximum use study, no correlation was seen between PK parameters (AUC and C_{max}) and PD parameters of serum albumin adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus. These are appropriate PD parameters since calcitriol facilitates absorption of calcium and phosphate in the small intestine and interacting with PTH, enhance the mobilization of calcium and phosphate from bone. Calcitriol also decreases the renal excretion of calcium and phosphate. The clinical pharmacology reviewer notes that the PD parameters were measured only for 21 days and therefore PD effects beyond 21 days were not evaluated.

It is evident via the increases seen in C_{max} and AUC that some calcitriol is absorbed. While the maximal use study is limited to 21 days of PD data, for the duration of the study it appears that the body's compensatory mechanisms are effective in limiting the effects of excess calcitriol as shown by PD parameters of serum albumin adjusted calcium, serum phosphorus, urinary calcium and urinary phosphorus.

In the maximal use study, it is not a critical shortcoming that PD parameters were not measured beyond 21. This study is a provocative study with subjects applying calcitriol 3µg/g ointment to psoriasis of at least 25% BSA with additional unaffected skin to total to 35% BSA. Subjects were to continue to apply the calcitriol ointment to 35 % BSA for the duration of the study, 21 days. It is under these conditions of exaggerated use that the mean values of C_{max} increased by approximately 36% and the mean value of $AUC_{(0-12h)}$ increased by 44% over baseline and no correlation with PD parameters was seen. By 21 days, one would expect to see an indication of calcitriol provoked changes in serum calcium. The elimination half-life of calcitriol after single doses of oral calcitriol, Rocaltrol®, is about 5 to 8 hours in normal subjects.¹ The duration of pharmacologic activity of a single oral calcitriol dose, Rocaltrol®, is about 3 to 5 days.² Rocaltrol® labeling also states: "Because of the short biological half-life of calcitriol, pharmacokinetic investigations have shown normalization of elevated serum calcium within a few days of treatment withdrawal..."³

In real world use, patients with mild to moderate psoriasis will apply the calcitriol ointment to areas of psoriasis (generally less than 35% BSA) that generally decrease over time. Changes seen in calcitriol C_{max} and $AUC_{(0-12h)}$ would be expected to be less than those seen in the maximal use study.

Pharmacodynamic parameters in the pivotal trials and open-label safety study:

As studied in the pivotal trials and the open label study, subjects applied calcitriol ointment, not a fixed % of BSA, but to areas of psoriasis (no more than 35% BSA). In the pivotal trials examination of the group mean for calcitriol vehicle versus active and screening versus final reveals no significant differences. Clinically significant changes

¹ Rocaltrol package insert, CLINICAL PHARMACOLOGY: Pharmacokinetics section; labeling approved 7/27/2004.

² Op. cit., Pharmacodynamics section; labeling approved 7/27/2004.

³ Rocaltrol package insert, ADVERSE REACTIONS; labeling approved 7/27/2004.

in mean values for total calcium, adjusted calcium, phosphorus and PTH were not seen. This is demonstrated in the following tables:

Calcium Homeostasis Values Study 18053: Group Means

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

¹ 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.

² Week 8 or last available post-baseline data if the subject discontinued prematurely

³ 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, p. 92.

Calcium Homeostasis Values Study 18054: Group Means

Laboratory Parameters and Expanded Normal Ranges ¹	Calcitriol Ointment 3µg/g		Vehicle Ointment		
	Screening	Week 8/Final ²	Screening	Week 8/Final ²	
Total Calcium (8.5-10.6 mg/dL) <i>Age 14-75, M or F</i>	N	38	36	39	40
	Mean	9.90	9.72	9.85	9.66
	SD	0.424	0.373	0.345	0.409
Adjusted Calcium (8.5-10.6 mg/dL) <i>Age 14-75, M or F</i>	N	38	36	39	40
	Mean	10.2	10.14	10.14	10.06
	SD	0.402	0.361	0.312	0.307

Phosphorus (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	36	39	40
	Mean	3.50	3.46	3.50	3.53
	SD	0.549	0.572	0.557	0.469
PTH (8-97 pg/mL) Age 14-75, M or F	N	37	36	36	39
	Mean	67.78	59.47	57.47	59.59
	SD	37.379	37.117	19.631	24.957
Calcitriol (15.9-55.6 pg/mL) Age 14-75, M or F	N	33	34	35	38
	Mean	52.56	50.91	48.03	47.39
	SD	20.993	18.906	19.450	20.518

¹ 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.

² Week 8 or last available post-baseline data if the subject discontinued prematurely

³ 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, p 93.

In the pivotal trial 18053, examination of calcitriol outliers (15 subjects with highest values) for elevation above baseline revealed no clear association between use of calcitriol versus vehicle and elevation of serum calcitriol levels. Elevation of serum calcitriol levels shows no clear association with elevation of albumin adjusted calcium levels. This is demonstrated in the following table:

Study 18053: Treatment and Calcitriol Outliers (15 Subjects with Highest Values)

Subject Number/site	Treatment	Highest calcitriol value after baseline <i>Ref range</i> 15.9-55.6 pg/mL	% above upper end of ref range	Highest Alb-adj. Ca value after baseline <i>Ref range</i> 8.5-10.6 mg/dL	% above upper end of ref range
1) 353/2102	vehicle	119.2	214%	10.5	
2) 287/2094	vehicle	99	78	11.0 H	4%
3) 477/439	calcitriol	96.5	74	10.8 H	2%
4) 277/2084	vehicle	82.7	49	10.4	
5) 286/2094	calcitriol	77.4	39	10.1	
6) 272/2102	calcitriol	75.4	36	10.7 H	1%
7) 285/2094	calcitriol	73.0	31	10	
8) 34/439	calcitriol	72.9	31	10.2	
9) 147/2149	calcitriol	70.3	26	10.8 H	2%
10) 278/2084	calcitriol	70	26	10.1	
11) 438/439	vehicle	68.2	23	10.8 H	2%
12) 41/2102	vehicle	67.7	22	9.8	
13) 355/2102	calcitriol	67.4	21	10.6	
14) 187/2149	calcitriol	66.7	20	10.1	
15) 417/2094	vehicle	65.5	18	10	

For study 18054, examination of calcitriol outliers (15 subjects with highest values) for elevation above baseline reveals no clear association between use of calcitriol versus vehicle and elevated serum calcitriol levels. Elevation of serum calcitriol levels shows no clear association with elevation of albumin adjusted calcium levels.

Study 18054: Treatment and Calcitriol Outliers (15 Subjects with Highest Values)

Subject number/site	Treatment	Highest calcitriol value after baseline <i>Ref range 15.9-55.6 pg/mL</i>	% above upper end of ref range	Highest Alb adj. Ca after baseline <i>Ref range 8.5-10.6 mg/dL</i>	% above upper end of ref range
1) 720/2095	vehicle	125.3	225%	10.3	
3) 556/2065	calcitriol	106.1	91	10.8 H	2%
4) 737/2065	vehicle	104.6	88	10.3	
5) 979/2036	calcitriol	95.1	71	10.8 H	2%
6) 778/438	vehicle	88.2	59	10.5	
7) 554/2065	calcitriol	83.8	51	10.9 H	3%
8) 794/2063	calcitriol	82.6	49	10	
9) 738/2065	calcitriol	77.8	40	10.7 H	1%
10) 780/438	calcitriol	72.8	31	10	
11) 568/438	calcitriol	76.8	38	10.8 H	2%
12) 717/2095	vehicle	76.5	38	10.1	
13) 561/2095	calcitriol	76.5	38	10.5	
14) 566/438	vehicle	76.1	37	10.4	
15) 761/438	vehicle	73.5	32	10.5	

In the open label study, 2663, examination of the group mean for calcitriol reveals a suggestion of a slight increase in over time; however this is small compared with the standard deviation. Significant changes in mean calcitriol, total calcium, albumin adjusted calcium, phosphorus, PTH, urinary 24 hour calcium, and urinary 24 hour phosphorus were not seen. Please see table below:

Calcium Homeostasis Values Study 2663: Group Means

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.

Conclusion of Discussion of Issues Relating to Systemic Bioavailability:

In the maximal use study increases in C_{max} and AUC indicate that some calcitriol is absorbed. No changes were seen in pharmacodynamic parameters. Although collection of pharmacodynamic data was limited to 21 days, if there were to be an effect on serum calcium it is expected that this would be seen before 21 days. Real-world use of calcitriol is expected generally to be less than that in the maximal use study and generally to decrease over time. As studied in the pivotal trials and the open-label safety study, use of calcitriol is for most subjects, known to be less than in the maximal use study.

Examination of group means for both pivotal and open label trials reveals no significant change in calcitriol levels from baseline through final study visits or between vehicle and active arms in the pivotal trials. Examination of calcitriol outliers for the two pivotal trials does not reveal a clear association between use of calcitriol versus vehicle and elevation of serum calcitriol. Additionally no clear association was seen between elevated serum calcitriol and elevated albumin adjusted calcium.

Genomics:

A genomic study was performed, study report # 2853, titled "Analysis of epidermal gene expression after 24, 48, and 72 hours of treatment with calcitriol 3µg/g applied under occlusion." By interaction with the vitamin D receptor (VDR), calcitriol stimulates differentiation and inhibits epidermal keratinocytes, T-cell proliferation, and production of inflammatory factors. The sponsor studied a VDR target gene, CYP24 that encodes 24-hydroxylase (24-OH) which is a mitochondrial cytochrome P450 that converts calcitriol into an inactive metabolite.

The study was designed to evaluate the effect of topical calcitriol 3µg/g ointment on CYP24 and other marker gene expression via examination of the differential effect on gene expression of calcitriol 3µg/g ointment in comparison to its vehicle and to a non-treated site. A total of 12 healthy Caucasian volunteers (6 females and 6 males) aged 20 to 53, completed the study and were included in the analysis.

According to the genomics reviewer, specific amplification of the cDNA encoding for 24-OH was not achieved, in addition, detailed gene expression profiling performed in two subjects did not find genes for which transcription was modulated by calcitriol treatment in the conditions of the experiment. The genomics reviewer suggested that it was a methodological flaw that the study was not conducted in subjects with psoriasis.

Additional methodologic problems involve the use of agarose gel electrophoresis for the quantitation of gene expression and failure in microarray procedures used. Furthermore genetic variation in VDR and other ligands could also explain the negative findings of the study.

This reviewer agrees with the clinical pharmacology reviewer, that due to methodological shortcomings and the negative results of the study, no information based on this study be included in product labeling.

Clinical Safety Issues:

Kidney Stones:

In study 2663, two subjects (169/site 5265, 233/site 5274) were diagnosed with kidney stones. A third subject (255/site 5273) was diagnosed with "renal colic" and may have had "sludge" without a kidney stone. For study 2663, this reviewer calculated of confirmed stones of 2/178 (person years) or 1.1% for those exposed to calcitriol. For the United States the yearly incidence rate of kidney stones is estimated at .37% or 1/272 persons per year.¹ However, comparison to the U.S rate may not be meaningful for these subjects since subject 169 is from a site in Hungary and subject 233 is from a site in Poland. According to the Oxford Handbook of Urology², many temperate areas have a high incidence of kidney stones e.g. Northern Europe and Scandinavia. Factors playing a role are reported to be "western life style" – excess food, inadequate fluid intake, and limited exercise combined with a genetic predisposition to stone formation. Genetically, Caucasians are more likely to have kidney stones.

Examination of laboratory findings (details in NDA 22-087 Review dated September 22, 2008, pp. 66-68) for these subjects revealed that subject 255 (site 5273/Poland - no confirmed stone) had elevated 24 hour calcium levels at baseline with no elevation in serum calcitriol at baseline. Throughout the study, this subject experienced no elevation of albumin adjusted serum calcium above the reference range. This subject may have had idiopathic hypercalciuria, a condition characterized by normocalcemia with unexplained hypercalciuria.³

Regarding the two subjects, 169 and 233, having confirmed kidney stones, for both the 24 hour urine calcium and calcitriol were elevated at baseline. During the course of study 2663, neither of these subjects experienced an elevation of albumin adjusted serum calcium above the reference range. It is likely that both of these subjects had a pre-existing abnormality of calcium metabolism.

¹ www.wronadiagnosis.com/k/kidney_stones/prevvalence.htm, accessed 8/27/08.

² Reynard, J and Biers, S. Kidney Stones – Epidemiology, p. 350 in Oxford Handbook of Urology, Oxford University Press © 2006.

³ Asplin, JR, Coe FL, and Favus MJ. Chapter 281. Nephrolithiasis in Harrison's Principles of Internal Medicine, 17th Ed: Fauci AS, et al., McGraw-Hill Companies, Inc. © 2008.

Information Request Responses:

In response to Division requests for information the sponsor has provided responses dated October 17, November 12, and December 4, 2008. Information submitted satisfied criteria for a major amendment. Significantly, the November 12 submission provided listings for calcium-phosphorus data outside the reference range for the pooled pivotal studies (SPR.18053 and SPR.18054) and open-label safety study (SPR.2663).

Pivotal Studies:

Calcium Phosphorus Product:

The calcium-phosphate product appears in Rocaltrol® labeling in the statement: "The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg²/dL²."¹ This is provided as a method to monitor for over dosage and 70 mg²/dL² (5.6 mmol²/L²) is identified as a threshold of concern for elevated risk of metastatic calcifications. Based on evaluation of hemodialysis patients a calcium-phosphate product of < 4.4 mmol²/L² (55 mg²/dL²) is recommended.²

The sponsor states that the reference range (1.73-3.84 mmol²/L² for females 23 to 73 and males 25 to 87) was calculated by multiplying the normal range of serum calcium by the normal range of serum phosphorus. The range used is consistent with those found in the literature. For adolescents (14 to 19 female and 13 to 19 male) the upper limit of normal is extended to 4.53 mmol²/L² for females and 4.8 mmol²/L² for males.

For the pooled pivotal studies (SPR.18053 and SPR.18054) subjects having laboratory testing, 7/74 subjects treated with calcitriol and having calcium phosphorus products starting within the normal range shifted to above normal range. This compares with 2/78 subjects treated with vehicle experiencing similar shifts. The elevations are sporadic (occurring only one time) in 6 of the subjects treated with active and less than 10% above the upper range of normal in 5 of the subjects treated with active. No elevation reaches the recommended threshold for adults of 4.4 mmol²/L², or the threshold of concern of 5.6 mmol²/L².

More information is provided in Appendix 1 regarding two subjects, both in the active arm, having calcium phosphorus product elevations 11% and 14% above the upper range of normal. One of these subjects also is the only subject having elevation of calcium phosphorus product for two episodes as opposed to one. Significant clinical impact of elevated calcium phosphorus product is not seen.

¹ Rocaltrol package insert, WARNINGS; labeling approved 7/27/2004.

² Terzi r et al. Comparison of Calcium Phosphate Product Values Using Measurement of Plasma Total Calcium and Serum Ionized Calcium. Hemodialysis International, 2007; 11:411-416.

Serum Calcium:

In the response dated November 4, 2008, the sponsor provided information on serum calcium from the pooled pivotal trials. The reference ranges provided are 2.13-2.65 mmol/L females 14-73 and for male 13-87. These are consistent with reference ranges found in the literature.

For the pooled pivotal studies (SPR.18053 and SPR.18054) subjects having laboratory testing, 5/74 subjects treated with calcitriol and having serum calcium starting within the normal range shifted to above normal range. This compares with 3/78 subjects treated with vehicle experiencing similar shifts. The elevations are sporadic (occurring only one time) in 3 of the subjects treated with active and 3% or less above the upper range of normal in 4 of the subjects treated with active. More information is provided in Appendix 1 on one subject (study 18053-active arm) having a 5% shift above the normal range for serum calcium and having an elevation for two episodes as opposed to one. Information is also provided on another subject (study 18054-active arm) having an elevation of serum calcium for two episodes as opposed to one. Significant clinical impact is not seen.

Serum Phosphorus:

In the response dated November 4, 2008, the sponsor has provided information on serum phosphorus from the pooled pivotal trials. The reference ranges provided by the sponsor are listed below. These are consistent with reference ranges found in the literature.

Serum Phosphorus Reference Ranges

Age	Gender	Reference ranges (mmol/L)
14 - 19	Female	0.81 - 1.71
23 - 73	Female	0.81 - 1.45
13 - 19	Male	0.81 - 1.81
25 - 87	Male	0.81 - 1.45

For the pooled pivotal studies (SPR.18053 and SPR.18054) subjects having laboratory testing, 8/74 subjects treated with calcitriol and having serum phosphorus starting within the normal range shifted to above normal range. This compares with 3/78 subjects treated with vehicle experiencing similar shifts. The elevations are sporadic (occurring only one time) in 6 of the subjects treated with active and in 2 of the subjects treated with vehicle. Two of subjects treated with active had elevation greater than 10% above normal, subject 477 - 16% and subject 324 - 18%. One subject, 438, treated with vehicle had an elevation greater than 10% above normal, 12%. More information is provided in Appendix 1 regarding 3 subjects having shifts greater than 10% above normal range. Information is also provided on the 3 subjects having more than one episode of elevated phosphorus. These two groups overlap in that two of the subjects having a greater than 10% phosphorus elevation also had more than one episode of elevation. Significant clinical impact is not seen.

Study 2663 (52 Week Open-Label Study):

Calcium Phosphorus Product:

With respect to calcium phosphorus product in the open label study, shifts of subjects are as follows:

Calcium phosphorus product reference range	Subjects
Within to Above	28/317
Above to Above	7/317
Above to Normal	2/317

A total of 6 subjects, having baseline calcium phosphorus products within reference range had a post-baseline value 10% or greater than the upper limit of normal. A total of two subjects having baseline calcium phosphorus products above reference range had a post-baseline value 10% or greater than the upper limit of normal. More information is provided for these subjects in Appendix 2. Significant clinical impact is not seen.

Summary of Clinical Safety Issues Section:

In the open label safety study, 2663, kidney stones were reported in three subjects and confirmed in two. A calculated yearly incidence of 1.1% for confirmed stones may not be meaningfully compared with the U.S. rate of .37%, since the subjects with confirmed stones were from sites in Hungary and Poland. For both of these subjects the 24 hour urine calcium and calcitriol were elevated at baseline and during the course of study 2663, neither of these subjects experienced an elevation of albumin adjusted serum calcium above the reference range. It is likely that both of these subjects had a pre-existing abnormality of calcium metabolism. The subject with no confirmed stone had elevated 24 hour calcium levels at baseline with no elevation in serum calcitriol. Throughout the study, this subject experienced no elevation of albumin adjusted serum calcium above the reference range. This subject may have had idiopathic hypercalciuria, a condition characterized by normocalcemia with unexplained hypercalciuria.¹

For the pooled pivotal trials, examination of calcium phosphorus product data for the pooled pivotal trials reveals no elevation reaching the recommended threshold for adults of 4.4 mmol²/L², or the threshold of concern of 5.6 mmol²/L². Examination of outliers for calcium phosphorus product, serum calcium, and serum phosphorus reveals no significant safety concerns. For calcium phosphorus product, serum calcium, and serum phosphorus, slightly greater numbers of subjects treated with active, versus those treated with vehicle, shift from normal values at baseline to above reference range values post-baseline.

For the open label study, 2663, examination of calcium phosphorus product data reveals no elevation reaching the threshold of concern of 5.6 mmol²/L². Examination of outliers reveals only two subjects that reach the recommended threshold for adults of 4.4 mmol²/L². One of these is a 25 year old male (subject 66/site 5268) who had a transient increase to 4.96

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

mmol²/L² which returned to normal. No AEs were reported for this subject and the subject was lost to follow up. The other subject was a 72 year old female (subject 250/site 5272) who had an increase to 4.50 mmol²/L² at day 43 with no subsequent lab values available. No AEs were reported and the subject was lost to follow up.

