CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-185

MEDICAL REVIEW(S)

Clinical Team Leader Review Memo

Date	April 10, 2008
From	Jill A. Lindstrom, MD
Subject	Clinical Team Leader Review
NDA #	NDA 22-185
Proprietary Name **Established Names**	Taclonex Scalp Topical Suspension Calcipotriene and betamethasone diproprionate
Dosage form **Strengths**	Topical Suspension Calcipotriene 0.005%, bethamethasone diproprionate 0.064%
Proposed Indication	Topical treatment of moderate to severe psoriasis vulgaris of the scalp in adults 18 years and older
Recommendation:	*Approval*

1. Introduction

Taclonex (calcipotriene 0.005% and betamethasone diproprionate 0.064%) Scalp Topical Suspension is a fixed-dose combination topical drug product for which the applicant seeks approval for the topical treatment of moderate to severe psoriasis vulgaris of the scalp.

2. Background

Taclonex Scalp Topical Suspension is not currently marketed in any jurisdiction. However, the applicant markets Taclonex (calcipotriene 0.005% and betamethasone diproprionate 0.064%) Ointment, the same fixed-dose combination in a different dosage form, for a similar indication, the topical treatment of psoriasis vulgaris; Taclonex Ointment has been marketed in the US since 2006 and the EU since 2001. Essentially, Taclonex Scalp Topical Suspension represents a line extension into a new dosage form to facilitate treatment of a distinct body area (scalp). Additionally, both monads, calcipotriene and betamethasone, are marketed in various formulations as single-active ingredient products for the indications of psoriasis, moderately severe psoriasis of the scalp, and corticosteroid-responsive dermatoses, respectively.

3. CMC

There are no unresolved CMC issues; the reader is referred to the CMC review by Zhengfang Ge, PhD.

The applicant initially identified their dosage form as a "gel." However, the product flows freely, which is not characteristic of gel formulations, and thus "suspension" is a more accurate appellation for the dosage form. The applicant agreed to identify their dosage form as a "suspension." To avoid confusion with oral suspension medications and reduce the risk of

ingestion-type medication errors, it was agreed that the modifier "topical" would precede "suspension."

4. Nonclinical Pharmacology/Toxicology

Although there are no unresolved pharmacology/toxicology issues (the reader is referred to the Nonclinical Pharmacology/Toxicology review by Norman See, PhD), there are informational needs not required for approval which the applicant has agreed to address post-approval. These include evaluation of the carcinogenic potential of calcipotriene and evaluation of the carcinogenic potential of betamethasone diproprionate. As a part of this NDA, the applicant has agreed to conduct a two-year oral carcinogenicity study of calcipotriene in rats. As part of NDA 21-852 (Taclonex Ointment), the sponsor agreed to conduct two carcinogenicity studies of betamethasone diproprionate in mice and rats, respectively; the data from these studies will inform the labeling of Taclonex Scalp Topical Suspension as well as Taclonex ointment.

5. Clinical Pharmacology/Biopharmaceutics

Systemic exposure under maximal usage conditions was evaluated in Study MBL404, in which subjects used both Taclonex Scalp Topical Suspension and Taclonex Ointment to simulate the anticipated extreme of exposure that would occur in with labeled use in a clinical setting. Systemic exposure was assessed by measurement of drug and metabolite levels in serum, as well as measurement of serum and urine calcium and serum cortisol before and after cosyntropin stimulation. The results are discussed in detail in the Clinical Pharmacology/Biopharmaceutics Review by Abi Adebowale, PhD.

In brief, serum drug levels were undectectable (below the limit of quantitation) for both active moieties in all subjects, although serum levels of their metabolites were detected in a few subjects. Formal pharmacokinetics for Taclonex Scalp Topical Suspension could not be obtained from this study because subjects were dosed with two products, Taclonex ointment and Taclonex Scalp Topical Suspension, to replicate maximal clinical exposure.