The data reviewed do not suggest a need for routine laboratory monitoring. The risk for perturbations in calcium homeostasis can be addressed in labeling. Overall, the recommendation for NDA approval, per review of September 22, 2008, is not changed.

Appears This Way
On Original

Appendix 1

Studies 18053 and 18054:

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

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

Calcium Phosphorus Product:

Subjects in Pooled Pivotal Trials (18053 and 18054) Ca x Phos Product > 10% above Upper Limit of Reference Range

Site/subj	Lab Day	Adj Ca (mg/dL) 8.5-10.6 mg/dL	Serum Ca (mmol/L) 2.13-2.65 mmol/L	Phos (mmol/L) 0.81- 1.45 mmol/L	Calcitriol (pg/mL) 15.9-55.6 pg/mL	Urine Ca (mg/24h) 100-300 mg/24hr	Ca x Phos (mmol ² /L ²) 1.87-3.84 mmol ² /L ²
439/477	-3	10.4	2.35	1.1	43.1	-	2.59
56 F	15	10.7 H	2.5	1.36	96.5 H	286	3.4
10 % BSA	37	10.8 H	2.5	1.45	-	354 H	3.63
326g/6.5g	43	10.6	2.53	1.68 H	-	204	4.25 H 11%
50 days	50	10.8 H	2.55	1.49 H	81.1 H	-	3.8
D/C subj r							
2129/324	-4	9.9	2.38	1.42	-	-	3.38
43 F	17	10.5	2.55	1.71 H	-	74 L	4.36 H 14%
4 % BSA	29	10.1	2.38	1.68 H	-	182	4 H
796g/14g	42	9.4	2.28	1.45	-	31 L	3.31
nl complet	56	10.2	2.43	1.55 H	-	41 L	3.77
No AEs							
56 days							

Subject 477 is a 56 year old female with a 10% BSA involvement at baseline (for this trial at baseline the mean % BSA involved was 9.6 ± 7.5). Subject 477 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. No action was taken with regard to study drug.

Subject 477 had a total medication use of 326g calcitriol ointment and the mean medication use for trial 18053 was 392 ± 390 grams. This subject had a daily use of 6.5g and for this trial the mean daily use was 7.1 ± 6.9 grams. Duration of use was 50 days. The elevation of calcium phosphorus product in this subject does not appear to be associated with excessive medication use. This subject did show elevated calcitriol and

was identified as an outlier for calcitriol elevation. However, note that elevation of urine calcium was sporadic and elevations of albumin adjusted calcium were at most only 2% above the upper range of normal.

Subject 324 (site 2129- trial 18053) is a 43 year old female having 4% BSA involvement at baseline. Total medication use (calcitriol arm) was 796g, daily use was 14g, and duration of use was 56 days. This use was above the mean for trial 18053; mean use was 392 ± 390 grams with a daily use of 7.1 ± 6.9 grams. Note that this subject showed no elevation of serum calcium or of urine calcium. No adverse events were listed and the subject completed the trial.

Serum Calcium:

Outliers for Serum Calcium in Pooled Pivotal Trials (18053 and 18054)

Site/subj	Lab Day	Adj Ca (mg/dL) 8.5-10.6 mg/dL	Serum Ca (mmol/L) 2.13-2.65 mmol/L	Phos (mmol/L) 0.81-1.45 mmol/L	Calcitriol (pg/mL) 15.9-55.6 pg/mL	Urine Ca (mg/24h) 100-300 mg/24hr	Ca x Phos (mmol ² /L ²) 1.87-3.84 mmol ² /L ²
2102/44	-4	10.4	2.55	1.26		-	3.21
25 M	15	10.1 H	2.78 H 5%	1.13	41.7	89.9 L	3.14
12 % BSA	29	11.1 H	2.73 H	1.45	44.8	171.1	3.96 H
31g/.55g	57	10.3	2.53	1.2		110.7	3.04
57 days							
nl complet							
2036/624	-3	10.5	2.55	1.36	-	-	3.47
60 F	13	10.5	2.55	1.2	17.8	205.8	3.06
6% BSA	23	11.1 H	2.68 H	1.13		265.5	3.03
87g/1.7g	34	11.3 H	2.7 H	1.39		58.5 L	3.75
51 days	51	10.3	2.48	1.07	34.9	50.4 L	2.65
nl complet							

Subject 44 (site 2129 – study 18053) is a 25 year old male having 12% BSA involvement at baseline. Total medication use (calcitriol arm) was 31g, daily use was .55g, and duration of use was 57 days. For this subject total medication use and daily medication use were below the mean for trial 18053. Note that no elevations occurred in urine calcium. No adverse events were listed and the subject completed the trial.

Subject 624 (site 2036 – study 18054) is a 60 year old female having 6% BSA involvement at baseline. This subject's albumin adjusted calcium of 11.3 (or 6.6% above the upper limit of normal) represents the highest albumin adjusted calcium value for the two pivotal trials. Total medication use (calcitriol arm) was 87g, daily use was 1.7g, and

duration of use was 51 days. For this subject total medication use and daily medication use were below the mean for trial 18053. Note that no elevations occurred in urine calcium. No adverse events were listed and the subject completed the trial.

Serum Phosphorus:

Outliers for Serum Phosphorus in Pooled Pivotal Trials (18053 and 18054)

Site/subj Treatment	Lab Day	Adj Ca (mg/dL) 8.5-10.6 mg/dL	Serum Ca (mmol/L) 2.13-2.65 mmol/L	Phos (mmol/L) 0.81-1.45 mmol/L	Calcitriol (pg/mL) 15.9-55.6 pg/mL	Urine Ca (mg/24h) 100-300 mg/24hr	Ca x Phos (mmol ² /L ²) 1.87-3.84 mmol ² /L ²
Active							
1) 439/477	-3	10.4	2.35	2.35	43.1	-	2.59
56 F	15	10.7 H	2.5	1.36	96.5 H	286	3.4
10% BSA	37	10.8 H	2.5	1.45	-	354 H	3.63
326g/6.5g	43	10.6	2.53	1.68 H 16%	-	204	4.25 H
50 days	50	10.8H	2.55	1.49 H	81.1 H	-	3.8
D/C subj req							
2) 2129/324							
43 F	-4	9.9	2.38	1.42	-	-	3.38
4% BSA	17	10.5	2.55	1.71 H 18%	-	74 L	4.36 H
796g/14g	29	10.1	2.38	1.68 H 16%	-	182	4 H
56 days	42	9.4	2.28	1.45	-	31 L	3.31
nl complet	56	10.2	2.43	1.55 H	-	41 L	3.77
3) 438/762							
40 F 54	-3	9.9	2.45	1.29	28.3		3.16
4% BSA	15	9.8	2.4	1.62 H 12%	65.6 H	180	3.89 H
39g/68	29	9.7	2.38	1.45		130.2	3.45
57 days	57	9.7	2.4	1.39	41.5	206.8	3.34
nl complet							
Vehicle							
1) 438/566	-2	10	2.45	1.45	35.6		3.55
36 M 54	15	10.2	2.5	1.26	76.1 H	87 L	3.15
18g/29	29	10.4	2.63	1.26		134.4	3.31
61 days	43	9.9	2.45	1.62 H 12%		331.8 H	3.97 H
nl complet	61	10	2.35	1.26	63.3 H	315.6 H	2.96
2) 439/458							
61 M 53	-7	10.4	2.5	1.45	62.8 H		3.63
6% BSA	15	10.6	2.53	1.58 H 9%	68.2 H	213.3	4 H
595g/10.4	29	10	2.4	1.32		110.4	3.17
57 days	43	10.3	2.5	1.39		153.3	3.48
nl complet	57	10.6	2.58	1.49 H 3%	53.9	92 L	3.84

	85	10.4	2.55	1.29		5.6 L	3.29
	99	10.8 H	2.65	1.45		-	3.84

Active:

Subject 1 above treated with active, 477 (site 439 – study 18053) is a 56 year old female having 10% BSA involvement at baseline. Total medication use was 326g, daily use was 6.5g, and duration of use was 50 days. For this subject total medication use and daily medication use were below the mean for trial 18053. This subject has also been discussed above under calcium phosphate product. This subject 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. No action was taken regarding study drug.

Subject 2 above treated with active, 324 (site 2129 – study 18054) is a 43 year old female having 4% BSA involvement at baseline. This subject has also been discussed above under calcium phosphate product. Total medication use was 796g, daily use was 14g, and duration of use was 56 days. For this subject total medication use and daily medication use were above the mean for trial 18054. No adverse events were listed and the subject completed the trial.

Subject 3 above treated with active, 762 (site 438 – study 18054) is a 40 year old female having 4% BSA involvement at baseline. Total medication use was 39g, daily use was .68g, and duration of use was 57 days. For this subject total medication use and daily medication use were below the mean for trial 18054. Adverse events listed were sinusitis and worsening arthritis, both considered by the investigator to be definitely unrelated. The subject completed the trial.

Vehicle:

Subject 1 above treated with vehicle, 566 (site 438 – study 18054) is a 36 year old male having 10% BSA involvement at baseline. Total medication use was 18g, daily use was .29g, and duration of use was 61 days. For this subject total medication use and daily medication use were below the mean for trial 18054. Adverse event listed was sinusitis, considered definitely unrelated.

Subject 2 above treated with vehicle, 458 (site 439 – study 18053) is a 61 year old male having 6% BSA involvement at baseline. Total medication use was 595g, daily use was 10.4g, and duration of use was 57 days. For this subject total medication use and daily medication use were above the mean for trial 18054. Adverse event listed was blockage of two coronary arteries, considered unlikely to be related.

Appendix 2

Study 2663

For study 2663 the mean baseline % BSA involvement was 16.1±8.4% and the adjusted mean daily drug use was 5.8±5 grams.

Calcium phosphorus product

Calcium Phosphorus Product Study 2663: Subjects Within to Above (Values ≥ 10%)

Site/subj	Lab Day	Adj Ca (mg/dL) 8.5-10.6 mg/dL	Serum Ca (mmol/L) 2.13-2.65 mmol/L	Phos (mmol/L) 0.81-1.45 mmol/L	Calcitriol (pg/mL) 15.9-55.6 pg/mL	Urine Ca (mmol/24h) 100-300 mg/24hr	Ca x Phos (mmol ² /L ²) 1.87-3.84 mmol ² /L ²
1) 5110/34	-6	2.38	2.47	1.13	25	4	2.79
62 M	43	2.51	2.64	1.36	27	4.6	3.59
10% BSA	85	2.31	2.41	1.17	32	5.1	2.82
0-15g daily	127	2.51 H	2.69 H	1.52 H	49	7.8 H	4.09 H 10%
175 days	176	2.43	2.56 H	1.13	29	4.2	2.89
NI compl							
No AEs							
2) 5124/279	-6	2.32	2.43	1.71 H	53 H	1.4 L	4.16 Adoles
14 M	43	2.36	2.41	1.78 H	26	1.8 L	4.29
12% BSA	98	2.46	2.53	1.71 H	43	1.4 L	4.33
0-14g daily	140	2.41	2.46	1.96 H	40	0.2 L	4.82
380 days	199	-	-	1.49	86 H	-	-
NI compl	269	2.43	2.51	1.55	64 H	1.5 L	3.89
No AEs	335	2.41	2.46	1.79 H	82 H	1.9 L	4.4 H 11%
	380	2.29	2.4	1.58	81 H	1.4 L	3.79
3) 5124/323	-11	2.34	2.41	1.43	45	4	3.45
54 F	52	2.23	2.28	1.5 H	49	3.2	3.42
29% BSA	87	2.36	2.45	1.7 H	35	4	4.17 H 13%
6.8g daily	130	2.25	2.35	1.52 H	45	3.7	3.57
370 days	230	2.38	2.4	1.53 H	71 H	3.2	3.67
NI compl	297	2.28	2.39	1.54 H	114 H	4.2	3.68
No AEs	376	2.29	2.36	1.44	37	4.1	3.4
4) 5262/92	-9	2.38	2.57 H	1.18	69 H	8.5 H	3.03
38 M	47	2.31	2.52	1.15	51 H	5.1	2.9
25% BSA	92	2.34	2.53	1.13	66 H	7.8 H	2.86
8.8g daily	138	2.32	2.51	1.72 H	69 H	8 H	4.32 H 17%
361 days	187	2.33	2.5	1.06	81 H	7.4	2.65
NI compl	236	2.34	2.49	1.09	58 H	13.6 H	2.71
+ AEs - not related	313	2.29	2.45	1.21	59 H	17.8 H	2.96
	362	2.49	2.67 H	1.2	86 H	6.3	3.2

Site/subj	Lab Day	Adj Ca (mg/dL) 8.5-10.6 mg/dL	Serum Ca (mmol/L) 2.13-2.65 mmol/L	Phos (mmol/L) 0.81-1.45 mmol/L	Calcitriol (pg/mL) 15.9-55.6 pg/mL	Urine Ca (mmol/24h) 100-300 mg/24hr	Ca x Phos (mmol ² /L ²) 1.87-3.84 mmol ² /L ²
5) 5268/66	-27	2.33	2.49	1.42	51 H	17.7 H	3.54
25 M	43	2.57	2.71 H	1.83 H	40	8.3 H	4.96 H 34%
30% BSA	92	2.39	2.48	1.06	17	10.1 H	2.63
5.2 g daily	134	2.32	2.44	1.3	30	6.9	3.17
219 days	219	2.34	2.49	1.31	45	8.9 H	3.26
No AEs							
Lost to F/U							
6) 5272/250	-6	2.48	2.54	1.04	24	1.1 L	2.64
72 F	43	2.72 H	2.76 H	1.63 H	25	1.9 L	4.5 H 21%
15% BSA							
22.1g daily							
43 days							
No AEs							
Lost to F/U							

1) Subject 34 above (site 5110) is a 62 year old male with a 10% baseline BSA involvement which is below the mean for the study (16.1±8.4%). This subject did not return used medication tubes for weighing and therefore the daily use is estimated as either 0 or as if all tubes were used completely. No AEs were reported and the subject completed the study.

2) Subject 279 (site 5124) is a 14 year old male with a 12% baseline BSA involvement which is below the mean for the study (16.1±8.4%). This subject did not return used medication tubes for weighing and therefore the daily use is estimated as either 0 or as if all tubes were used completely. No AEs were reported and the subject completed the study.

3) Subject 323 (site 5124) is a 54 year old female with a 29% baseline BSA involvement which is above the mean for the study (16.1±8.4%). Daily use was estimated at 6.8 grams which is above the mean for the study (5.8±5 grams). No AEs were reported and the subject completed the study.

4) Subject 92 (site 5262) is a 38 year old male with a 25% baseline BSA involvement which is above the mean for the study (16.1±8.4%). Daily use was estimated at 8.8 grams which is above the mean for the study (5.8±5 grams). This subject did experience adverse events including infection of skin, lab test abnormal (high calcitriol level), urine abnormal (high calcium), and pruritus. The study drug was not discontinued. This subject began the study with calcitriol and 24 hour urine calcium above reference range. This subject completed the study.

5) Subject 66 (site 5268) is a 25 year old male with a 30% baseline BSA involvement which is above the mean for the study (16.1±8.4%). Daily use was estimated at 5.2 grams which is

below the mean for the study (5.8 ± 5 grams). No AEs were reported. The subject was lost to follow up.

6) Subject 250 (site 5272) is a 72 year old female with a 15% baseline BSA involvement which is below the mean for the study ($16.1 \pm 8.4\%$). Daily use was estimated at 22.1 grams which is above the mean for the study (5.8 ± 5 grams). No AEs were reported. The subject was lost to follow up.

Calcium Phosphorus Product Study 2663: Subjects Above to Above (Values $\geq 10\%$)

Site/subj	Lab Day	Adj Ca (mg/dL) 8.5-10.6 mg/dL	Serum Ca (mmol/L) 2.13-2.65 mmol/L	Phos (mmol/L) 0.81-1.45 mmol/L	Calcitriol (pg/mL) 15.9-55.6 pg/mL	Urine Ca (mmol/24h) 100-300 mg/24hr	Ca x Phos (mmol ² /L ²) 1.87-3.84 mmol ² /L ²
1) 5108/11	-6	2.45	2.49	1.52 H	26	-	3.78 H
77 F	43	2.37	2.42	1.54 H	34	1.3 L	3.73 H
20% BSA	99	2.45	2.5	1.63 H	32	1.1 L	4.08 H 10%
.9g daily	131	2.54	2.62 H	1.28	71 H	2.6	3.35
369 days	173	2.51	2.53	1.35	41	1.3 L	3.42
No AEs	243	2.29	2.35	1.49	8 L	4.9	3.5
nl complet	309	2.42	2.39	1.43	20	2.5 L	3.42
	369	2.35	2.37	1.46	35	1.4 L	3.46
2) 5110/46	-10		2.68 H	1.66 H	29		4.45 H 20%
27 M	-5	2.36	2.62 H	-		9 H	-
30 %	39	2.41	2.6 H	1.58 H	35	4	4.11 H 11%
2.2g daily							
39							
No AEs							
Subj request							

1) Subject 11 (site 5108) is a 77 year old female with a 20% baseline BSA involvement which is above the mean for the study ($16.1 \pm 8.4\%$). Daily medication use was estimated at .9 grams which is below the mean for the study (5.8 ± 5 grams). No AEs were reported and the subject completed the study.

2) Subject 46 (site 5110) is a 27 year old male with a 30% baseline BSA involvement which is above the mean for the study ($16.1 \pm 8.4\%$). Daily medication use was estimated at 2.2 grams which is below the mean for the study (5.8 ± 5 grams). No AEs were reported. The subject discontinued the study at the subject's request.

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/s/

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1/16/2009 06:33:25 PM
MEDICAL OFFICER

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CLINICAL REVIEW

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Established Name Calcitriol Ointment, 3mcg/g
(Proposed) Trade Name Silkis Ointment
Therapeutic Class Psoriasis Product
Applicant Galderma Laboratories, L.P.

Priority Designation S

Formulation Ointment
Dosing Regimen Twice Daily
Indication Plaque psoriasis
Intended Population Adults

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

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends that Tradename calcitriol 3µg/g ointment be approved for topical treatment of mild to moderate psoriasis in adults age 18 and older.

1.2 Risk Benefit Assessment

Approximately 7.5 million people in the United States have psoriasis. A majority of these people are likely to have mild to moderate chronic plaque psoriasis. Treatments generally considered appropriate for this group include topical steroids of various strengths, calcipotriene (Dovonex) a vitamin D3 analogue available as cream and solution, and tazarotene. Topical steroids place users at risk for local side effects of atrophy, telangiectasia, and dyspigmentation. If overused or used improperly, topical steroids also can affect the hypothalamic-pituitary-adrenal (HPA) axis. Tazarotene, being a teratogen, has the potential to cause birth defects. There is a public health need for a product for use in psoriasis with a more favorable side effect profile than seen with the products noted above.

Tradename calcitriol 3µg/g ointment has been demonstrated to be efficacious in two well-controlled pivotal trials. The results are solid. Calcitriol 3µg/g ointment was also more effective than vehicle in all subgroups.

Safety was evaluated in the two pivotal trials and in an open-label long term safety study. Supportive safety data was also evaluated from 12 other controlled trials. In the clinical program, one death and 24 SAEs were evaluated and considered to be unrelated to study drug. In uncontrolled studies 2 SAEs, erythema annulare centrifugum and worsening of psoriasis, were considered possibly related to study drug.

Examination of adverse events reveals a potential for local effects such as pruritus, discomfort of skin, and pain. These may be related to components of the vehicle. Cutaneous safety testing revealed that calcitriol ointment showed roughly equivalent levels of irritation to white petrolatum and, as studied, was not sensitizing. Calcitriol 3µg/g ointment as studied did not show evidence of phototoxicity or of photosensitization.

Calcium homeostasis parameters were monitored in approximately 80 subjects in calcitriol and vehicle arms of the two pivotal trials. In trials 18053 and 18054, 22 subjects in the calcitriol arm and 15 subjects in the vehicle arm had at least one albumin-adjusted calcium above the normal range. In the pivotal trials, for 24 hour urine calcium, 16 subjects in the calcitriol arm and 26 in the vehicle arm had values above the normal range. Clinical symptoms of hypercalcemia were not noted.

In the open label safety study, 2663, 10 subjects experienced hypercalcemia. The distribution of events of hypercalcemia was roughly even through the 4 quarters of the study. A total of 20 subjects had hypercalciuria reported as an adverse event. Events of hypercalciuria as an adverse event were distributed roughly evenly through the 4 quarters of the study. Two subjects in this study were found to have kidney stones. In both cases laboratory parameters of calcium metabolism were above normal at baseline (either calcitriol or 24 hour urine calcium).

The adverse event profile observed, including effects on calcium metabolism, indicates that if tradename calcitriol ointment is used as labeled (no more than 30 g day) under a physicians care, it is safe.

1.3 Recommendations for Post-Marketing Risk Management Activities

The standard risk management measures of prescription status, professional labeling, and spontaneous adverse event reporting are adequate risk management activities for this drug at this time. Adverse events that would be of particular interest would be those suggesting possible systemic effects from absorption of the active ingredient, calcitriol, and would reflect an impact on calcium metabolism.

1.4 Recommendations for other Post-Marketing Study Commitments

The sponsor should conduct a PK/PD study under maximum use conditions to assess systemic exposure in children. The sponsor should evaluate the effect of their product on calcium in all subjects.

The sponsor should conduct a vehicle-controlled trial (or trials) in pediatric subjects with plaque psoriasis, to understand the efficacy and broad safety profile which would include local and systemic safety. The sponsor should evaluate the effect of their product on calcium in all subjects.

The sponsor should conduct a long-term safety study in children. An open-label study may be acceptable.

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2 Introduction and Regulatory Background

2.1 Product Information

The sponsor, Galderma Laboratories, L.P., has submitted a 505(b)(1) application for calcitriol ointment 3µg/g (0.0003% w/w). Calcitriol ointment 3µg/g is a single-phase, white translucent semi-solid product that contains calcitriol (0.0003% w/w), white petrolatum, mineral oil, and vitamin F. The product is intended for twice daily topical treatment of plaque psoriasis in adult aged 18 and above.

b(4)

The ointment is packaged in aluminum tubes. The tubes are closed with screw caps. Tube sizes proposed for marketing are 100g. A 5g size is proposed for samples.

b(4)

According to the chemistry reviewer, calcitriol is a well-established compendial drug substance whose structure has been fully elucidated. Calcitriol has been marketed in various formulations since 1978. According to the sponsor, calcitriol ointment 3mcg/g (Silkis), is currently approved in 42 countries and marketed in 28 countries.

The non-proprietary name for the proposed drug product is calcitriol ointment. The proposed proprietary name is Silkis. The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not recommend the use of the proposed proprietary name because the name overstates the efficacy of the product. The Division of Dermatology and Dental Products (DDDP) supported DDMAC's objection to the name based on promotional concerns. The sponsor was notified with a letter dated June 23, 2008 and was invited to submit two new trade names.

2.2 Tables of Currently Available Treatments for Proposed Indications

Discussion will be limited to those products having indications similar to the indication being considered in the current application, topical treatment of mild to moderate chronic plaque psoriasis.

Table 1: Currently available Treatments

Treatment	Formulations	Indication	ages
Steroids (sampling)			
Desonide	Cream .05% Ointment .05% Lotion .05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	
Hydrocortisone butyrate	Cream 0.1% Ointment 0.1% Solution 0.1%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	

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Treatment	Formulations	Indication	ages
Fluticasone propionate	Cream 0.05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	3 months and older
	Ointment .005%	same	adults
Fluocinonide	Cream	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	12 years and older
Clocortolone pivalate	Cream 0.1%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	
Halcinonide	Cream 0.1%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	
Betamethasone dipropionate	Ointment .05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	13 and older
	Lotion .05%		
Halobetasol propionate	Cream 0.05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	12 and older
	Ointment 0.05%		
Clobetasol propionate	Foam 0.05%	Relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses	12 and older
	Lotion 0.05%		
Non-steroids			
Calcipotriene	Ointment 0.005%	Plaque psoriasis	adults
Calcipotriene	Cream 0.005%		
Calcipotriene 0.005% and betamethasone dipropionate 0.064%	Ointment	Psoriasis vulgaris	Adults 18 and above
Tazarotene	Cream .05%	plaque psoriasis	
	Cream 0.1%		
	Gel 0.05%	Stable plaque psoriasis of up to 20% BSA	
	Gel 0.1%		

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Adverse Reactions/Contraindications/Warnings and Precautions:

Adverse reactions with topical corticosteroids can include epidermal atrophy (usually reversible), dermal atrophy with development of striae, and HPA axis suppression. Burning and itching may also occur at sites of application. Corticosteroids are pregnancy category C drug products.

For calcipotriene, the most frequently reported adverse reactions are burning, itching, and skin irritation. Calcipotriene should not be used by patients with hypercalcemia or evidence of vitamin D toxicity. Calcipotriene is a pregnancy category C drug product.

For calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment, adverse reactions include hypercalcemia, reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, skin atrophy, pigmentation changes, telangiectasia, pruritus, rash, skin burning, erythema, folliculitis, skin irritation, and psoriasis. Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is contraindicated in patients with known or suspected disorders of calcium

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metabolism. This product is also contraindicated in patients with erythrodermic, exfoliative and pustular psoriasis. Calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment is a pregnancy category C product.

With respect to tazarotene, for the gel form, the most frequently reported adverse reactions in clinical trials were pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, and skin pain. For the cream form the most frequently reported adverse reactions were pruritus, erythema, and burning. For both cream and gel, because of heightened burning susceptibility, exposure to sunlight should be avoided unless deemed medically necessary. According to labeling, a negative pregnancy test should be obtained two weeks prior to starting therapy and therapy should start during a normal menstrual period. Women of childbearing potential should also employ adequate birth control while using tazarotene. Tazarotene is a pregnancy category X product.

2.3 Availability of Proposed Active Ingredient in the United States

Since 1978 calcitriol has been marketed in the United States in various formulations. The formulations include Rocaltrol available as oral capsules (0.25µg and 0.5µg, NDA 18-044) for management of secondary hyperparathyroidism in chronic renal failure, hypocalcemia in dialysis patients, and patients with idiopathic or pseudohypoparathyroidism. Rocaltrol is also available as an oral solution (1 µg/mL, NDA 21-068) for treatment of secondary hyperparathyroidism in patients having moderate to severe chronic renal failure and who are not yet undergoing dialysis. Calcijex is available as injectable solutions (.001 and .002 mg/mL, NDA 18-874) for management of hypocalcemia in patients undergoing chronic renal dialysis.

Calcipotriene (Dovonex, originally approved 1993) was the first vitamin D analog approved in the United States for the treatment of plaque psoriasis in adults. Currently Dovonex is available as a cream (.005%, NDA 20-554) for treatment of plaque psoriasis and as a solution (.005%, NDA 20-273) for topical treatment of chronic, moderately severe psoriasis of the scalp. Taclonex® Ointment, containing calcipotriene 0.005% and betamethasone dipropionate 0.064%, was approved in 2006 for the topical treatment of psoriasis vulgaris in adults 18 years of age and above for up to 4 weeks. In 2008 Taclonex Scalp® Topical Suspension, containing calcipotriene 0.005% and betamethasone dipropionate 0.064%, was approved for the topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults 18 years and older.

2.4 Important Safety Issues with Consideration to Related Drugs

A safety concern is the effect of the vitamin D analogue on calcium homeostasis. As indicated by the results of a pharmacokinetic/pharmacodynamic study performed under conditions of maximal use, systemic absorption of calcitriol does occur. Calcitriol acts on intestine, kidney, and bone to control plasma calcium and phosphorous levels. The plasma half-life of calcitriol in humans is estimated to be between 3 and 5 days.

Calcitriol ($1\alpha,25$ -dihydroxyvitamin D_3) is endogenously produced and is the active hormone form of vitamin D_3 . In humans, calcium and phosphorous levels in plasma are regulated by the vitamin D_3 /parathyroid hormone (PTH)/calcitonin system. Vitamin D 1α -hydroxylase is the enzyme that controls levels of calcitriol. If serum calcium increases, serum PTH and the activity of 1α hydroxylase decrease, resulting in inhibition of calcitriol synthesis. At the same time the activity of 24 -hydroxylase increases and induces calcitriol catabolism. If serum calcium decreases, calcitriol synthesis increases. Calcitriol facilitates absorption of calcium and phosphate in the small intestine and interacts with PTH to enhance the mobilization of calcium and phosphate from bone. Calcitriol also decreases the renal excretion of calcium and phosphate. Through a feedback loop excess calcitriol would be expected to increase serum calcium and phosphorus and decrease levels of PTH. Hypercalciuria can follow due to decreased parathyroid hormone stimulated calcium reabsorption. Hypercalciuria can lead in turn to the formation of insoluble calcium salts and kidney stone formation.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

A Pre-IND/End of Phase 2 meeting was held November 15, 1999. Principal areas of concern addressed by the Agency included the primary efficacy parameters; the Investigator's global assessment dichotomized to success/failure was recommended. The Agency stated that all lesions should be treated and evaluated regarding erythema, scaling, and plaque thickness. Scalp lesions could be excluded. More than one target lesion should be assessed in each patient. The Agency stated that information will be needed about efficacy in knee/elbow lesions as compared to trunk lesions. Secondary efficacy variables preferably should include all treated lesions. Prior to NDA submission, the sponsor should perform topical safety studies with the final-to-be marketed formulation. Additionally, long term safety studies should include at least 300 patients of all ages, pregnant and lactating, unless there is a convincing rationale for any exclusion.

A pre-NDA meeting with the sponsor was held May 17, 2006 and among the issues discussed was the sponsor's request

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sponsor indicated that they would submit a Proposed Pediatric Study Request.

The current submission is a resubmission of an application originally submitted in September 2006. The reason for refusal to file was incomplete CMC data to support the manufacturing process at the designated commercial manufacturing site, Galderma Production Canada, Inc. The designated commercial manufacturing site and process were different from those of the Phase 3 clinical studies (Galderma Industrial Development France). Bridging data to support these changes were missing.

2.6 Other Relevant Background Information

Calcitriol ointment, 3mcg/g, was initially developed by _____ in the late 1980's, licensed to _____ then acquired by Galderma in 1996. According to the sponsor, calcitriol ointment 3mcg/g (Silkis), is approved in 42 countries and is marketed in 28 countries.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

1) DSI inspections were requested with the following rationale:

Please inspect sites 1170 and 2123 in study 18053. Site 2123 has a relatively large sample size and a high treatment effect (zero response for the vehicle and nearly 50% response for the active) which is considerably larger than the overall treatment effect of 12%. Site 1170 enrolled 20 subjects of which 0/10 of subjects treated with active responded, whereas 3/10 treated with vehicle responded resulting in a treatment effect favoring vehicle. As this is not consistent with results from other centers, interest lies in how one might be able to explain such an extreme deviation from the overall study conclusions and if such results are due to study conduct at this site.

Site # 2123, was inspected with the conclusion: "The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication."

Site # 1170, was inspected with comments: "Review of the records noted above" (for all 20 enrolled subjects) "revealed no significant discrepancies/regulatory violations. "Data appear acceptable in support of the respective application." "Review of the establishment inspection report (EIR) for Dr. Breneman is pending. An addendum to this inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR."

2) The sponsor's analyses were reviewed. The review team performed independent analyses.

3.2 Compliance with Good Clinical Practices

Responding to an information request for a statement of Good Clinical practice for all of the clinical studies the sponsor submitted an amendment to the NDA on April 29, 2008 with the following statement:

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Clinical studies submitted in this application comply with recognized Good Clinical Practice standards. Elements to ensure the protection of human subjects include the review of human research by an independent Institutional review Board, compliance with the principles of research described in the Declaration of Helsinki, and the informed consent of subjects participating in each study.

3.3 Financial Disclosures

The sponsor has provided FDA form 3454 certifying that the sponsor has not entered into financial arrangements with the listed clinical investigators. The listed clinical investigators included 85 with study 18053 and 78 with study 18054. The sponsor also certified that the listed clinical investigators did not disclose any proprietary interests in this product or a significant equity in the sponsor. The sponsor further certified that none of the listed investigators was the recipient of significant payments of other sorts.

The sponsor also provided FDA form 3455 with additional information pertaining to _____ who was principal investigator at site _____, in study _____. This site also had _____ sub-investigators. It was disclosed that Galderma Laboratories, L.P. provides an educational grant to the _____. The sponsor states that this center is a health services research unit that performs projects to improve the care of patients with skin disease. The grant primarily funds the Center's infrastructure. The sponsor states: "The funding of this grant is in no way associated with the outcome of the research conducted."

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

At the time of this review the final chemistry review was not available. The chemistry reviewer is Jane L. Chang, Ph.D.

Calcitriol ointment 3µg/g is a single-phase, white translucent semi-solid product that contains the following:

Table 2: Composition of Calcitriol

Names of Ingredients	Percent Formula (%w/w)	Function
Calcitriol	0.00003	Active ingredient
White petrolatum		
Mineral oil		
Vitamin E		

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Source: Sponsor's NDA, Module 2, Vol. 1.1, 2.3.P.1

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According to the sponsor, an ointment dosage form was selected. The ointment base consists of a mixture of white petrolatum and mineral oil. The concentrations of which were selected to provide [redacted] As stated in the chemistry review, these excipients [redacted]

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As stated in the chemistry review [redacted]

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According to the chemistry reviewer; "The same formulation [redacted] was used for all clinical studies conducted by Galderma. Vitamin E was [redacted] Clinical batches were manufactured at Galderma Industrial Development (DI) in Alby sur Chéran-France [redacted] Galderma Manufacturing facilities in Alby sur Chéran-France [redacted] and [redacted] The drug product for the two Phase 3 pivotal studies (RD.06.SRE.18053 and RD.06.SRE.18054) was manufactured at DI.

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4.2 Clinical Microbiology

This is not applicable since this is not an antimicrobial product.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/ toxicology reviewer states; "The clinical formulation of the drug product and the individual components of the product have been adequately evaluated for safety in nonclinical studies. The database supports the safety of the proposed use of the product." The pharmacology/ toxicology reviewer concludes that the product is approvable with respect to nonclinical concerns.

The pharmacology/ toxicology reviewer suggests the following labeling:

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4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The sponsor has proposed the following labeling:

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The mechanism of action of calcitriol in the treatment of psoriasis is thought to involve inhibition of keratinocyte proliferation. However, the precise mechanism by which calcitriol affects keratinocyte differentiation and proliferation is unknown.

4.4.2 Pharmacodynamics

The sponsor has proposed the following labeling:

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The statements above are not established in _____ and will not appear in labeling.

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

4.4.3 Pharmacokinetics

The pivotal PK/PD study was RD.03.SRE.40005, "Pharmacokinetics and Pharmacodynamics of Calcitriol following twice daily application of Calcitriol 3 µg/g ointment for 3 weeks under conditions of maximal exposure in subjects with psoriasis." This was a multi-center, open label study designed to determine the PK and PD of calcitriol 3 µg/g ointment formulation.

According to the clinical pharmacology reviewer, there was an increase in the mean calcitriol plasma concentrations upon twice-daily application of a maximum dose of calcitriol 3 µg/g ointment (30 g daily) for 21 days in subjects with chronic plaque psoriasis. The geometric mean values of C_{max} increased by approximately 36% and the mean value of $AUC_{(0-12h)}$ increased by 44% over baseline.

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

The sponsor has proposed the following labeling:

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The clinical pharmacology reviewer proposes the following labeling:

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

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5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Table 3: Controlled Clinical Studies in Subjects on Calcitriol Therapy

Study Category	Overview of Study Design	Study ¹
Pivotal Vehicle-controlled Studies	Multi-center, randomized, double-blind, vehicle-controlled, parallel-group with calcitriol ointment 3µg/g BID-8 weeks	RD .06.SRE.18053 (SRE.18053) RD .06.SRE.18054 (SRE.18054)
Other Vehicle-controlled Studies	Single-center, randomized, double-blind, vehicle-controlled, left-right comparative study with calcitriol ointment 3µg/g BID-8 weeks (2-wk run-in, 6-wk treatment)	H.141.5006A/M (5006/AM)
	Multi-center, randomized, double-blind, three parallel-group study: calcitriol ointment 3µg/g ointment (vs.) vehicle (vs.) betamethasone valerate 0.1 % BID-7 weeks (1-wk run-in, 6-wk treatment)	H.141.5009M ² (5009/M)
Active Controlled Studies	Multi-center, randomized, investigator-masked, left-right comparative study with calcitriol ointment 3µg/g (vs.) calcipotriol ointment 50µg/g, BID-6 weeks	RD.03.SRE.2653 (SRE.2653)
	Multi-center, randomized, single-blind, parallel-group with calcitriol ointment 3µg/g (vs.) calcipotriol ointment 50µg/g, BID-12 weeks	RD.03.SRE.2684
	Multi-center, randomized, active comparator-controlled, investigator-blinded, left-right comparative study calcitriol ointment 3µg/g (vs.) calcipotriol ointment 50µg/g BID-6 weeks (after 3 days salicylic acid 10% ointment)	RD.03.SRE.29013
	Multi-center, randomized, double-blind, parallel-group comparative study with calcitriol ointment 3µg/g (vs.) betamethasone dipropionate 0.05% ointment, BID-7 weeks (1-wk run-in, 6-wk treatment)	H.141.901M/C

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Study Category	Overview of Study Design	Study ¹
	Multi-center, randomized, open, parallel-group comparative study with calcitriol ointment 3µg/g BID (vs.) dithranol (0.25% to 2%) cream QD-9 weeks (1-wk run-in, 8-wk treatment)	H.141.902M/C
	Multi-center, randomized, double-blind, parallel-group study with calcitriol ointment 3µg/g (vs.) calcipotriol ointment 50µg/g, BID-9 weeks (1-wk run-in, 8-wk treatment)	H.141.908M/C
Other concentrations	Single-center, randomized, double-blind, vehicle-controlled, left-right comparative study, with calcitriol ointment 15µg/g, QD-10 weeks (2-wk run-in, 6-wk comparative, 2-wk treatment -free)	H.141.5005/M
	Single-center, randomized, double-blind, vehicle-controlled, left-right comparison with calcitriol ointment 15µg/g, BID-8 weeks (2-wk run-in, 6-wk treatment)	H.141.5005/M

¹ Studies H.141 were performed by [redacted] Studies RD were performed by Galderma.

² H.141.5009M is both vehicle and active controlled

Source: Sponsor's NDA, adapted from Table 2, Integrated Summary of Safety, pp.16-17.

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5.2 Review Strategy

The pivotal Phase 3 trials SRE.18053 (US) and SRE (US) were reviewed in detail for safety and efficacy.