Effect on stimulated cortisol and calcium metabolism were also evaluated. The reader is referred to the reviews by Abi Adebowale, PhD, and Brenda Carr, MD, for full discussion of the results. In summary, HPA axis suppression was demonstrated following use of Taclonex Scalp Topical Suspension and Taclonex Ointment, and alterations in calcium metabolism were observed in a small number of subjects. Alterations in calcium metabolism (increased urinary excretion in 2 of 35 subjects in study MBL404, and albumin-corrected serum calcium above the reference range in 5 of 1085 subjects in phase 3 studies) were not clinically significant in that they did not represent significant discursions from normal values nor did they result in related adverse events.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

7.1 Dose identification/selection and limitations

The concentrations of calcipotriene and betamethasone diproprionate in Taclonex Scalp Topical Suspension are the same as those in Taclonex ointment, as well as in products containing either calcipotriene or betamethasone diproprionate singly as active ingredients. Marketed products containing either or both of these active moieties have frequencies of application of qd to BID. Although the vehicle for Taclonex Scalp Topical Suspension is different than that of other marketed products, and differences in vehicle can impact safety and efficacy for topical products, nonetheless there is considerable clinical knowledge about the safety and efficacy of these two active moieties, both singly and in combination, in various topical formulations.

Regarding concentration, the applicant conducted a small dose-range finding study in 22 subjects with psoriasis (MBL0201FR) to evaluate various combinations of the two actives at concentrations of 0, 25 and 50ug of calcipotriene and 0, 0.25 and 0.50 mg of betamethasone, and Taclonex ointment and Taclonex Scalp Topical Suspension vehicle. Weaknesses of the study include the different location (body rather than scalp), small sample size, short treatment duration (3 wks), and lack of bracketing (no higher concentrations). A weak trend, apparently driven by betamethasone, favored the higher concentrations of both actives.

The applicant did not investigate frequency of application of their product. The applicant elected to pursue once daily application based on extrapolation of safety and efficacy seen with Taclonex ointment, and on the presumption that cosmetic intolerance (of the effect of the product on hair appearance and styling) would preclude patient compliance with BID use.

7.2 Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

The applicant conducted two pivotal trials, MBL405 and MBL406, to investigate the safety and efficacy of their product used once daily for up to eight weeks in the treatment of scalp psoriasis; both trials included arms for the monads, and MBL405 also included a vehicle arm.

The applicant initiated both trials prior to attending an End-of-Phase 2 meeting with the Agency. At the EOP2 meeting, the applicant was informed that the Agency would not consider subjects who achieved only a one-grade improvement on the IGA scale to be a success; thus subjects with "mild" disease would need to improve to "absence of disease" to be considered a win. The applicant subsequently revised the enrollment criteria for both trials to limit the remaining population to subjects with moderate to severe disease, and revised their analysis plan to include a second analysis (Amended Analysis) which excluded subjects with "mild" disease at baseline.

MBL405

The first pivotal trial, MBL405, was an international, multi-center, prospective, randomized, double-blind, parallel group study with four arms: Taclonex Scalp Topical Suspension, betamethasone in vehicle, calcipotriol in vehicle, and vehicle. After randomization in a 4:4:2:1 ratio, 1505 subjects applied their respective study drug once daily for up to eight weeks. The primary endpoint was a static Investigator's Global Assessment (IGA) score dichotomized to success (ie, "absence of disease" or "very mild disease") and failure, assessed week 8. Table 1, below, from Dr. Mat Soukup's biostatistics review, describes the results for the IGA:

Table 1: Investigator Gloval Results (ITT_LOCF) – Study 405

	Taclonex	Betamethasone	Calcipotriene	Vehicle
Applicant's Original Analysis				
N	541	556	272	136
Success (%)	378 (71.2%)	356 (64.0%)	100 (36.8%)	31 (22.8%)
p-value[1]		0.011	<.001	<.001
Applicant's Amended Analysis				
N	494	531	256	126
Success (%)	346 (70.0)	335 (63.1)	94 (36.7)	25 (19.8)
p-value[2]		0.0205	<.001	*<.001*
FDA Analysis				
N	541	556	272	136
Success (%)	400 (73.9)	399 (71.8)	125 (46.0)	40 (29.4)
p-value[1]		0.3963	<.001	<.001

[1]Cochran-Mantel-Haneszal test stratified by pooled site

[2]Fisher's Exact test due to small stratum in pooled sites

Source: Statistical Review and Evaluation of NDA 22-185, p.14, Mat Soukup, PhD

The Applicant's Original Analysis included subjects who had "mild" disease at baseline, and considered as successes those subjects who achieved "absence of disease" or "very mild disease" at week 8, but did not require a two-grade improvement. Thus subjects with mild disease at baseline who achieved "very mild"disease at week 8 (one grade improvement) were counted as a success.