The safety review of the sponsor's product will focus on adverse events and systemic safety (laboratory evaluation), and local safety (cutaneous signs and symptoms at application sites in Phase 2 and Phase 3 studies). The safety database consists primarily of the pooled data from the 2 pivotal trials, SRE.18053 (US) and SRE 18054 (US) wherein calcitriol ointment was studied at 3µg/g BID for 8 weeks. This data is used for subgroup analysis. The safety data base also includes supportive data from the other 12 controlled trials. Of these, only one, H.141.908M/C (UK), has the same concentration of active and a very similar dosing regimen (BID for 9 weeks: 1-week run in, 8 weeks of treatment).

The safety database also includes data from the long term safety study, SRE.2663 (INT non-US). This was performed open label, with calcitriol ointment 3µg/g for up to 52 weeks.

Special safety studies are discussed in section 7.4.5 and include:

- a) CG.03.SRE.2598 (FR) repeat insult/21-day cumulative irritancy
- b) RD.03.SRE.2652 (FR) repeat insult/21-day cumulative irritancy

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- c) CG.03.SRE.2600 (UK) cumulative irritancy and cutaneous contact sensitization
- d) CG.03.SRE.2602 (UK) photo-toxicity
- e) CG.03.SRE.2601 (FR) photo-allergy

5.3 Discussion of Individual Studies

Study Design:

The phase 3 pivotal trials performed as part of the clinical development program were of identical design. The protocol review that follows will apply to both studies unless otherwise noted.

Pivotal Phase 3 Studies:

Protocol Number: RD.06.SRE.18053

Protocol Number: RD.06.SRE.18054

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

Study 53 was performed in the United States and had 25 investigators. The first subject was enrolled January 21, 2002 and the last subject completed July 18, 2002.

Table 4: Subject Enrollment by Center Study 18053 (ITT Population)

Analysis Center	Investigator number	Investigator Name	Location	Calcitriol (N=209)	Vehicle (N=209)	Total Subjects enrolled
1	2019	Javier Flores, MD	Miami, FL	13 (6.2%)	13 (6.2%)	26 (6.2%)
2	2028	Alicia Bucko, DO	Albuquerque, NM	13 (6.2%)	12 (5.7%)	25 (6.0%)
3	2029	Bruce Miller, MD	Portland, OR	12 (5.7%)	12 (5.7%)	24 (5.7%)
4	2121	Toivo Rist, MD	Knoxville, TN	12 (5.7%)	12 (5.7%)	24 (5.7%)
5	2066	Eugene Monroe, MD	Milwaukee, WI	11 (5.3%)	10 (4.8%)	21 (5.0%)
6	1170	Debra Breneman, MD	Cincinnati, OH	10 (4.8%)	10 (4.8%)	20 (4.8%)
7	2129	David M. Pariser, MD	Norfolk, VA	10 (4.8%)	10 (4.8%)	20 (4.8%)
8	2069	David L. Kaplan, MD	Overland Park, KS	9 (4.3%)	9 (4.3%)	18 (4.3%)
8	2101	Scott Clark, MD	Longmont, CO	9 (4.3%)	10 (4.8%)	19 (4.5%)
9	2094	Keith Loven, MD	Goodlettsville, TN	8 (3.8%)	9 (4.3%)	17 (4.1%)
9	2124	Steven Feldman, MD	Winston-Salem, NC	9 (4.3%)	9 (4.3%)	18 (4.3%)
10	2106	Karl Boutner, MD	Vallejo, CA	8 (3.8%)	9 (4.3%)	17 (4.1%)
10	2123	Elizabeth Arthur, MD	Rochester, NY	9 (4.3%)	8 (3.8%)	17 (4.1%)
11	2120	Terry Jones, MD	Bryan, TX	8 (3.8%)	8 (3.8%)	16 (3.8%)
11	2127	Jerry Bagel, MD	East Windsor, NJ	8 (3.8%)	8 (3.8%)	16 (3.8%)
12	1086	Jonathan Weiss, MD	Snellville, GA	7 (3.3%)	8 (3.8%)	15 (3.6%)
12	2128	Steven Cohen, MD	New York, NY	8 (3.8%)	8 (3.8%)	16 (3.8%)
13	2045	Adelaide Habert, MD	Houston, TX	8 (3.8%)	7 (3.3%)	15 (3.6%)

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13	2052	David Wilson, MD	Lynchburg, VA	7 (3.3%)	8 (3.8%)	15 (3.6%)
14	429	Leonard Swinyer, MD	Salt Lake City, UT	7 (3.3%)	7 (3.3%)	14 (3.3%)
14	2023	Daniel Stewart, DO	Clinton Township, MI	6 (2.9%)	6 (2.9%)	12 (2.9%)
15	385	Alan, Menter, MD	Dallas, TX	5 (2.4%)	5 (2.4%)	10 (2.4%)
15	439	Michael Jarrat, MD	Austin, TX	5 (2.4%)	4 (1.9%)	9 (2.2%)
15	2084	L Eichenfield, MD	San Diego, CA	1 (0.5%)	1 (0.5%)	2 (0.5%)
15	2149	Linda Stein, MD	Detroit, MI	6 (2.9%)	6 (2.9%)	12 (2.9%)

Source: Sponsor's NDA, 5.3.5.1.1.01, Study Report RD.06.SRE.18053, Text Table 1 pp. 27-30 and Table SUB 1.2, pp. 105-106.

Study 54 was performed in the United States and had 25 investigators. The first subject was enrolled January 19, 2002 and the last subject completed July 2, 2002.

Table 5: Subject Enrollment by Center Study 18054 (ITT Population)

Analysis Center	Investigator number	Investigator Name	Location	Calcitriol (N=210)	Vehicle (N=211)	Total Subjects enrolled
1	2186	Thomas Fleming, MD	Sandusky, OH	16 (7.6%)	16 (7.6%)	32 (7.6%)
2	2038	Jerold Powers, MD	Scottsdale, AZ	16 (7.6%)	15 (7.1%)	31 (7.4%)
3	2185	Arthur Balin, MD	Media, PA	15 (7.1%)	16 (7.6%)	31 (7.4%)
4	2095	Steven Kempers, MD	Fridley, MN	12 (5.7%)	12 (5.7%)	24 (5.7%)
5	2188	J. John Goodman, MD	West Palm Beach, FL	12 (5.7%)	12 (5.7%)	24 (5.7%)
6	2190	Marina Peredo, MD	Smithtown, NY	12 (5.7%)	12 (5.7%)	24 (5.7%)
7	2091	Manuel Morman, MD	Rutherford, NJ	11 (5.2%)	10 (4.7%)	21 (5.0%)
8	2107	Robert Glinert, MD	Madison, WI	10 (4.8%)	9 (4.3%)	19 (4.5%)
8	2153	Harry Sharata, MD	Madison, WI	9 (4.3%)	10 (4.7%)	19 (4.5%)
9	2065	Ronald Savin, MD	New Haven, CT	9 (4.3%)	9 (4.3%)	18 (4.3%)
9	2187	Mitchell Goldman, MD	Encinitas, CA	9 (4.3%)	9 (4.3%)	18 (4.3%)
10	438	David Whiting, MD	Dallas, TX	7 (3.3%)	8 (3.8%)	15 (3.6%)
10	2189	Charles Hudson, MD	Evansville, IN	8 (3.8%)	8 (3.8%)	16 (3.8%)
11	2036	Elyse Rafal, MD	Stony Brook, NY	7 (3.3%)	7 (3.3%)	14 (3.3%)
11	2192	R Swaminathan, MD	Peoria, IL	8 (3.8%)	7 (3.3%)	15 (3.6%)
12	2184	James Aton, MD	Marinez, GA	7 (3.3%)	8 (3.3%)	14 (3.3%)
12	2194	David McDaniel, MD	Virginia Beach, VA	7 (3.3%)	7 (3.3%)	14 (3.3%)
13	2050	Michael Gold, MD	Nashville, TN	6 (2.9%)	6 (2.8%)	12 (2.9%)
13	2183	David Adams, MD	Hershey, PA	6 (2.9%)	7 (3.3%)	13 (3.1%)
14	2103	Joseph Fowler, MD	Louisville, KY	6 (2.9%)	6 (2.9%)	12 (2.9%)
14	2191	Mary Sheehan, MD	Pittsburgh, PA	6 (2.9%)	6 (2.8%)	12 (2.9%)
15	2001	Anne Lucky, MD	Cincinnati, OH	0	1 (0.5%)	1 (0.2%)
15	2063	Dow Stough, MD	Hot Springs, AR	3 (1.4%)	3 (1.4%)	6 (1.4%)
15	2179	Steven Davis, MD	San Antonio, TX	5 (2.4%)	6 (2.8%)	11 (2.6%)
15	2182	Barry Abraham, MD	Philadelphia, PA	3 (1.4%)	2 (0.9%)	5 (1.2%)

Source: Sponsor's NDA, 5.3.5.1.1.02, Study Report RD.06.SRE.18054, Text Table 1 pp. 27-31 and Table SUB 1.2, pp. 106-107.

Objectives Studies 53 and 54:

The objective of these studies was to determine the safety and efficacy of Calcitriol Ointment, 3µg/g versus its vehicle in the treatment of subjects having mild to moderate chronic plaque psoriasis.

Overall Study Design:

These studies were conducted as multi-center, randomized, vehicle-controlled, double-blind, parallel-group comparisons.

Protocol:

The protocol for study 18053 was amended 3 times. The first version of the protocol was dated September 6, 2000.

Protocol amendment 1 was dated November 9, 2001 and included the following significant changes: a) inclusion of women of childbearing potential, while pregnant and lactating women are excluded; b) score 1 of the Global Severity Scale modified to read "minimal" and to include erythema defined as "up to mild (up to light red or pink coloration)".

Protocol amendment 2 was dated September 7, 2001 and included the following significant changes: a) changes in the schedule of laboratory assessments; b) pruritus added as secondary efficacy criterion; c) addition of study visit windows; d) method of contraception clarified in inclusion criterion #2.

Protocol amendment 3 was dated November 28, 2001 and included the following significant changes: a) change in approximate number of enrolled subjects at each site from 25 to 16; b) change number of study sites 16 to 25; c) addition of exclusion criterion (subjects taking thiazide diuretics required a two-week washout period) and clarification of exclusion criterion # 4; d) addition of screening visit at selected centers collecting blood samples.

The protocol for study 18054 was amended 3 times. The first version of the protocol was dated September 6, 2000. The first amendment was dated November 9, 2000, the second amendment was dated September 7, 2001, and third amendment (final version) was dated December 3, 2001. The content of the protocol amendments was similar to those listed above for study 18053.

Inclusion Criteria:

- 1) Male or female, 12 years of age or older (only centers selected to perform laboratory assessments and photographs will be permitted to enroll subjects between the ages of 12 and 17).
- 2) If female subjects are of childbearing potential, documented means of effective birth control (abstinence, implanted contraceptives, injectable contraceptives, oral contraceptives [must have been on a stable dose for 6 months prior to study entry], intrauterine contraceptive devices, bilateral tubal ligation or has a vasectomized partner), and a negative pregnancy test is required.
- 3) Subjects with a diagnosis of stable mild to moderate chronic plaque psoriasis (global severity score equal to 2-3) and \leq 35% of the body surface involved.

- 4) Subjects with at least 2 target lesions of 10 cm² with one on a bony area and one on a non-bony area.
- 5) Subjects 18 years and older must sign the approved informed consent form prior to any participation in the study. Subject under the age of 18 may sign an assent to participate form, but must also have a parent or guardian sign the informed consent form prior to receiving any study treatment.
- 6) Subjects willing and capable of co-operating to the extent and degree required by the protocol.

Exclusion Criteria:

- 1) Subjects with a history or ongoing physical or psychiatric condition, which in the investigator's opinion may put the subject at risk, may confound the study assessments, or may interfere with the subject's participation in the study
- 2) Subjects who are pregnant or lactating
- 3) Subjects with acute guttate or pustular psoriasis, erythrodermic psoriasis or rapidly progressing unstable psoriasis
- 4) Subjects with history of hypercalcemia, severe hepatic or biliary disease, renal dysfunction or calcium-based calculi
- 5) Subjects who used any of the following topical treatments within the given washout period:
 - Corticosteroids 2 weeks
 - Anthralin 2 weeks
 - Other preparations containing coal tar, salicylic acid, 2 weeks
 - Vitamin D derivatives 2 weeks
 - UV-light therapy including sunbathing 2 weeks
 - Retinoids 2 weeks
- 6) Subjects who used any of the following systemic treatments within the given washout period:
 - Corticosteroids or ACTH analogs 4 weeks
 - Retinoids such as acitretin or isotretinoin 12 weeks
 - Cyclosporin, interferon, methotrexate or other immunomodulating drugs 8 weeks
 - PUVA therapy 8 weeks
 - Homeopathic and herbal preparations 4 weeks
- 7) Subjects with a treatment known to worsen psoriasis (such as lithium, beta-blockers, iodides, ACE inhibitors, and indomethacin) will require a 2 week wash-out period unless they have been on the medication for 6 months and are considered stable.
- 8) Subjects with concomitant medical or dermatological disorder(s), which might preclude accurate evaluation of the psoriasis
- 9) Subjects taking thiazide diuretics require a 2 week wash-out period.
- 10) Subjects with underlying systemic or other dermatological conditions that require the use of systemic supplements of calcium or vitamin D: Subjects are not to exceed the US Recommended Daily Allowance for Calcium (1,000mg) or Vitamin D (400IU).
- 11) Subjects likely to receive excessive sun exposure during the study (e.g. sunbathing, tanning salon use, etc.).
- 12) Subjects with known sensitivities to any of the study preparations.

13) Subjects who have participated in a clinical drug or device research study within the last 60 days.

Concomitant Medications/Allowed therapy:

All medications listed in the exclusion criteria were prohibited during the study. No other topical treatments, other than the test materials were permitted on the psoriatic lesions. Emollients on healthy skin areas were permitted during the course of the study. Subjects with scalp psoriasis were allowed to use shampoos containing ketoconazole, salicylic acid, sulfur, selenium, tar, or zinc pyrithione.

Withdrawal Criteria:

- 1) Subject's request
- 2) Pregnancy
- 3) Investigator's request, especially when there was a safety concern (e.g. severe adverse reactions or unauthorized concomitant therapy)
- 4) Major protocol violation, as determined by the investigator
- 5) Subject lost to follow-up

Blinding:

This study was considered double-blinded. According to the sponsor, prior to initiation of the study, test materials were determined to be indistinguishable as demonstrated by a visual testing procedure comparing the external appearance of the test materials and the test material packaging. The sponsor states that no obvious differential effects are known which could enable the Investigator or the subject to distinguish between the test materials.

Study Procedures:

A total of 418 subjects were enrolled in study 18053 and 421 in study 18054. Qualified subjects were randomized (1:1) to receive either calcitriol 3µg/g ointment or its vehicle for a period of 8 weeks. Subjects applied the treatment twice daily, once in the morning and once in the evening. Test material was applied on all psoriatic lesions not to exceed 35% body surface area (BSA). Total dosage of test materials was not to exceed 30g/day. Subjects were instructed to avoid any contact of study drug with the eyes, lips, and facial skin "because this might cause irritation." Subjects were further told: "In the case of contact, rinse thoroughly with water." Subjects were also instructed to wash hands thoroughly after use.

Subjects were evaluated at baseline and Weeks 2 (day 14 ± 2 days), 4 (day 28 ± 2 days), 6 (day 42 ± 2 days), and 8 (day 56 ± 2 days). At visits, Weeks 2, 4, 6, and 8, target lesions and global severity of disease were assessed. The BSA (Body Surface Area Involved by Psoriasis) involved was recorded using the "rule of nines": head (9%), two arms (18%), two legs (36%), trunk (36%), genitalia (1%).

In selected centers, standard photographs of the subjects were taken at baseline and week 8. Two target lesions were chosen, photographed and followed throughout the study. A standard procedure was presented in Appendix 13.3 of the protocol.

Table 6: Study Flow Chart

PROCEDURES	Screening ⁶	Week 0/ Baseline ⁷	Week 2	Week 4	Week 6	Week 8/ Early Term
Inclusion / exclusion criteria	X	X ⁸				
Informed consent	X					
Previous therapy	X					
Medical History	X					
Demographic data	X					
Physical examination ²	X					X
Urine Pregnancy test - child bearing potential	X					X
Record total Body Surface Area %		X	X	X	X	X
Calcium Homeostasis ³	X		X	X	X	X
Hematology and Chemistry ³	X			X		X
PTH ³	X		X	X	X	X
24-hour urine collection (urinalysis) ³			X	X	X	X
Calcitriol (Plasma level) ³	X		X			X
Identify and Assess 2 Target Lesions	X (identify only)	X	X	X	X	X
Clinical Disease Evaluation (Global Severity, Erythema, Plaque Elevation, Scaling, Pruritus)		X	X	X	X	X
Medication Dispensed, Returned and Compliance ⁴		D ¹	D/R/C	D/R/C	D/R/C	R/C
Concomitant therapy	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Global Improvement by the physician						X
Subject's Global Assessment of Improvement						X
Photographs (for scientific purpose) ⁵		X				X
Exit Report ⁵						X

¹ For centers performing laboratory evaluations, study medication was dispensed within 5 days after labs were drawn

² Review of basic systems

³ Only in selected centers

⁴ Drug amounts not to exceed 30g per day: First application to be made under the supervision of the Investigator or designee

⁵ Or at any time in case of premature termination

⁶ Centers performing laboratory testing will have a Baseline visit within 5 days of the Screening visit.

⁷ For non-lab centers the Baseline/Week 0 Visit should occur on the same day as the Screening visit.

⁸ Reconfirm that subject continues to meet inclusion/exclusion criteria

Efficacy Measurements:

Global Severity and pruritus evaluations were to be performed at all visits on all treated areas. Erythema, plaque elevation, scaling and a Dermatologic Sum Score (DSS = sum of plaque elevation, erythema, and scaling) were evaluated on 2 target lesions at all visits.

One target lesion was designated on a non-bony area and the other on a bony area (knee, elbow or sacrum). A Global Assessment of Improvement was performed by both the investigator and subjects at the final visit.

Primary Efficacy Measurement:

Global Severity (as evaluated on all treated areas)

Global severity (lesion severity) was evaluated at baseline and Weeks 2, 4, 6 and 8 on a 0 to 5 point scale. The following definitions were used to score global severity:

0	Clear	Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale) Erythema = \pm (hyperpigmentation, pigmented macules, diffuse faint pink or red coloration)
1	Minimal	Plaque elevation = \pm (possible but difficult to ascertain whether there is slight elevation above normal skin) Scaling = \pm (surface dryness with some white coloration) Erythema = up to mild (up to light red or pink coloration)
2	Mild	Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (coarse scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (coarse, non-tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)
5	Very Severe	Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)

In the above scale the category "clear" is not clear for erythema and could lead to the overstatement of efficacy. The following could be erroneously included in efficacy; subjects

who started as 2 or "mild" and then after treatment being graded as 0 or "clear" although they were not clear for erythema. Please see section 6.1.7 for further discussion regarding this issue. It is also noted that category descriptors for scaling and erythema that are not clinically distinct for all categories. This scale was examined in a Phase 3 protocol review signed out December 9, 2001.

Secondary Efficacy Measurements: Erythema, Scaling, Plaque Elevation

Erythema defined as abnormal redness of skin was evaluated at Baseline and at Weeks 2, 4, 6, and 8 on a 0 to 4 scale. The following definitions were used to score erythema:

0	None	No detectable erythema. Skin of normal color
1	Mild	Slight pinkness present
2	Moderate	Definite redness, easily recognized
3	Severe	Intense redness
4	Very Severe	Very intense redness

Scaling defined as abnormal shedding of epidermal stratum corneum material was evaluated at Baseline and at Weeks 2, 4, 6, and 8 on a 0 to 4 scale. The following definitions were used to score scaling:

0	None	No shedding
1	Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing
2	Moderate	Obvious but not profuse shedding
3	Severe	Heavy scale production
4	Very Severe	Very thick scales

Plaque elevation defined as abnormal thickness of the psoriasis lesion was evaluated at Baseline and at Weeks 2, 4, 6, and 8 on a 0 to 4 scale. The following definitions were used to score plaque elevation:

0	None	Normal skin thickness: No elevation of skin
1	Mild	Barely perceptible elevation (by touching) of the psoriasis plaques
2	Moderate	Obvious elevation above the normal skin level; moderate thickening
3	Severe	Definite thick elevation above normal skin level
4	Very Severe	Very thick elevation

Erythema, scaling, and plaque elevation were assessed on bony and non-bony areas.

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(It is noted that bony areas, usually located on knees, elbows, and sacrum, when affected by psoriasis can be more difficult to treat than non-bony areas.)

The Dermatologic Sum Score is the sum of plaque elevation, erythema, and scaling scores as evaluated on a bony and a non-bony area.

Pruritus defined as an itching sensation was evaluated at Baseline and at Weeks 2, 4, 6, and 8 on a 0 to 4 scale. The following definitions were used to score pruritus:

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

Global Assessment of Improvement Measured by Physician: (as evaluated on all treated areas).
 A global assessment of improvement was performed by the investigator at the end of the study compared to baseline, using the scale below:

Global Improvement		Investigator's Global Assessment of Improvement From Baseline
5	Clear	All signs and symptoms of disease have resolved (100% improvement from baseline)
4	Almost Clear	All signs and symptoms almost cleared (90% from baseline). Only minimal residual signs and symptoms remain
3	Marked Improvement	Majority of the signs and symptoms have resolved (about 75% improvement from baseline)
2	Moderate Improvement	Significant improvement, but many signs and symptoms remain (about 50% improvement from baseline)
1	Minimal Improvement	Slight overall improvement, but not clinically significant (about 25% improvement from baseline)
0	No Change	Overall severity similar to baseline
-1	Worse	Worse than baseline

Appears This Way
 On Original

Global Assessment of Improvement Measured by Subject

At the final visit, the Investigator asked each subject to assess his/her improvement as compared to Baseline on all treated areas using the scale below:

Global Improvement	Subject's Global Assessment of Improvement
5 Clear	All signs and symptoms of disease have resolved
4 Almost Clear	All signs and symptoms almost cleared
3 Marked Improvement	Majority of the signs and symptoms have resolved
2 Moderate Improvement	Significant improvement, but many signs and symptoms remain
1 Minimal Improvement	Slight overall improvement, but not clinically significant
0 No Change	Overall severity similar to baseline
-1 Worse	Worse than baseline

Efficacy Assessment:

The primary variable was success rate at Week 8 Endpoint. Success is defined as a subject with a Global Severity Score of 0 (clear) or 1 (minimal). Success rates at other post-baseline time points were analyzed as supporting information.

The secondary efficacy variables were the following measurements:

- Global Severity Score (full scale)
- Erythema, plaque elevation, scaling and DSS on the targeted non-bony area (stats: bony vs non-bony not meaningful)
- Erythema, plaque elevation, scaling and DSS on the targeted bony area
- Pruritus on all treated areas
- Global Assessment of Improvement by the physician at final visit
- Global Assessment of Improvement by the subject at final visit

Safety Assessment:

Safety was assessed by monitoring the frequency and severity of adverse events and through monitoring of laboratory measurements.

Any pregnancy occurring during the clinical trials where the fetus could have been exposed to the investigational drug was to have been followed-up until outcome. In the case of a pregnancy in a clinical trial subject the Investigator was to follow a specified procedure as defined in the study protocol.

Laboratory Measurements:

The following laboratory parameters were assessed at selected centers only:

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- Serum calcium homeostasis parameters at Screening, and Weeks 2, 4, 6, and 8: serum total calcium, total alkaline phosphatase, albumin, albumin-adjusted serum total calcium (calculated), urea, creatinine and phosphorus.
- PTH levels at Screening and Weeks 2, 4, 6, and 8; Calcitriol plasma levels at Screening and Weeks 2 and 8
- Hematology (Hct, Hgb, RBC, WBC, Differential, Platelets) and clinical serum chemistry (protein, albumin, ALT (SGPT), AST (SGOT), lactic dehydrogenase, urea nitrogen, uric acid, glucose, sodium, potassium, chloride, cholesterol, triglycerides, total bilirubin) at Screening and at Weeks 4 and 8.
- Urinalysis on the 24-hour urine samples at Weeks 2, 4, 6, and 8: Calcium, phosphorus, creatinine, creatinine clearance, and urinary calcium/creatinine ratio.

In a review of the protocol RD.06.SPR.18053, dated 12/9/01, the clinical reviewer states:

The Sponsor agreed to perform all laboratory parameters on all subjects (Sponsor fax of April 2, 2001). However, with submission of this protocol, the Sponsor proposes an alternative plan: calcium homeostasis only on 100 subjects (50 treated with their drug, 50 treated with vehicle), across four to five centers. Specifically, the following parameters will be monitored: serum calcium, albumin, creatinine, parathyroid hormone (PTH), and 24-hour urine calcium levels (urinalysis), will be measured at each visit (baseline, weeks 2,4,6,8, and any unscheduled visits). Additionally, hematologies and serum chemistries will be performed at baseline, and at weeks 4 and 8 across four to five centers. The Sponsor bases this proposal on their review of safety data submitted in the original IND and amendments to it.

The sponsor was reminded that it had agreed to perform all laboratory parameters on all subjects. This comment was faxed to the sponsor on December 27, 2001.

Laboratory Results:

For all parameters analyzed, the reference ranges of the central laboratory were used. In the event of unexplained or unexpected laboratory test value abnormalities, a new blood sample had to be taken within one week and all tests repeated and followed-up until the results returned to reference range and/or an adequate explanation for the abnormality was found. The Investigator clearly marked on the laboratory report all laboratory values that were assessed as clinically significant and gave comments on the report. An AE form was to be completed in the case of a clinically significant biological variation. If the clinically significant abnormal value persisted, the Investigator could decide to discontinue the subject for safety reasons.

Calcium Alert Level:

Hypercalcemia was defined as an albumin-adjusted serum total calcium concentration above the upper limit of the reference range for this variable.

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The calcium alert level was defined as 10% above the upper limit of the reference range. In such a case, an adverse event form should have been filled in, a new blood sample taken within one week and all tests repeated. If the calcium level of the repeated blood sample was still over the alert level, the decision to discontinue subject from the study was made at the discretion of the Investigator; if in his/her opinion the abnormality was related to the administration of the study medication. The subject was to be followed-up with additional blood samples taken until the serum calcium level had returned to reference range and/or an adequate explanation for the abnormality was found.

If the calcium level of the repeated blood sample returns below the alert level, the subject was allowed to continue the study.

Albumin-Adjusted Serum Total Calcium:

Albumin-adjusted serum total calcium was calculated at each visit where a blood sample was taken and at Endpoint (at week 8 or before in case of treatment discontinuation).

The serum total calcium concentration is a combined variable of active ionized calcium and inactive protein-bound (mainly to albumin) calcium. To be able to judge whether changes in serum total calcium are not due to changes in the fraction of inactive albumin-bound calcium but due to changes in the fraction of active ionized calcium, the following formula was used to adjust serum total calcium concentrations for changes in serum albumin concentrations:

Albumin adjusted serum total calcium (mmol/l) =
serum total calcium measured (mg/dL) + (4.5 - serum albumin g/dL) x 0.8

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

In a review of the protocol RD.06.SPR.18053, dated 12/9/01, the clinical reviewer states:

In their April 2nd fax, the Sponsor committed to direct measurement of serum free calcium levels on all subjects, at all visits. However, the submitted protocol does not provide for this specific measurement. On p. 42 of the "Summary of Safety Information," the Sponsor states that, "Albumin-adjusted serum calcium is the most accurate measure in determining disturbances in calcium homeostasis." The Sponsor provides no reference for this statement. It is unclear why the protocol does not include direct measurement of serum free calcium, as was the Sponsor's agreement.

The sponsor was reminded that it had committed to direct measurements of serum free calcium levels on all subjects, at all visits (Sponsor fax of April 2, 2001). This comment was faxed to the sponsor on December 27, 2001.

Open-Label 52 Week Safety Study:
Protocol Number: RD.03.SPR.2663.R01

Title: "Multicentre, open-label, non comparative long term safety study to assess the local and systemic safety of calcitriol 3µg/g ointment applied twice daily up to 52 weeks in subjects suffering from mild to moderate chronic plaque psoriasis."

Study RD.03.SPR.2663, hereinafter referred to as study 2663, was conducted in 30 centers; 8 in France, 6 in Germany, 5 in Hungary, 5 in Belgium, and 6 in Poland. The first subject was enrolled September 13, 2001 and the last subject completed March 18, 2003.

Objectives of Study 2663:

The objectives were to assess the local and systemic safety of calcitriol 3µg/g ointment applied twice daily, morning and evening up to 52 weeks, in subjects suffering from mild to moderate chronic plaque psoriasis. This was measured by the assessment of laboratory parameters and evaluation of reported adverse events over the study period.

Overall study design:

Study 2663 was a multicenter, non-comparative, open-label study.

Initially the treatment period planned was 26 weeks; however the protocol was amended to allow treatment duration up to 52 weeks. As stated by the sponsor study termination at the week 26 and 52 visits was considered as 'normal completion.'

Subjects were male or female aged 12 (except German centers where the minimum age was 18 years) or older having mild to moderate chronic plaque psoriasis with up to 35% body surface area involvement.

The treatment period was preceded by a screening period to prevent inclusion of subjects with abnormal laboratory parameters. Study visits occurred every 6 weeks up to 18 weeks and every 8 or 9 weeks to 52 weeks. Subjects applied calcitriol 3µg/g ointment twice daily, morning and evening. Subjects whose psoriatic lesions cleared before the end of the study were allowed to discontinue study drug application. For subjects showing a score of 1, with mutual agreement between the subject and the investigator, study drug application may have been continued if the subject wished to continue in the study. Psoriatic lesion clearance was defined as a global severity score of 0 (clear) or 1 (minimal). The global severity scale was the same as that used in the pivotal trials, 18053 and 18054. Efficacy was also evaluated by Global Assessment of Improvement (self assessment).

If subjects discontinued study drug application, they were contacted by phone on a monthly basis until completion of the 52-week study period. If clearance occurred between two study visits,

the investigator was to conduct an unscheduled visit to confirm the clearance and ask the subject to discontinue study drug application.

If the investigator assessed relapse after study drug discontinuation, during the clearance period, the subject was to return to the site for an unscheduled study visit and restart study drug application until completion of the 26 or 52 week study period. If relapse occurred less than 6 week before the end of the 26 or 52 week study period, the subject was to be discontinued.

Safety was assessed by recording spontaneous adverse events at each study visit and by monitoring laboratory parameters.

Laboratory parameters included the following:

Biochemistry:

Plasma: albumin adjusted serum total calcium, total calcium, alkaline phosphatase, lactate dehydrogenase, total protein, albumin, urea, creatinine, phosphorus, AST, ALT, total bilirubin, direct bilirubin, cholesterol, triglycerides, glucose, uric acid, sodium, potassium, chloride

Urine: 24h-urine calcium, phosphorus, creatinine, and creatinine clearance

Hematology:

Hematocrit, hemoglobin, Red Blood Cells, White Blood Cells, differential count, platelets

Hormonal Assay:

Calcitriol plasma level determination

Parathormone plasma level determination

Number of subjects: A total of 300 subjects were planned and 324 subjects were enrolled.

233 subjects completed at least 180 days

103 (31.8%) subjects discontinued the study at Week 26

116 subjects completed at least 360 days

136 (42%) subjects completed the Week 52 study visit (the Week 52 visit for 20 subjects occurred before 360 days)

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. All 324 subjects were included in the All Patients Treated (APT) population. For the APT population at baseline, the mean Body Surface Area (BSA) was 16.1 % and the mean Global severity score was 3.2 (on a scale of 0 to 5). At Baseline, 71 (21.9%) of subjects had 25-35% BSA involvement.

To aid in data analysis, the study was divided into 4 even intervals, 90 days each, and defined as periods 1 to 4.

- 1) 324 subjects entered period 1 (day 1-90)
- 2) 285 subjects entered period 2 (days 91-180)
- 3) 233 subjects entered period 3 (days 181-270)
- 4) 140 subjects entered period 4 (days 271-360)

Table 7: Subject Disposition Study 2663

Disposition	Period 1 (1-90 days) N = 324 n (%)	Period 2 (91-180 days) N = 285 n (%)	Period 3 (181-270 days) N = 233 n (%)	Period 4 ≥271 days N = 140 n (%)	All periods N = 324 n (%)
Subjects at period start	324 (100 %)	285 (100%)	233 (100%)	140 (100 %)	324 (100 %)
Completed the 52-week study	NA	NA	NA	136 (97.1%)	136 (42.0%)
Discontinued during study period	39 (12.0 %)	52 (18.2 %)	93 (39.9 %)	4(2.9%)	188 (58.0%)
Discontinued at Week 26(*)	NA	26 (9.1 %)	77 (33.0 %)	NA	103 (31.8%)
Subject request	19 (5.9 %)	17 (6.0 %)	10 (4.3%)	1 (0.7%)	47 (14.5%)
Lost to follow-up	7 (2.2%)	3 (1.1 %)	4 (1.7%)	1 (0.7 %)	15 (4.6%)
Lack of efficacy	7 (2.2) %	5 (1.8 %)	1 (0.4 %)	0	13 (4.0)%
Adverse event	4 (1.2)%	1 (0.4) %	1(0.4)%	2 (1.4)%	8 (2.5%)
Protocol violation	1 (0.3 %)	0	0	0	1 (0.3%)
Pregnancy	1 0.3%)	0	0	0	1 (0.3%)

(*) The study was initially planned for 26 weeks and the protocol was revised to 52 weeks. Subjects had an option to extend their participation to 52 weeks but some decided to stop at Week 26.

Source: Sponsor's NDA, 5.3.5.2.07.Study Report RD.03.SRE.2663 p. 57.

The most common reason for subject discontinuation was 'subject request' 47(14.5%). The next most common reasons were lost to follow-up 15 (4.6%) and lack of efficacy 13 (4%). A total of 8 subjects (2.5%) discontinued due to adverse events.

The sponsor states that compliance was not calculated as planned since the dates of start and end of treatment application, obtained from subjects, were not considered reliable enough to be used for analysis. The sponsor explains that this was partly due to the extension of the study period from 26 to 52 weeks since some subjects stopped treatment before commencing the extension period. The sponsor states that Investigator/study site personnel were to check on compliance through questioning and examination of study medication at each post-baseline visit.

Tubes of product that were returned were weighed. The sponsor created an adjusted mean estimate of total quantity of product used by assuming that all non-returned tubes were used in the same way as returned tubes. The adjusted mean estimate of total quantity of product used was 1366 grams over the study period. The adjusted men daily use was 5.76 grams. The minimum adjusted daily quantity of product used was 0 and the maximum was 38.35 grams.

Adverse events for Study 2663 are reviewed in section 7, Review of Safety.

6 Review of Efficacy

Efficacy Summary

Pivotal Phase 3 trials 18053 and 18954 were multi-center, randomized, double-blind, vehicle controlled, parallel group comparisons. These trials were of adequate design and sufficiently powered to study the safety and efficacy of Tradename calcitriol ointment 3µg/g at a dose of twice daily for two weeks in subjects with mild to moderate plaque psoriasis.

A majority of the subjects exposed to calcitriol were Caucasian (89%) with a mean age of 47.4 years. These characteristics were balanced across the treatment groups. Of those exposed to calcitriol 68% were male and 32% were female. Of those exposed to vehicle 59% were male and 41 % were female. Assessment of baseline disease severity reveals that the majority of subjects of subjects enrolled had an IGA of moderate balanced across treatment arms.

The primary endpoint was defined as the proportion of subjects with an IGA (Investigator Global Assessment) score of 'clear' or 'minimal' at week 8. In study 18053, ITT population, calcitriol ointment showed statistical superiority over vehicle (34.4% versus 22.5% with a p value of .0047). In study 18054, ITT population, calcitriol also showed statistical superiority over vehicle (33.3% versus 12.3% with a p value of <.001). Analysis of the per protocol population reveals similar treatment effects.

It is noted that the response rate to vehicle in study 18053 (22.5%) is higher than that in study 18054 (12.3%). The FDA biostatistician performed an analysis of efficacy by US region, West, South, Midwest, and Northeast. When response rates were examined, within the same regions, the response rates for vehicle were generally higher in study 18053. The biostatistician concluded that this analysis was not able to explain the differences in response rates for vehicle in study 18053 versus 18054.

The FDA biostatistician has performed sensitivity analyses with success defined as the proportion of subjects having a two grade improvement in IGA. Using this definition, calcitriol showed statistical superiority over vehicle in both studies, although treatment effects are smaller. For labeling it is preferable to use results wherein IGA success is defined as the proportion of ITT subjects having a two grade improvement. This ensures that successes are clinically meaningful.

In both pivotal studies results for the primary endpoint were examined in the subpopulations; gender, race, and age. Response rates to calcitriol by gender were similar in study 18053 (male 34% versus female 34%) however the response rate of females to vehicle (31%) was higher than that for males (18%) In study 18054 response rates to calcitriol were higher for males (38%) versus female (25%). Response rates for vehicle were lower (9%) for males than for females (16%). The majority of subjects enrolled were Caucasian. Definitive conclusions regarding comparative response rates in non-Caucasians are precluded due to small numbers. The majority of subjects enrolled were in the 18 to 64 year old age group and response rates for this

age group (approximately 31%) were similar in both studies, however the vehicle response rate for this age group was higher in study 18053.

6.1.1 Indication

The proposed indication is the topical treatment of plaque psoriasis in adults age 18 and older.

6.1.2 Methods

The efficacy evaluation will focus upon a detailed review of pivotal trials SRE.180.53 (Study 53) and SRE 18054 (study 54).

6.1.3 Demographics

Table 8: Demographics by Treatment (Study 18053 and 18054)

	Study 18053		Study 18054	
	Calcitriol (N = 209)	Vehicle (N = 209)	Calcitriol (N = 210)	Vehicle (N = 211)
Age (mean ± SD)	46.9 ± 13.9	47.3 ± 13.9	48.0 ± 15.3	49.1 ± 14.1
Gender : Female	30% (62)	37% (78)	35% (73)	45% (94)
Race : Caucasian	84% (175)	84% (175)	94% (197)	95% (201)
Black	3% (6)	2% (5)	1% (2)	1% (2)
Asian	1% (2)	1% (3)	1% (3)	0% (1)
Hispanic	11% (24)	11% (24)	4% (8)	2% (5)
Other	1% (2)	1% (2)	0% (0)	1% (2)

Numbers after percents are frequencies.

Source: Adapted from analysis by biostatistician, Mat Soukup, Ph.D.: Statistical Review and Evaluation, Appendix A.1, Table 12.