The Applicant's Amended Analysis excluded subjects who had "mild" disease at baseline and considered as successes those subjects who achieved "absence of disease" or "very mild disease" at week 8, which is by definition a two-grade improvement.

The FDA Analysis included subjects who had "mild" disease at baseline and considered as successes those subjects who achieved a two-grade improvement. This was performed as a supportive analysis.

In all three analyses, Taclonex Scalp Topical Suspension is superior to vehicle. In both of the applicant's analyses, the combination also beats the monads. However, in the FDA analysis, which includes the subjects with "mild" disease at baseline and uses more stringent criteria to define success (two grade improvement), the contribution of calcipotriene is not demonstrated.

MBL406

The second pivotal trial, MBL406, was not identical to MBL405; MBL 406 was an international, multi-center, prospective, randomized, double-blind, parallel group study with three arms: Taclonex Scalp Topical Suspension, betamethasone in vehicle, and calcipotriol in vehicle. After randomization in a 2:2:1 ratio, 1418 subjects applied their respective study drug once daily for up to eight weeks. The primary endpoint was a static Investigator's Global Assessment (IGA) score dichotomized to success (ie, "absence of disease" or "very mild disease") and failure, assessed week 8. Table 1, below, from Dr. Mat Soukup's biostatistics review, describes the results for the IGA:

Table 2: Investigator Gloval Results (ITT_LOCF) – Study 406

	Taclonex	Betamethasone	Calcipotriol
Applicant's Original Analysis			
N	567	562	286
Success (%)	388 (68.4%)	343 (61.0%)	124 (43.4%)
p-value[1]		0.0079	< .001
Applicant's Amended Analysis			
N	512	517	251
Success (%)	344 (67.2%)	308 (59.6%)	103 (41.0%)
p-value[1]		0.0089	<.001
FDA Analysis			
N	567	562	286
Success (%)	428 (75.5%)	390 (69.4%)	142 (49.7%)
p-value[1]		0.0181	<.001

[1]Cochran-Mantel-Haneszal test stratified by pooled site
Source: Statistical Review and Evaluation of NDA 22-185, p.23, Mat Soukup, PhD

The Applicant's Original Analysis included subjects who had "mild" disease at baseline, and considered as successes those subjects who achieved "absence of disease" or "very mild disease" at week 8, but did not require a two-grade improvement. Thus subjects with mild disease at baseline who achieved "very mild"disease at week 8 (one grade improvement) were counted as a success.

The Applicant's Amended Analysis excluded subjects who had "mild" disease at baseline and considered as successes those subjects who achieved "absence of disease" or "very mild disease" at week 8, which is by definition a two-grade improvement.

The FDA Analysis included subjects who had "mild" disease at baseline and considered as successes those subjects who achieved a two-grade improvement. Again, this was performed as a supportive analysis.

In MBL406, the contributions of the monads are both demonstrated in all three analyses.

In summary, in their pivotal trials MBL405 and MBL406, the applicant demonstrated that Taclonex Scalp Topical Suspension applied once daily for up to 8 weeks is significantly superior to vehicle as well to each monad in the treatment of moderate to severe scalp psoriasis. The robustness of the pivotal trial data, as well as the consistency of the results from the supportive studies (detailed in the excellent reviews by Drs. Brenda Carr and Mat Soukup), allow determination of efficacy.

7.3 Other efficacy studies

The applicant also submitted results from three non-pivotal studies: two with active comparators, and one long-term safety study that was vehicle-controlled. The results were supportive.

7.4 Discussion of primary and secondary reviewers' comments and conclusions

I concur with the efficacy assessments articulated in the reviews of the clinical and biostatistical reviewers, Brenda Carr, MD, and Mat Soukup, PhD, respectively, and with their conclusions that the applicant has demonstrated the efficacy of Taclonex Scalp Topical Suspension and the contribution of each monad.