A majority of the subjects exposed to calcitriol were Caucasian (89%) with a mean age of 47.4 years. These characteristics were balanced across the treatment groups. Of those exposed to calcitriol 68% were male and 32% were female. Of those exposed to vehicle 59% were male and 41 % were female.

Assessment of baseline severity of disease reveals that the majority of subjects of subjects enrolled had an IGA of moderate balanced across treatment arms. Baseline % BSA involvement was balanced across treatment arms in both studies 18053 and 18054.

Table 9: Baseline Severity of Disease by Treatment (Study 18053 and 18054)

	Study 18053		Study 18054	
	Calcitriol (N = 209)	Vehicle (N = 209)	Calcitriol (N = 210)	Vehicle (N = 211)
Total Body Surface Area Involved % (mean ± SD)	9.5 ± 7.46	9.5 ± 7.23	11.0 ± 8.0	12.1 ± 9.11
Global Severity :				
Mild	19% (39)	19% (40)	31% (66)	26% (55)
Moderate	81% (169)	81% (169)	69% (144)	74% (156)
Severe	0% (1)	0% (0)	0% (0)	0% (0)

Numbers after percents are frequencies.

[†]Mean score of the score from bony and non-bony areas

Source: Adapted from analysis by biostatistician, Mat Soukup, Ph.D.: Statistical Review and Evaluation, Appendix A.2, Table 13.

Other aspects of baseline disease severity; erythema, pruritus, scaling, and plaque elevation were also balanced across treatment groups with the majority of subjects scored as moderate.

6.1.4 Patient Disposition

Table 10: Subject Disposition Study 18053

Disposition	Calcitriol Ointment, 3µg/g (N =209)		Vehicle Ointment (N =209)	
	n	(%)	n	(%)
Enrolled	209	100%	209	100%
ITT population	209	100%	209	100%
Safety population	209	100%	209	100%
PP population	188	90.0%	179	85.6%
Completed study	185	88.5%	178	85.2%
Discontinued	24	11.5%	31	14.8%
Adverse event	1	0.5%	6	2.9%
Subject request	12	5.7%	13	6.2%
Protocol violation	4	1.9%	3	1.4%
Lost to follow-up	6	2.9%	8	3.8%
Other	1	0.5%	1	0.5%

Source: Sponsor's NDA, Study report RD.06.SRE.18053, adapted from Text Table 8, p. 65

Table 11: Subject Disposition Study 18054

Disposition	Calcitriol Ointment, 3µg/g (N=210)		Vehicle Ointment (N=211)	
	n	(%)	n	(%)
Enrolled	210	100%	211	100%
ITT population	210	100%	211	100%
Safety population	210	100%	211	100%
PP population	185	88.1%	176	83.4%
Completed study	187	89.0%	181	85.8%
Discontinued	23	11.0%	30	14.2%
Adverse event	6	2.9%	5	2.4%
Subject request	8	3.8%	20	9.5%
Protocol violation	0	0%	0	0%
Lost to follow-up	9	4.3%	4	1.9%
Pregnancy	0	0%	1	0.5%

Source: Sponsor's NDA, Study report RD.06.SRE.18054, adapted from Text Table 8, p. 66

For both studies 18053 and 18054, approximately 89% of subjects in the calcitriol arms and 85 to 86% of subjects in the vehicle arms completed the studies. Also similar for both studies was the number of subjects who discontinued, roughly 11% of those randomized to calcitriol and 14 to 15% of those randomized to vehicle. Subject request was the most common reason for subject withdrawal for both studies in both calcitriol and vehicle arms. Subject request was not further discussed in the study reports. Withdrawals due to adverse events were .5% (study 18053) and 2.9% (study 18054) for those randomized to calcitriol. For those randomized to vehicle, withdrawals due to adverse events were 2.9% (study 18053) and 2.4% (study 18054). Withdrawals/Discontinuations due to adverse events are discussed further in the review of safety, section 7.3.3.

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Protocol Violations:

Table 12: Protocol Violations: Combined Studies

Major Protocol Violation	Studies 18053 and 18054			
	Calcitriol Ointment 3µg/g N=419		Vehicle Ointment N=420	
	n	(%)	n	(%)
Entrance Criteria Violation	13	3.1%	13	3.1%
Insufficient Treatment ^a	15	3.6%	25	6%
No Post-baseline Data ^b	6	1.4%	10	2.4%
Non-compliance ^c	3	.7%	11	2.6%
Prohibited Medication	9	2.1%	6	1.4%
Total	46	10.1%	65	15.4%

^a Subjects whose treatment duration was less than 28 days (50% of scheduled treatment days)

^b Subjects who dropped out prior to the Week 2 visit or did not have any post-Baseline data.

^c Subjects who missed doses completely for five or more consecutive days while participating in the study or completely/partially stopped medication more than three days immediately prior to the final efficacy assessment.

Source: Based on Sponsor's NDA, Study Reports RD.06.SRE.18053 and RD.06.SRE.18054, adapted from Text Tables 9, pp. 67 and 68 respectively.

Across both studies more subjects were excluded from the Per Protocol population (PP) in the vehicle arms (15.4%) than in the active arms (10.1%). More subjects were withdrawn from the vehicle arms for insufficient treatment, no post-baseline data, and non-compliance.

6.1.5 Analysis of Primary Endpoint(s)

The primary endpoint was defined as the proportion of subjects with an IGA (Investigator Global Assessment) score of 'clear' or 'minimal' at week 8. The analysis follows for the ITT population.

Table 13: Investigator Global Results: ITT

Treatment	Study 18053		Study 18054	
	Calcitriol	Vehicle	Calcitriol	Vehicle
N	209	209	210	211
Success (%)	72 (34.4%)	47 (22.5%)	70 (33.3%)	26 (12.3%)
p-value†	-	.0047	-	<.001

† p-values are based on CMH stratified by pooled site.

Source: Sponsor's NDA, Study Reports RD.06.SRE.18053 and RD.06.SRE.18054, adapted from Text Tables 13, pp. 73 and 74 respectively.

Calcitriol ointment showed statistical superiority in both studies.

The FDA biostatistician has reproduced the results obtained by the sponsor. The treatment effect for study 18053 is 11.9% and that for study 18054 is 20%. It is noted that the response to the active calcitriol ointment is similar across both studies but the response to the vehicle ointment is 22.5% in study 18053 and 12.3% in study 18054.

Since subjects could enter these studies with investigator global assessment (IGA) scores of 2 to 3 (mild to moderate disease) the primary endpoint as defined above allows subjects to be counted as treatment successes while experiencing only a one grade improvement in IGA.

When the primary endpoint is analyzed in the Per Protocol (PP) similar results are seen.

Table 14: Investigator Global Results: PP

Treatment	Study 18053		Study 18054	
	Calcitriol	Vehicle	Calcitriol	Vehicle
N	188	179	185	176
Success (%)	69 (36.7%)	43 (24.0%)	67 (36.2%)	24 (13.6%)
p-value†	-	.0048	-	< .001

† p-values are based on CMH stratified by pooled site.

Source: Statistical Review and Evaluation by Mat Soukup, Ph.D., Table 7, p. 13.

6.1.6 Analysis of Secondary Endpoints

The sponsor lists secondary efficacy variables as the following measurements:

- Global Severity Score (full scale-not dichotomized)
- Erythema, plaque elevation, scaling and DSS on a target lesion on a non-bony area
- Erythema, plaque elevation, scaling and DSS on a target lesion on a bony area
- Pruritus on all treated areas
- Global Assessment of Improvement by the physician at final visit
- Global Assessment of Improvement by the subject at final visit

These were not considered for inclusion in labeling and will not be discussed further.

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6.1.7 Other Endpoints

A) Sensitivity analyses were performed by the FDA biostatistician employing IGA success defined as the proportion of subjects with a two grade improvement by week 8, both for the ITT and the PP.

Table 15: Investigator Global Results (Two Grade Improvement): ITT

Treatment	Study 18053		Study 18054	
	Calcitriol	Vehicle	Calcitriol	Vehicle
N	209	209	210	211
Success (%)	9 (23.4%)	30 (14.4%)	43 (20.5%)	14 (6.6%)
p-value†	-	.0142	-	< .001

† p-values are based on CMH stratified by pooled site.

Source: Statistical Review and Evaluation by Mat Soukup, Ph.D., Table 6, p. 10.

Table 16: Investigator Global Results (Two Grade Improvement): PP

Treatment	Study 18053		Study 18054	
	Calcitriol	Vehicle	Calcitriol	Vehicle
N	188	179	185	176
Success (%)	47 (25.0%)	29 (16.2%)	42 (22.7%)	14 (8.0%)
p-value†	-	.0269	-	< .001

† p-values are based on CMH stratified by pooled site.

Source: Statistical Review and Evaluation by Mat Soukup, Ph.D., Table 8, p. 13.

In both of these analyses, the comparison of calcitriol ointment to vehicle ointment achieves statistical success, though treatment effects are smaller than those seen with success defined as IGA score of 0 or 1.

For labeling it is preferable to use results wherein IGA success is defined as the proportion of ITT subjects having a two grade improvement. This ensures that successes are clinically meaningful.

B) In the scale used to assess global severity (see primary efficacy measurement in section 5.3) the category "clear" is not clear for erythema and could lead to the overstatement of efficacy. The following could be erroneously included in efficacy; subjects who started as 2 or "mild" and then after treatment being graded as 0 or "clear" although they were not clear for erythema.

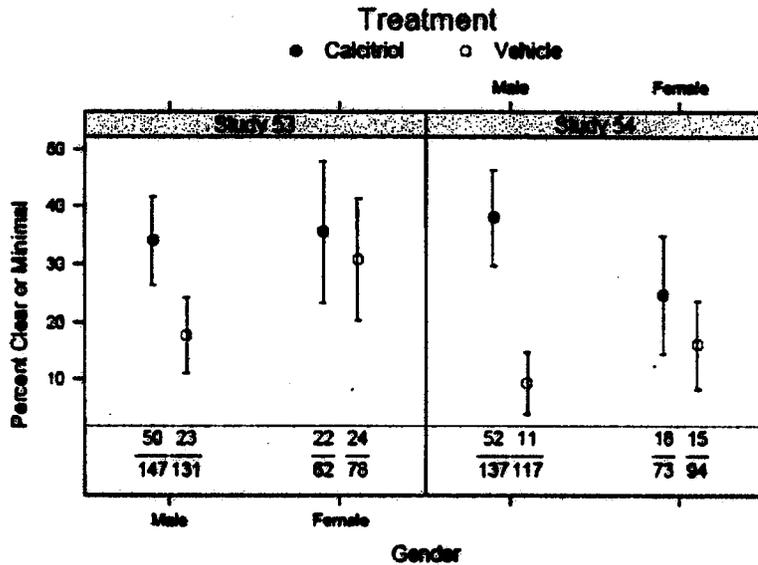
The FDA biostatistician has performed a secondary analysis showing how subjects (entering with IGA of 2) scoring 0 for disease severity at end of treatment compared with those (entering with IGA of 2) scoring 0 for erythema at end of treatment. In study 18053 one subject entering with an IGA of 2 was scored as 0 on IGA at end of treatment while having a score of 1 for erythema. If success is defined as a two grade improvement in IGA score, removal of this subject from the group having treatment success would have negligible effect on efficacy. In study 18054 all subjects entering with an IGA of 2 were scored as 0 on IGA and 0 for erythema at end of treatment. Please see appendix 9.1 for analysis data.

6.1.8 Subpopulations

The following plots show mean response rates with unadjusted 95% confidence intervals.

Gender

Table 17: Percent IGA success by Gender



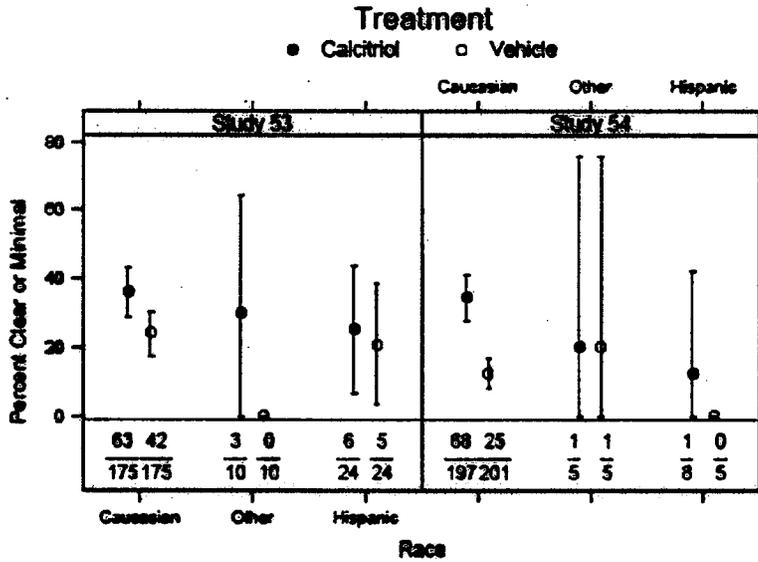
Source: Statistical Review and Evaluation: NDA 22-087, Mat Soukup Ph.D., Figure 5.

In general treatment effects were greater in males than females.

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Race:

Table 18: Percent IGA success by Race

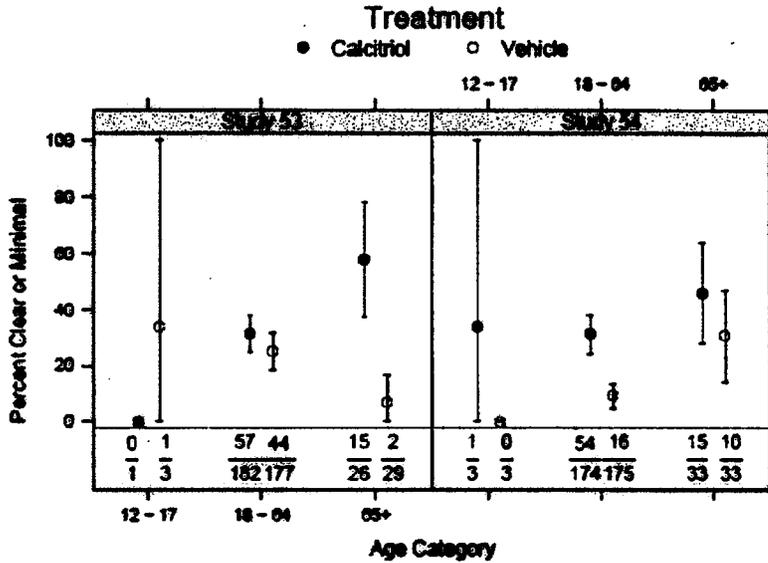


Source: Statistical Review and Evaluation: NDA 22-087, Mat Soukup Ph.D., Figure 6.

The majority of subjects enrolled were Caucasian. Definitive conclusions regarding non-Caucasians are precluded by small numbers.

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Age Group:
Table 19: Percent IGA Success by Age Group



Source: Statistical Review and Evaluation: NDA 22-087, Mat Soukup Ph.D., Figure 7.

In both studies the response rate for subjects 18 to 64 years of age were similar, however the response to vehicle was higher in this age group in study 18053.

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Calcitriol ointment, 3mcg/g, was initially developed by _____ in the late 1980's, licensed to _____ then acquired by Galderma in 1996.

b(4)

Two studies were performed to evaluate the optimal dose to be used in the pivotal Phase 3 studies. These studies were both conducted by _____

b(4)

┌

b(4)

These studies were not conducted with the final-to-be-marketed formulation.

└

b(4)

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~~_____~~

b(4)

It is in the 3µg/g concentration that calcitriol ointment (Silkis) is approved in 42 countries and marketed in 28 countries.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

Analyses of persistence of efficacy and/or tolerance not performed.

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7 Review of Safety

Safety Summary

To evaluate safety the sponsor conducted 2 pivotal trials, SRE.18053 (US) and SRE.18054 (US) and a long term safety study, SRE.2663 (International-non US). These three studies were conducted with the final-to-be marketed formulation.

The two pivotal trials included a total of 419 subjects who were exposed to calcitriol ointment 3µg/g. Median duration of exposure was 57 days. The long-term safety study enrolled 324 subjects with median exposure of 187.5 days. Of the subjects in the long-term safety study, 239 were exposed for at least six months and 116 were exposed for at least one year. The 4 month safety update was reviewed and did not contain new safety information.

In the overall clinical program there was one death reported in study H.141.902 (an active controlled study). Post-mortem revealed atheroma and this was assessed as not related to study drug.

In the two pivotal trials a total of five Serious Adverse Events (SAEs) were reported: on vehicle events included arteriosclerosis, hypoxia, and coronary occlusion. On active, events included cellulitis of leg and syncope. A relationship between these and study drug is unlikely.

In the long-term safety study eight SAEs were reported; skin ulcer, left hip subluxation, two cases of metrorrhagia, heart failure, arteriosclerosis, breast cancer, and infection (due to dog bite). These events were unlikely to be related to study medication.

In the controlled studies excluding the pivotal trials, subjects exposed to calcitriol ointment 3µg/g, SAEs included; headache, three cases of MI, upper respiratory tract infection, appendicitis, abdominal pain and appendectomy, and bone fracture (auto accident); all considered unrelated to study drug.

In the uncontrolled studies, subjects exposed to calcitriol 3µg/g, two SAEs, erythema annulare centrifugum and worsening of psoriasis are considered possibly related. SAEs of knee injury, lymphedema, and angina pectoris are considered unrelated to study drug.

In the pivotal studies, 18 adverse events led to discontinuation: 7/419 in the calcitriol 3µg/g group and 11/420 in the vehicle group. In the calcitriol group, the adverse experiences that led to withdrawal were; pain at treatment sites (probably related to study drug), pruritus (possibly related to study drug), discomfort of skin pruritus and erythema (probably related to study drug), cellulitis (unlikely to be related to study drug), worsening of psoriasis and worsening of scalp/head psoriasis (unlikely to be related to study drug), and anxiety (unlikely to be related to study drug). In the vehicle group, adverse experiences leading to withdrawal were; four cases of worsening of psoriasis (possibly related to study drug), two cases of discomfort of skin

(definitely related to study drug), edema on leg (possibly related to study drug), three cases of worsening of psoriasis (unlikely to be related to study drug), and worsening of scalp psoriasis (unrelated to study drug).

For the pivotal trials, roughly the same percentage of subjects 35% (147/419) exposed to calcitriol ointment as those 34% (141/420) experienced adverse events. Across study arms the most common adverse event reported was lab test abnormality, occurring in 4.5% (19/419) of subjects exposed to calcitriol and in 4.5% (19/420) in subjects exposed to vehicle. The second most common adverse event across study arms was flu syndrome, occurring in 3.8% (16/419) of those exposed to active and in 3.6% (15/420) of those exposed to vehicle. The third most common adverse event across study arms was discomfort of skin, occurring in 3.1% (13/419) exposed to active and in 2.1% (9/420) of those exposed to vehicle.

Cutaneous safety was evaluated in the five Phase 1 studies, CG.03.SRE.2598, RD.03.SRE.2652, CG.03.SRE.2600, CG.03.SRE.2602, and CG.03.SRE.2601. Calcitriol 3µg/g ointment showed roughly equivalent levels of irritation to white petrolatum and was not sensitizing. As studied, calcitriol 3µg/g ointment did not show evidence of phototoxicity or photosensitization.

Calcium homeostasis parameters were monitored in approximately 80 subjects in calcitriol and vehicle arms of the two pivotal trials. In trials 18053 and 18054, 22 subjects in the calcitriol arm and 15 subjects in the vehicle arm had at least one albumin-adjusted calcium above the normal range. In the pivotal trials, for 24 hour urine calcium, 16 subjects in the calcitriol arm and 26 in the vehicle arm had values above the normal range. Clinical symptoms of hypercalcemia were not noted.

In the open label safety study, 2663, 10 subjects experienced hypercalcemia. The distribution of events of hypercalcemia was roughly even through the 4 quarters of the study. A total of 20 subjects had hypercalciuria reported as an adverse event. Events of hypercalciuria as an adverse event were distributed roughly evenly through the 4 quarters of the study. Two subjects in this study were found to have kidney stones. In both cases laboratory parameters of calcium metabolism were above normal at baseline (either calcitriol or 24 hour urine calcium).

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Forty-five studies have been conducted with calcitriol ointment at various concentrations. Safety data were collected by the sponsor in all 45 studies.

a) 14 Phase 1 studies in healthy subjects and subjects with psoriasis

- b) 25 controlled and uncontrolled studies evaluating calcitriol ointment as monotherapy in subjects with psoriasis
- 14 controlled studies including the 2 U.S. key pivotal studies, SRE.18053 and SRE.18054
 - 11 open-label uncontrolled studies including long-term study SRE.2663, and 10 additional supportive studies
- c) Five concomitant therapy studies in patients with psoriasis
- d) One exploratory study for ichthyosis
- e) Eight other studies
- Two post-marketing surveillance studies (Germany and Korea)
 - Six locally sponsored post-approval Phase 4 studies in Taiwan (2), Singapore (1), Italy (1), Korea (1), and Brazil (1)

The safety review of the sponsor's product will focus on adverse events and systemic safety (laboratory evaluation), and local safety (cutaneous signs and symptoms at application sites in Phase 2 and Phase 3 studies). The safety database consists primarily of the pooled data from the 2 pivotal trials, SRE.18053 (US) and SRE 18054 (US) wherein calcitriol ointment was studied at 3µg/g BID for 8 weeks. This data is used for subgroup analysis. The safety data base also includes supportive data from the other 12 controlled trials. Of these, only one, H.141.908M/C (UK), has the same concentration of active and a very similar dosing regimen (BID for 9 weeks: 1-week run in, 8 weeks of treatment).

The safety database also includes data from the long term safety study, SRE.2663 (INT non-US). This was performed open label, with calcitriol ointment 3µg/g for up to 52 weeks.

Special safety studies are discussed in section 7.4.5 and include:

- a) CG.03.SRE.2598 (FR) repeat insult/21-day cumulative irritancy
- b) RD.03.SRE.2652 (FR) repeat insult/21-day cumulative irritancy
- c) CG.03.SRE.2600 (UK) cumulative irritancy and cutaneous contact sensitization
- d) CG.03.SRE.2602 (UK) photo-toxicity
- e) CG.03.SRE.2601 (FR) photo-allergy

For all clinical studies deaths, serious adverse events, and clinically important adverse events were examined. Discontinuations due to adverse events were examined carefully for the pivotal trials 18053, 18054, open label safety study 2663, and special safety studies.

7.1.2 Adequacy of Data

Adverse events for the calcitriol 3µ ointment formulation were coded using COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms).

For pivotal studies 18053 and 18054 and for the open-label safety study 2663, the sponsor's classification of verbatim terms to preferred terms appears acceptable.

7.1.3 Pooling Data across Studies to Estimate and Compare Incidence

Adverse event data from the pivotal Phase 3 studies (SRE.18053 and SRE.18054) were pooled together. Test product, dose, mode of administration, and duration of treatment were the same for both studies.

The sponsor also created three other groups of studies:

- a) All 14 controlled studies, including key pivotal studies
- b) Long-term uncontrolled study SRE.2663
- c) All 11 uncontrolled studies, including the long-term uncontrolled study SRE.2663

7.2 Adequacy of Safety Assessments

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

In Phase 1 a total of 512 healthy subjects and 58 subjects with psoriasis were exposed to calcitriol. The following table includes only those subjects exposed who had psoriasis.

Table 20: Subjects Exposed Phase 1

	Study ID	Calcitriol Ointment 3µg/g
Bioavailability: 3µg/g healthy subjects and subjects with psoriasis	H.141.6002	6/14
Bioavailability: subjects with psoriasis after 5-6 week pretreatment with 3µg/g BID alone or concomitantly with diprosone, diprosone/salicylates, or irradiation	H.141.6003	21 ^b
PK and PD in subjects with psoriasis	SRE.40005	23

^a Subjects with psoriasis bold

^b 22 enrolled

Source: Sponsor's NDA, adapted from Table 13, Integrated Summary of Safety, p. 35.

In the 25 trials with calcitriol monotherapy, total of 1068 subjects in both vehicle and active controlled studies were exposed to calcitriol ointment 3µg/g twice daily. Of these 559 were exposed in studies having vehicle controls.

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Table 21: Subjects with Psoriasis Exposed, Vehicle Controlled Studies, at 3µg/g

Study	Calcitriol ointment 3µg/g	Calcitriol ointment <3µg/g	Calcitriol ointment >3µg/g	Calcitriol Vehicle ointment
H.141.5006A	29			29
H.141.5009	68			65
H141.5012M	42	84	39	82
SRE.18053	209			209
SRE.18054	210			211
Total	559			596

Source: Sponsor's NDA, adapted from Table 14, Integrated Summary of Safety, p. 36.

For the pivotal trials the median exposure was 57 days (Table ISS 1.2)

The duration of exposure in uncontrolled trials is summarized in the following table.

Table 22: Summary of Duration of Exposure

		Study SRE.2663 (Long-term safety)	Combined Uncontrolled
Duration of exposure	N	324	849
	Missing	-	5 (0.6%)
	<6 months N(%)	85 (26.2%)	427(50.3%)
	At least 6 months (>180 Days) N(%)	239(73.8%)	417(49.1%)
	At least 12 months (>360 Days) N(%)	116(35.8%)	190(22.4%)
	At least 18 months (>540 Days) N(%)	-	14(1.6%)

Source: Sponsor's NDA, Table 15, Integrated Summary of Safety, p. 37.

For the long-term safety study the median duration of exposure was 187.5 days (Table ISS 1.4)

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Table 23: Demographic Data Pivotal Studies

		Pooled Pivotal Studies SRE.18053 and SRE.18054		
		Calcitriol ointment 3µg/g	Calcitriol vehicle ointment	
Gender	N	419	420	
	Female N (%)	135 (32.2)	172 (41.0)	
	Male N (%)	284 (67.8)	248 (59.0)	
Race	N	419	420	U.S. Population ¹
	Asian N (%)	5 (1.2)	4 (1.0)	
	Black N (%)	8 (1.9)	7 (1.7)	12.3%
	Caucasian N (%)	372 (88.8)	376 (89.5)	75.1%
	Hispanic N (%)	32 (7.6)	29 (6.9)	12.5% ¹
	Other N (%)	2 (0.5)	4 (1.0)	
Age (Years)	N	419	420	
	12 to <18 Years N (%)	4 (1.0)	6 (1.4)	
	18 to <65 Years N (%)	356 (85.0)	352 (83.8)	
	≥ 65 Years N (%)	59(14.1)	62 (14.8)	
	Mean ±SD	47.4 ± 14.6	48.2 ± 14.0	
	Median	47.0	48.0	
	(Min, Max)	(13.0, 87.0)	(12.0, 84.0)	

¹In the Census 2000, "Hispanic or Latino" was employed as a category for ethnicity. In the safety summary, "Hispanic" is a category for race.

Source: Sponsor's NDA Integrated Summary of Safety with adaptation, Table 25, p. 48.

A majority of subjects exposed to calcitriol were Caucasian (89%) and male (67%). The mean age was 47.4 years old. In the United States the prevalence of psoriasis was 2.5 % in Caucasians and 1.3 % in African-Americans². Psoriasis affects men slightly more than women and the highest overall annual rate of incidence of psoriasis is in the 60 to 69 year old age group.³

¹ Overview of Race and Hispanic Origin, U.S. Census Bureau, Census 2000 Brief, March 2001, p.3.

² Gelfand JM, Stern RS, Nijsten TN et al. The prevalence of psoriasis in African Americans: Results from a population-based study. *J Am Acad Dermatol* 2005;52:23-26.

³ Neimann AL, Porter SB, and Gelfand JM. The epidemiology of psoriasis. *Expert Rev. Dermatol.* 2006;1:63-75.

Table 24: Summary of Medication Usage ITT Population: Study 18053

		Calcitriol ointment 3µg/g	Vehicle ointment
Total medication use (g)^a	N	209	209
	Mean + SD	392 + 390	433 + 441
	Median	253	266
	(Min, Max)	(-3.4, 1844)	(-6.8, 1867)
Daily medication use (g/day)^b	Mean + SD	7.1 + 6.9	8.2 + 7.9
	Median	4.6	5.4
	(Min, Max)	(-2.1, 32.9)	(-5.5, 33.3)
	Daily medication use, n(%) of subjects		
	< 30 (g/day)	208 (99.5%)	208 (99.5%)
	> 30 (g/day)	1 (0.5%)	1 (0.5%)

^a Total medication used = total dispensed weight (g) – total returned weight (g).
 Dispensed weight is approximate only. No weighing occurred at dispensing individual tube.

^b Daily medication used = total medication used (g)/treatment duration (day).

Source: Sponsor's NDA, Table SUB 5.1, Study Report RD.06.SRE.18053, 5.3.5.1.1.01, p. 123.
 Figures rounded by reviewer.

Table 25: Summary of Medication Usage ITT Population: Study 18054

		Calcitriol ointment 3µg/g	Vehicle ointment
Total medication use (g)^a	N	210	211
	Mean + SD	414 + 461	373 + 369
	Median	257	230
	(Min, Max)	(-8.8, 1866)	(-7.8, 1583)
Daily medication use (g/day)^b	Mean + SD	8.8 + 19	8.8 + 21
	Median	4.8	4.6
	(Min, Max)	(-8.8, 255)	(-1.9, 288)
	Daily medication use, n(%) of subjects		
	< 30 (g/day)	203 (96.7%)	209 (99.1%)
	> 30 (g/day)	7 (3.3%)	2 (0.9%)

^a Total medication used = total dispensed weight (g) – total returned weight (g).
 Dispensed weight is approximate only. No weighing occurred at dispensing individual tube.

^b Daily medication used = total medication used (g)/treatment duration (day).

Source: Sponsor's NDA, Table SUB 5.1, Study Report RD.06.SRE.18054, 5.3.5.1.1.02, p. 124.
 Figures rounded by reviewer.

Mean daily medication use was similar in the pivotal studies 18053 and 18054 respectively, 7.1 ± 6.9 g and 8.8 ± g. Mean total medication use was also similar in the pivotal studies, 392 ± 390g and 414 ± 461 g.

Table 26: Summary of Medication Use (Pooled Pivotal Studies and Long-term Study)

		Pivotal Studies 18053, 18054		Long-term study
		Calcitriol ointment 3µg/g	Vehicle ointment	Calcitriol ointment 3µg/g
Total medication use (g)^a	N	419	420	308
	Mean + SD	403 + 427	403 + 407	1380 + 1325
	Median	256	248	998
	(Min, Max)	(-8.8, 1866)	(-7.8, 1867)	(2.2, 6104)
Daily medication use (g/day)^b	Mean + SD	7.3 + 7.5	7.7 + 7.6	5.8 + 5.0
	Median	4.8	4.9	4.3
	(Min, Max)	(-1.1, 33)	(-2.3, 34)	(0.0, 37)
Daily medication use, n(%) of subjects	< 30 (g/day)	411 (98.1)	417 (99.3)	307 (99.7)
	> 30 (g/day)	8 (1.9)	3 (.7)	1 (0.3)

^a Total medication used = total dispensed weight (g) – total returned weight (g) based on the same number of tube

^b Daily medication used = total medication used (g)/treatment duration (day).

Source: Sponsor's NDA, Table 16, Integrated Summary of Safety, 5.3.5.3.02, p. 38.

Figures rounded by reviewer.

Mean daily study drug use was 7.3 g/day for the pivotal studies and 5.8 g/day for the long-term safety study.

Adequacy of Clinical Exposure:

An adequate number of subjects was exposed to calcitriol 3µg/g ointment at the proposed dosing regimen to assess safety for use twice daily for 8 weeks. The two pivotal trials included a total of 419 subjects who were exposed to calcitriol ointment 3µg/g. Median duration of exposure was 57 days. The long-term safety study enrolled 324 subjects with median exposure of 187.5 days. Of the subjects in the long-term safety study, 239 were exposed for at least six months and 116 were exposed for at least one year. A body of information is also available for the marketed product, same formulation, in Europe and other countries.

Topical safety was adequately evaluated in the development program and included assessment for local adverse events and 5 dermal safety studies. The number of subjects evaluated in the dermal safety studies was generally as recommended.

Systemic safety was adequately evaluated in the development program and included monitoring of calcium homeostasis.

7.2.2 Explorations for Dose Response

One controlled trial, H.141.5012/M (Europe) explored doses of calcitriol; 0.3, 1, 3, and 9µg/g in white petrolatum ointment and employing 1 week of run-in period (all psoriatic lesions treated with vehicle) followed by 8 weeks of BID treatment to all psoriatic lesions on the body. To enter

the study, subjects had to have severe chronic plaque psoriasis as indicated by a score of at least 3 on a 0 to 4 point scale. At baseline mean % BSA involvement was 20% ± SD of 16. A total of 247 subjects were enrolled in the study and of these 7 subjects discontinued early due to intolerance and local skin reaction (3 in the 1µg/g group, 1 in the 3µg/g group, 1 in the 9µg/g group, and 2 in the vehicle group). Skin irritation was noted in 7% of subjects treated with 1µg/g calcitriol ointment, 2% of subjects treated with 3µg/g calcitriol ointment, and 4% of subjects treated with vehicle. Laboratory parameters including mean 24-hour urinary calcium and 24-hour urinary creatinine and serum total calcium were within normal limits for the different treatments. However, there was a small statistically significant increase in the urinary calcium excretion in those treated with 9µg/g calcitriol ointment. Please see following table.

Table 27: Mean Values of 24-Hour Urinary Calcium Excretion (mmol/24h)

Assessment	0.3 µg/g	1 µg/g	3 µg/g	9 µg/g	Vehicle
Baseline	3.88	3.92	3.92	3.87	4.03
Week 2	4.11	4.82	3.87	4.87	9.16
Week 4	4.58	4.12	3.84	5.15	3.97
Week 6	3.86	3.91	4.00	4.94	4.09
Week 8	3.86	4.32	3.82	4.74	3.83
Endpoint (week 8)	3.82	3.99	3.68	4.64	3.86
N endpoint	39	41	41	38	79
P baseline/endpoint	0.73	0.94	0.68	0.046	0.31

N = Number of subjects

Source: Sponsor's NDA, 5.3.5.1.1.05 Study report H.141.5012/M, Table X.4, p. 70.

7.2.3 Special Animal and/or In Vitro Testing

A submission specific safety concern is effect of calcitriol on calcium homeostasis. The pharmacology/toxicology reviewer states that studies involving repeated doses of calcitriol did show effects upon calcium homeostasis including elevated concentrations of calcium in serum and urine, microscopic evidence of stimulation of bone formation, and mineralization of the kidney. Preclinical studies were adequate to show that little transdermal absorption of calcitriol occurs (if treated animals are prevented from ingesting the applied material).

Calcitriol as evaluated as a co-carcinogen with UV light and preclinical testing performed appears adequate to demonstrate that calcitriol does not enhance photo-induced carcinogenesis. According to the pharmacology/toxicology reviewer data do suggest, "that the vehicle of calcitriol ointment slightly enhances UV-induced skin tumor formation (possibly by enhancing UV penetration into the skin)."

7.2.4 Routine Clinical Testing

The routine clinical testing performed was adequate to assess the safety and efficacy of use for 8 weeks.

7.2.5 Metabolic, Clearance, and Interaction Workup

Sponsor proposed language for labeling is as follows:

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

The sponsor has performed adequate evaluation for adverse events associated with drugs of the same class as calcitriol. Forms of evaluation include dermal safety studies, collection of adverse event data, and collection of laboratory data for detection of potential systemic effects (on calcium metabolism).

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the pivotal studies SRE.18053 and SRE.18054.

In the overall clinical program one death, subject 11455 in study H.141.902 (an active controlled study) was reported. The subject was a 46 year old Asian male, non-smoker, with a 12 year history of psoriasis, global severity moderate at beginning of study. During the study no abnormalities were noted in blood pressure or serum biochemistry values. The subject was not receiving concomitant medication. The subject was randomized to calcitriol 3g/g topical ointment twice daily for 8 weeks. The death was reported one day after completing the study. A post mortem revealed extensive atheroma. This event was considered by the investigator not related to study drug.

7.3.2 Nonfatal Serious Adverse Events

The sponsor notes that there are noted differences between the historical studies and the recent clinical studies with regard to data collection methods, handling, and processing. The sponsor states that as a result of limitations in AE data collection, the ISS SAE dataset is incomplete. The sponsor has tried to correct this by performing manual tabulation of deaths and serious event listings.

Table 28: Serious Adverse Events in Pivotal Studies (SRE.18053 and SRE.18054)

Study Number	Subject No. Age/ Gender	Treat-ment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Discontinue
SRE.18053	130 77/M	Calcitriol vehicle ointment	Blocked arteries heart (Arteriosclerosis)	Definitely unrelated	Resolved, residual effects	Severe	No
	398 55/M	Calcitriol vehicle ointment	Decreased oxygen level after surgery (Hypoxia)	Definitely unrelated	Resolved, no residual effects	Severe	No
	441 71/F	Calcitriol ointment 3/µg/g	Left leg cellulitis (Cellulitis)	Unlikely	Resolved, residual effects	Severe	Drug & study
	458 61/M	Calcitriol vehicle ointment	Blockage of two coronary arteries (Occlus coronary)	Unlikely	Resolved, residual effects	Moderate	No
SRE.18054	977 841M	Calcitriol ointment 3/µg/g	Loss of consciousness (Syncope)	Definitely unrelated	Resolved, no residual effects	Severe	No

Source: Sponsor's NDA Integrated Summary of Safety, 5.3.5.3.02, p 114.

Study SRE.18053

- Subject 130 (blocked arteries; 77 y/o male) and subject 398 (decreased oxygen levels after surgery; 55 y/o male) were both treated with calcitriol vehicle ointment twice daily. This reviewer agrees with investigator assessment that these events were unrelated to study medication, vehicle.

-† Subject 441 (left leg cellulitis) is a 71 y/o female treated with calcitriol 3 µg/g twice daily. This subject had a history that included arthritis, psoriasis itch, and scalp psoriasis and at the start of the study was undergoing treatment with piroxicam, topical salicylic acid, and guaifenesin. The subject was hospitalized for left leg cellulitis from study day 50 to 54 and again from day 58 to day 63. The subject was treated with dicloxacillin and rifampin. The event resolved day 74 with residual redness, edema, and tenderness of the left lower extremity. The subject discontinued study treatment day 48 and was discontinued from the study day 81 due to the adverse event. The investigator assessed the event as unlikely to be related to study drug. This reviewer can only state that the relationship is uncertain.

- Subject 458 (blockage of 2 coronary arteries) is a 61 y/o male treated with calcitriol vehicle ointment twice daily. This reviewer has reviewed the narrative summary and agrees with the investigator assessment that this event is unrelated to study treatment.

Study SRE.18054

- Subject 977 (loss of consciousness) is a 84 y/o male treated with calcitriol 3 µg/g twice daily. This reviewer agrees with investigator assessment that this event was unrelated to study medication.