7.5 Pediatric use/PREA waivers/deferrals

The applicant requested a partial waiver for pediatric patients aged 0 to 11 years because the product would be unsafe in this age group. The primary safety concern is the potential adverse effects associated with betamethasone diproprionate, a potent corticosteroid. Hypothalamic-pituitary-adrenal (HPA) axis suppression can occur with corticosteroid use, and the risk is generally proportional to potency. Because of their higher body surface area to mass ratio, children are thought to be at higher risk of HPA axis suppression than adults. The sponsor summarized data from HPA axis suppression studies with Diprosone (betamethasone diproprionate) Ointment in pediatric patients that demonstrated increased risk of HPA axis suppression with decreasing age. There are no ultrapotent topical corticosteroids (including moieties other than betamethasone diproprionate) approved for use in children less than 12 years of age, although not all have been studied in children below this age. Accepted clinical practice guidelines advise use of the lowest potency steroid that is effective in children. Because Taclonex Scalp Topical Suspension is a fixed drug combination, and there are topical corticosteroid products which are lower potency than betamethasone diproprionate and are approved for use in children, Taclonex Scalp Topical Suspension would not be appropriate as a first-line therapy in children. Because of the risk of HPA axis suppression from betamethasone diproprionate, a potent corticosteroid, Taclonex Scalp Topical Suspension has safety concerns that preclude its study in children and a waiver for children 0 to 11 years is appropriate.

The applicant requested a deferral for pediatric patients aged 12 to 17, and proposed a safety and efficacy study in this population to be conducted post-approval. The [redacted] the proposed study would be to evaluate the safety of Taclonex Scalp Topical Suspension with

b(4)

b(4)

regard to HPA axis suppression and calcium metabolism in adolescents aged 12 to 17 years. Enrollment of – subjects was proposed.

Little effect on calcium metabolism was identified in adult subjects studied in the phase 3 trials. However, the impact of any disturbance in calcium metabolism in the adolescent population, who may be still growing, could be more profound, and therefore needs to be characterized with greater precision than the proposed sample size would allow. The applicant will need to study calcium metabolism in 100 adolescent subjects, with assessment of HPA axis function in a subset of 30 subjects.

b(4)

The application was presented to the Pediatric Review Committee (PeRC) on March 19, 2008. The committee

b(4)

7.6 Discussion of notable efficacy issues (resolved or outstanding).

There are no outstanding efficacy issues.

8. Safety

8.1 General safety considerations

The safety database is adequate. No unexpected safety signals emerged.

8.2 Safety findings from submitted clinical trials

There were no deaths or SAEs attributable to Taclonex Scalp Topical Suspension during the development program. The most frequently reported adverse event was pruritus. Collection of adverse events and assessment of local tolerance did not reveal unexpected safety signals.

The reader is referred to the Clinical Review by Brenda Carr, MD, for full discussion.

8.4 Special safety concerns

HPA axis suppression and effects on calcium metabolism are special safety concerns with this combination drug product.

The effect of Taclonex Scalp Topical Suspension on the HPA axis was assessed in a single study (MBL404) in 32 adult patients with extensive psoriasis involving at least 30% of the scalp and 15% to 30% of the total body surface area. Subjects were treated with both Taclonex Ointment to their non-scalp lesions and Taclonex Scalp Topical Suspension to the scalp for the first four weeks, and if not cleared, with Taclonex Scalp Topical Suspension alone for weeks four to eight. HPA axis suppression was documented in 5 of 32 subjects (15.6%) at four weeks, and in two of eleven subjects (18.2%) who continued treatment for eight weeks. The risk of HPA axis suppression is expected because the product contains betamethasone diproprionate and it is addressed in labeling.