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Table 29: Serious Adverse Events (Controlled Studies Excluding Pivotal Studies)

Study Number	Subject No. Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Discontinue
H.141.901/MC	10940 41/F	Calcitriol ointment 3µg/g	Headache (Headache)	Unrelated	Not available	Moderate	No
	11020 39/F	Betamethasone	Thrombosis venous deep (Thrombophlebitis deep)	Unrelated	resolved	Severe	Not available
	11282 68/M	Calcitriol ointment 3µg/g	Myocardial infarction (Infarction myocardial)	Unrelated	resolved	Moderate	Drug for 8 days
H.141.902/MC	11422 69/M	Calcitriol ointment 3µg/g	Myocardial infarct (Infarction myocardial)	Unrelated	resolved	Moderate	No
	11530 33/F	Calcitriol ointment 3µg/g	Upper respiratory tract infection (Infection)	Unrelated	Not available	Mild	No

Source: Sponsor's NDA Integrated Summary of Safety, 5.3.5.3.02, p 116, with reviewer additions.

Study H.141.901/MC:

- Review of narrative reveals subject 10940 (headache) had a medical history of migraines. During the study the subject received paracetamol plus caffeine as concomitant medication for headaches. The subject started study medication 10/23/91 and had her first headache 10/21/91. The event was not recorded as an SEA or AE in the CRF, relationship to study medication was not recorded. This event appears to be unrelated to study medication.
- Subject 11020 was treated with betamethasone.
- Review of narrative reveals 68 y/o male subject 11282 (myocardial infarction) had medical history of hypercholesterolemia and cholecystectomy. This reviewer agrees with the assessment that the event was unrelated to study medication.

Study H.141.902/MC

- Subject 11422 had a history of angina pectoris and was receiving glyceryl trinitrate at the start of the study. On study day 41 the subject experienced a myocardial infarction, however this was reclassified as an angina attack by the general practitioner since no MI was documented on ECG. This reviewer agrees with assessment that this is unrelated to study medication.
- Subject 11530 (upper respiratory tract infection) was a 33 y/o female without significant medical history. This reviewer agrees with investigator assessment that this event was unrelated to study medication.

Subjects who had serious adverse events not recorded in the database but found by manual review by the sponsor of the clinical study reports and the case report forms.

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Table 30: Serious Adverse Events Identified from CSR* or CRF† Controlled Clinical Trials

Study Number	Subject No.# Age/Gender	Treatment	Verbatim term (COSTART Term)	Relation to Study Drug	Discontinue
H.141.5004M	10090 70/M	Calcitriol oint. 3µg/g QD	Myocardial infarction/Not available	Not related	Yes
H.141.5012	11606 25/F	Calcitriol oint. 1µg/g BID	Appendicitis/abdominal syndrome acute	Not related	No
	11730 46/F	Vehicle BID	Pain in the treated plaques with ankle edema/Edema periph	Highly Probable	Yes
	11776 50/F	Calcitriol oint. 9µg/g BID	Abdominal pain and appendectomy/Not available	Not related	No
	11797 62/F	Vehicle BID	Ablatio retinae and laser therapy/Retinal detach	Not related	No
	11844 62/F	Vehicle BID	Fracture of right forearm/Not available	Not related	No
	11874 63/F	Calcitriol oint. 0.3µg/g BID	Bone fracture from automobile accident/Not available	Not related	Yes
H.141.902/MC	11455 46/M	Calcitriol oint. 3µg/g BID	Death (extensive atheroma per post mortem)/Not available	Not related	No (death report 1 day post study per CSR)
H.141.908	12475 54/M	Calcipotriol 50µg/g BID	Short breath on exertion/Dyspnea	Unrelated	Yes (dc'd due to psoriatic lesion pain)

*CSR= Clinical Study Report

†CRF= Case report Form

Source: Sponsor's NDA Integrated Summary of Safety, 5.3.5.3.02, p 117.

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Study H.141.902/MC
 - Subject 11455 (death) the narrative is discussed in section 7.3.1.

Study H.141.908
 - Subject 12475 (shortness of breath on exertion) was treated with calcipotriol.

In the long term safety study 8 subjects had serious adverse events.

Table 31: Serious Adverse Events Long-term Safety Study (SRE.2663)

Subject No. Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Discontinue Yes/No
161 47/M	Calcitriol ointment 3µg/g	Skin ulceration of the right lower extremity (Ulcer skin)	Unlikely	Resolved, no residual effects	Moderate	No
171 30/F	Calcitriol ointment 3µg/g	Left hip subluxation with tendon injuries	Unlikely	Resolved, no residual effects	Severe	No
214 46/F	Calcitriol ointment 3µg/g	Metrorrhagia (Metrorrhagia)	Unlikely	Resolved, no residual effects	Severe	No
234 67/F	Calcitriol ointment 3µg/g	Heart failure congestive - circulatory failure (Heart failure right)	Unlikely	Resolved, no residual effects	Severe	Yes

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261 63/M	Calcitriol ointment 3µg/g	Arteriosclerosis obliterans (Arteriosclerosis)	Unlikely	Resolved, residual effects	Mild	No
299 61/F	Calcitriol ointment 3µg/g	Breast cancer (Carcinoma breast)	Unlikely	Continuing	Severe	Yes
361 55/F	Calcitriol ointment 3µg/g	Infection due to dog bite on the left lower leg - distal (Infection)	Unlikely	Resolved, residual effects	Severe	No
383 52/F	Calcitriol ointment 3µg/g	Metrorrhagia (Metrorrhagia)	Unlikely	Resolved, no residual effects	Moderate	No

Source: Sponsor's NDA Integrated Summary of Safety, 5.3.5.3.02, p 119.

Study SRE.2663

- Subject 161 (skin ulcer) is a 47 y/o male treated with calcitriol ointment 3 µg/g twice daily. The subject's medical history included hypertension and phlebothrombosis cruris approximately 3 and 5 years before study inclusion. The subject was undergoing treatment with betamethasone and mometasone at the beginning of the study. On study day 125 the subject experienced a skin ulcer of the right lower extremity that led to hospitalization for local treatment, antibiotics and anticoagulation with acenocoumarol. The event resolved on study day 137 with no residual effects. The subject continued in the study. The event was assessed as unlikely to be related to study drug.

- Subjects 171 (hip subluxation with tendon injuries; 30 y/o female), 214 (metrorrhagia; 46 y/o female), 234 (heart failure; 67 y/o female), 261 (arteriosclerosis obliterans of lower extremities; 63 y/o male), 299 (breast carcinoma; 61 y/o female), 361 (dog bite of leg; 55 y/o female), and 383 (metrorrhagia; 52 y/o female) were treated with calcitriol ointment 3 µg/g twice daily. This reviewer agrees with the investigator assessment that these events were unlikely to be related to study medication.

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Table 32: Serious Adverse Events Uncontrolled Studies

Study Number	Subject No. Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Discontinue
H.141.901E	11216 62/M	Calcitriol ointment 3µg/g	Cerebrovascular accident (Cerebrovascular accident)	Unrelated	Complete recovery	Severe	N/A
H.141.906	11952 65/M	Calcitriol ointment 3µg/g	Eryhema annulare centrifugum (Eryhema multiforme)	Probable	N/A	Moderate	N/A
SRE.2635	18 36/M	Calcitriol ointment 3µg/g	Worsening of psoriasis (Worse treated disease)	Possible	Resolved, no residual effects	Severe	Yes

Source: Sponsor's NDA Integrated Summary of Safety, 5.3.5.3.02, p 119.

Study H.141.901E

- Subject 11216 (ischemic cerebrovascular accident) is a 62 y/o male treated with calcitriol ointment 3µg/g twice daily for 6 weeks in a double-blind phase prior to treatment in the extension phase. . This reviewer agrees with the assessment that the event was unrelated to study medication.

Study H.141.906/MC

- *Subject 11952 (erythema annulare centrifugum) is a 65 y/o male treated with calcitriol ointment 3µg/g twice daily. The subject had a history of hepatic insufficiency. The subject's total body surface area affected by psoriasis at baseline was 35% with grade 3 global severity. On study day 6 the subject experienced a dermatosis that was diffuse over the body and that required hospitalization and treatment with steroid cream. On study day 42 the subject discontinued treatment and on study day 43 was discontinued from the study due to inefficacy. The adverse event resolved 9 days after discontinuing treatment. The investigator assessed the event was probably related to study medication. This reviewer believes that there may be a relationship between study medicine and this event.

Study SRE.2635

- *Subject 18 (worsening of psoriasis) is a 36 y/o male treated with calcitriol ointment 3µg/g twice daily. The pertinent medical history included atopic eczema for which the subject was undergoing treatment with a topical steroid and antibiotics at the beginning of the study. (Review of the CRF indicates date of onset for atopic dermatitis of 1980, same as that given for the onset of psoriasis. On intake exam it is noted that eczema is present on the eyelids. Prior to study intake exam subject was using Trimovate to flexures. The distribution of psoriasis at intake was body, arms and legs.) The subject's total body surface area affected by psoriasis at baseline was 30% with a global severity of moderate. Approximately 5 weeks after start of

treatment the subject experienced irritation. The subject's psoriasis worsened, he was admitted to the hospital, and he was treated with betamethasone plus fusidic acid. The subject discontinued treatment on study day 43 and was discontinued from the study on day 51 due to the adverse event. The event resolved 24 days after treatment discontinuation. This reviewer agrees with the assessment that the event was possibly related to study medication.

Table 33: Serious Adverse Events from CSR or CRF Uncontrolled Clinical Studies

Study Number	Subject Number Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Discon- tinue
H.141.5012E	11812 61/F	Calcitriol ointment 3µg/g BID	Left knee injury Joint disorder (Musculoskeletal)	Not related	No
	11832 59/M	Calcitriol ointment 3µg/g BID	Lymphedema/ (later diagnosed as lung cancer) Lymphedema (Hematological)	Not related	Yes
H.141.901/E	11188 69/M	Calcitriol ointment 3µg/g BID	Angina pectoris/ Angina pectoris (Cardiovascular)	Not related	Yes
SRE.2635	513303 60/M	None (pre-test drug application)	Acute generalized exanthematous pustulosis/ Psoriasis (Skin)	Definitely unrelated	(pre- baseline)

Source: Sponsor's NDA Integrated Summary of Safety, 5.3.5.3.02, p 122.

Study H.141.5012/E

- Subject 11812 (left knee injury) is a 61 y/o female treated with 8 weeks of double-blind calcitriol ointment 9 µg/g twice daily prior to treatment in the extension phase at 3µg/g. This reviewer agrees with the assessment that the event was unrelated to study medication.
- Subject 11832 (lymphedema, lung cancer) is a 59 y/o male completing 8 weeks of double-blind vehicle ointment treatment prior to beginning study treatment in the extension phase. This reviewer agrees with the assessment that the event was unrelated to study medication.

Study H.141.901/E

- Subject 11188 (angina pectoris) is a 69 y/o male treated with calcitriol ointment 3µg/g twice daily for 6 weeks in a double-blind phase prior to treatment in the extension phase. This reviewer agrees with the assessment that the event was unrelated to study medication.

Study SRE.2635

- Subject 513303 (acute generalized exanthematous pustulosis) is a 61 year old male. The event occurred before study treatment was started. The subject was admitted to the hospital and

underwent treatment. The subject continued in the study. The event was unrelated to study medication.

Serious adverse events were reported in concomitant therapy studies, 4 subjects with six SAEs.

Table 34: Serious Adverse Events from CSR & CRF; Studies with Concomitant Therapy

Study Number	Subject No. Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Discontinue
SRE.2647	047 66/F	Calcitriol ointment 3µg/g	Eventration surgery (Surgical/medical/procedure)	Unlikely	Continuing	Severe	Yes
H.141.904 (from CSR)	12328 74/F	Calcitriol ointment 3µg/g plus UV-B phototherapy 3 times weekly	Fever (Fever)	Unrelated	Continuing	Severe	Yes
			Pain to pressure on the left lower abdomen (Abdominal pain)	Unrelated	Continuing	Severe	Yes
			Meteorism (Flatulence)	Unrelated	Continuing	Severe	Yes
H.141.904 (from CRF)	12260 59/F	Vehicle plus UV-B	Hospitalization-unspecified event	Not available	Not available	Not available	Yes
	12342 32/M	Calcitriol ointment 3µg/g BID plus UV-B	Hospitalization-unspecified event	Not available	Not available	Not available	Yes

Source: Sponsor's NDA Integrated Summary of Safety, 5.3.5.3.02, pp. 124-125.

Study SRE.2647

- Subject 47 (surgery procedure, repair of eventration of intestines) is a 66 y/o female treated with calcitriol ointment 3 µg/g twice daily and UV-B phototherapy. This reviewer agrees with the investigator assessment that this event was unlikely to be related to study medication.

Study H.141.904 (from CSR)

- Subject 12328 (fever, abdominal pain, meteorism) is a 74 y/o female treated with calcitriol ointment 3 µg/g twice daily and UV-B phototherapy three times a week. The events were ongoing. This reviewer agrees with the investigator assessment that these events were unrelated to study medication.

Study H.141.904 (from CRF)

- Subject 12260 (hospitalization, unspecified event) is a 60 y/o female treated with calcitriol vehicle ointment. According to the CRF the subject was hospitalized (event and date not

specified) and was discontinued from the study on day 7 due to inefficacy. No further information was provided.

- Subject 12342 (hospitalization, unspecified event) is a 33 y/o male calcitriol ointment 3 µg/g twice daily and UV-B phototherapy. The subject was hospitalized (event and date not specified). On day 29 the subject discontinued study treatment and on day 42 was discontinued from the study due to causes unrelated to study treatment. (After discharge from the hospital the subject dropped out of the study.) No further information was provided.

7.3.3 Dropouts and/or Discontinuations

In study SRE.18053 of 7 events leading to discontinuation, 6 involved subjects on vehicle. Of these 6, 3 involved worsening of psoriasis. This could be expected off of therapy. Two cases involved stinging or burning at application site, possibly related to components of vehicle. One case involved edema of lower leg, relation to study medication indicated as possible. The case of cellulitis on calcitriol active was discussed with narratives of non-fatal serious events. The relationship of the event to study drug is uncertain.

Table 35: Adverse Events Leading to Discontinuation in Study 18053

Study Number	Subject No. Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Serious
SRE.18053	67 67/F	Calcitriol vehicle ointment	Worsening of psoriasis (Psoriasis)	Probable	Continuing	Mild	No
	80 50/M	Calcitriol vehicle ointment	Stinging and burning of skin (Discomfort skin)	Definitely related	Resolved, no residual effects	Mild	No
	249 65/F	Calcitriol vehicle ointment	Edema on left lower leg (Edema peripheral)	Possible	Resolved, no residual effects	Mild	No
	277 17/M	Calcitriol vehicle ointment	Worsening of psoriasis (Psoriasis)	Possible	Continuing	Moderate	No
	300 75/F	Calcitriol vehicle ointment	Burning at application sites (Discomfort skin)	Definitely related	Resolved, no residual effects	Mild	No
	426 361M	Calcitriol vehicle ointment	Worsening of psoriasis (Psoriasis)	Unlikely	Continuing	Mild	No
	441 71/F	Calcitriol ointment 3µg/g	Left leg cellulitis (Cellulitis)	Unlikely	Resolved, residual effects	Severe	Yes

Source: Sponsor's NDA Integrated Summary of Safety, 5.3.5.3.02, Table 71, p 130.

In study SRE.18054 a total of 11 events were noted leading to discontinuation. Of these 5 involved subjects on vehicle ointment. Of these 5, 4 involved worsening of psoriasis, again to be expected off of therapy. A case of worsening of hypertension is probably not related to vehicle. A total of 6 cases of discontinuation was noted on calcitriol active. Three cases involved worsening of psoriasis. Two cases involved pain at treatment site or increased burning, itching, or redness. These could represent vehicle effects. A case of panic attack, anxiety, is unlikely to be related to calcitriol active.

Table 36: Adverse Events Leading to Discontinuation in Study 18054

Study Number	Subject No. Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Serious
SRE.18054	508 71/F	Calcitriol vehicle ointment	Worsening hypertension (Hypertension)	Unlikely	Continuing	Moderate	No
	535 31/M	Calcitriol ointment 3µg/g	Worsening hypertension (Hypertension)	Probable	Resolved, no residual effects	Moderate	No
	540 50/F	Calcitriol vehicle ointment	Worsening of psoriasis (Psoriasis)	Unlikely	Continuing	Severe	No
	583 19/F	Calcitriol ointment 3µg/g	Worsening of psoriasis (Psoriasis)	Unlikely	Continuing	Moderate	No
	602 51/M	Calcitriol ointment 3µg/g	Pruritus worsening - trunk, legs, and elbows (Pruritus)	Possible	Resolved, no residual effects	Severe	No
	603 62/M	Calcitriol vehicle ointment	Flare of psoriasis (Psoriasis)	Possible	Resolved, no residual effects	Moderate	No
	735 46/F	Calcitriol ointment 3µg/g	Increased burning lower extremities (Discomfort skin)	Probable	Resolved, no residual effects	Moderate	No
			Increased itching lower extremities (Pruritus)	Probable	Resolved, no residual effects	Moderate	No
			Increased redness, lower extremities (Erythema)	Probable	Resolved, no residual effects	Moderate	No
	805 49/M	Calcitriol vehicle ointment	Psoriasis worsening (Psoriasis)	Possible	Continuing	Moderate	No

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Study Number	Subject No. Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Serious
	826 55/F	Calcitriol vehicle ointment	Worsening scalp psoriasis (Psoriasis)	Definitely unrelated	Continuing	Moderate	No
	838 67/F	Calcitriol ointment 3µg/g	Worsening of scalp/head psoriasis (Psoriasis)	Unlikely	Continuing	Moderate	No
	911 41/F	Calcitriol ointment 3µg/g	Panic attack (Anxiety)	Unlikely	Resolved, no residual effects	Moderate	No

Source: Sponsor's NDA Integrated Summary of Safety, 5.3.5.3.02, Table 71, p 131.

In the open label safety study, 8 cases of discontinuation were noted. All involved active drug as this was an open label study. Of these 2 cases of worsening of psoriasis were noted. One case of irritation and one case of pruritus were noted. Of note, one case of renal colic and one case of abnormal urine calcium level were noted. Unlikely to be related to the study drug was a case of right heart failure and a case of breast carcinoma.

Table 37: Adverse Events Leading to Discontinuation Open Label Study

Subject Number Age/Gender	Treatment	Verbatim Term (COSTART Term)	Relation to Study Drug	Outcome	Severity	Serious
126 19/M	Calcitriol ointment 3µg/g	Exacerbation of psoriasis - clinically significant worsening (Worse treated disease)	Unlikely	Continuing	Moderate	No
233* 43/M	Calcitriol ointment 3µg/g	Renal colic (Pain kidney)	Possible	Resolved, no residual effects	Moderate	No
234 67/F	Calcitriol ointment 3µg/g	Heart failure congestive-circulatory failure (Heart failure right)	Unlikely	Resolved, no residual effects	Severe	Yes
248 46/F	Calcitriol ointment 3µg/g	Significant worsening of skin lesions (Worse treated disease)	Unlikely	Continuing	Moderate	No
255* 35/M	Calcitriol ointment 3µg/g	Abnormal urine calcium level (Urine abnormal)	Possible	Continuing	Moderate	No
277 45/M	Calcitriol ointment 3µg/g	Irritation (Irritant dermatitis)	Probable	Resolved, no residual effects	Moderate	No