Calcium metabolism was assessed by measurement of urinary calcium levels in study MBL 404 (described above), and measurement of albumin corrected serum calcium in the Phase 3 studies. In Study MBL404, two subjects manifested 24-hour urinary calcium levels above the normal range, one at 4 weeks (this subject also had an elevated 24-hour urinary calcium level at baseline) and the other at 8 weeks; no subjects had serum calcium values above the reference range. In the Phase 3 studies (MBL 405, MBL406, and MBL502), 5 subjects had albumin-corrected serum calcium levels during treatment that were above the reference range. However, the discursions were not large ($\leq$0.11mmol/L) and not considered clinically significant. Additionally, the rates of hypercalcemia were similar across all arms (Dovobet, calcipotriene, betamethasone, and vehicle), and mean albumin corrected calcium values were similar across all arms at end of treatment. Hence routine laboratory monitoring of serum calcium does not appear necessary with labeled use. The reader is referred to the reviews by Brenda Carr, MD, and Abi Adebowale, PhD, for full discussion.

9. Advisory Committee Meeting

No Advisory Committee meeting was necessary or held.

10. Other Relevant Regulatory Issues

Not applicable.

11. Labeling

Labeling negotiations were ongoing at the time of completion of this review.

12. Risk Benefit Assessment

Taclonex Scalp Topical Suspension was demonstrated to be effective in the treatment of moderate to severe scalp psoriasis in adult patients. No unexpected safety signals were identified. The risk-benefit calculus for this product is appropriate for the indication of moderate to severe scalp psoriasis in adult patients.

13. Conclusions and Recommendations

13.1 Regulatory action

I concur with the recommendation of the multi-disciplinary review team for approval of NDA 22-185, pending agreement of the applicant with the recommended post-marketing commitments and revised labeling.

13.2 Postmarketing Risk Management Activities

Postmarketing risk management beyond professional labeling, prescription status, and routine pharmacovigilance (already in place) is not needed.

13.3 Postmarketing studies

The applicant should conduct studies to fulfill the following post-marketing commitments:

1. The applicant should evaluate the carcinogenicity of calcipotriene in a two-year oral study in rats. The sponsor should submit a protocol for this study with appropriate supporting documents for evaluation by the executive carcinogenicity assessment committee of CDER following approval of NDA 22-185.

Protocol Submission: [redacted]
Study Start: [redacted]
Final Report Submission: [redacted]

b(4)

2. The applicant should conduct a study in pediatric patients with scalp psoriasis, ages 12 to 17 years. Enrollment should be sufficient to allow for 100 evaluable subjects. The sponsor should evaluate the effect of their product on calcium metabolism in all subjects and the effects of their product on the hypothalamic-pituitary-adrenal axis in a subset of 30 subjects.

Protocol Submission: [redacted]
Study Start: [redacted]
Final Report Submission: [redacted]

b(4)

Discussion with the applicant regarding the second study was ongoing at the time of completion of this review.

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

/s/

Jill Lindstrom
4/23/2008 12:54:57 PM
MEDICAL OFFICER

Stanka Kukich
4/23/2008 06:00:10 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-185
Submission Code	N
Letter Date	June 19, 2007
Stamp Date	June 28, 2007
PDUFA Goal Date	April 28, 2008
Reviewer Name	Brenda Carr, M.D.
Review Completion Date	April 14, 2008
Established Name	calcipotriene and betamethasone dipropionate
(Proposed) Trade Name	Taclonex Scalp® suspension
Therapeutic Class	vitamin D analog and corticosteroid
Applicant	LEO Pharmaceutical Products Ltd. A/S
Priority Designation	S
Formulation	suspension
Dosing Regimen	once daily for up to 8 weeks
Indication	Psoriasis vulgaris of the scalp
Intended Population	adults 18 years and above

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

PAREXEL International (Parexel) has submitted a marketing application for a fixed combination suspension product containing the two active ingredients, calcipotriene hydrate 50 mcg/g (a vitamin D analog) and betamethasone dipropionate 0.5 mg/g (a corticosteroid). The combination product is proposed for the once daily topical treatment of psoriasis vulgaris of the scalp (scalp psoriasis), in adults aged 18 years and above.

The new product is not marketed anywhere. However, both active ingredients have been approved individually in various formulations for marketing in the United States. Additionally, the applicant markets a fixed combination ointment product containing the same active ingredients as the new product and at the same concentrations. In the United States, the ointment is marketed under the trade name "Taclonex".

The applicant has adequately demonstrated that their product is safe and effective for the treatment of moderate to severe psoriasis of the scalp in subjects 18 years and older under the proposed conditions of use of once daily for up to eight weeks.

From a clinical perspective, it is recommended that the application be approved.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Adverse events of particular interest would be those that suggest possible systemic effect(s) from the product as a function of systemic exposure to either of the two active ingredients. Such events would include those that suggest that calcium metabolism and/or the hypothalamic-pituitary-adrenal (HPA) axis have been impacted. Local adverse events would also be of interest and would include those related to use of a topical corticosteroid, such as telangiectasias, atrophy, hypopigmentation, etc.

1.2.2 Required Phase 4 Commitments

The applicant should conduct a study in pediatric patients with scalp psoriasis, ages 12 to 17 years. Enrollment should be sufficient to allow for 100 evaluable subjects. The sponsor should evaluate the effect of their product on calcium metabolism in all subjects and the effects of their product on the hypothalamic-pituitary-adrenal axis in a subset of 30 subjects. A protocol should be submitted

b(4)

The study will start

and final clinical study report submission will be

The applicant should evaluate the carcinogenicity of calcipotriene in a two-year oral study in rats. The applicant should submit a protocol for this study with appropriate supporting documents for evaluation by the executive carcinogenicity assessment committee of CDER following approval of NDA 22-185.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The applicant conducted two adequate and well-controlled pivotal trials: MBL 0405 INT and MBL 0406 INT. Study MBL 0405 INT (0405) was active and vehicle controlled. Specifically, the treatment arms were: the applicant's product, betamethasone in the applicant's vehicle (betamethasone), calcipotriol in the applicant's vehicle (calcipotriol), and vehicle. Study MBL 0406 INT (0406) did not include a vehicle arm (i.e. active controls only), but was otherwise identical in design to 0405 in regard to Inclusion and Exclusion Criteria, clinical assessments, efficacy assessments, etc. Both pivotal trials were appropriately designed to allow for demonstration of the contribution to efficacy for each of the active ingredients in the fixed combination product. Each active ingredient was adequately shown to contribute to efficacy, and thus 21 CFR 300.50 was adequately addressed.

The applicant submitted data from four additional trials that included controlled (active or vehicle), 8-week treatment periods as being supportive of efficacy. The primary efficacy criterion was the proportion of subjects who achieved "Controlled disease" (defined as "Absence of disease" or "Very mild disease") according to an investigator's global assessment (IGA) of disease severity at Week 8 (end of treatment).

1.3.2 Efficacy

The applicant conducted two pivotal trials. Efficacy of the combination product was adequately demonstrated in both pivotal trials. The combination product was superior to all comparators in each study for the proportion of subjects with "Controlled Disease" at Week 8, as assessed on a static global severity scale. ("Controlled Disease" was defined as subjects with "absence of disease" or "very mild disease" at efficacy assessment.) The degree of superiority was statistically significant for all comparisons in both pivotal trials:

Study 0405

Combination	Betamehasone	Calcipotriene	Vehilce

Sample Size	494	531	256	126
Success (%)	346 (70.0)	335 (63.1)	94 (36.7)	25 (19.8)
p-value[g]	-	0.0205	< .001	< .001

Study 0406

	Combination	Betamehasone	Calcipotriene
Sample Size	512	517	251
Success (%)	344 (67.2)	308 (59.6)	103 (41.0)
p-value[f]	-	0.0089	< .001

The combination product was superior to each monad and to vehicle in MBL 0405 INT, and the combination product was superior to each active comparator in MBL 0406 INT.

Supportive evidence of efficacy was provided from four additional trials which included once daily treatment for 8 weeks under controlled conditions (i.e. the 8-week period included a control of some sort, active or vehicle): MBL 0502 US, MBL 0503 INT, MBL 0401 INT, and MBL 0407 INT. The combination product was superior to comparator in each of the supportive studies.

The applicant had adequately demonstrated that their combination product is effective in the treatment of moderate to severe psoriasis of the scalp.

1.3.3 Safety

The four most common adverse events in the combination gel group were nasopharyngitis [79 subjects (4.0%)], headache [66 subjects (3.4%)], pruritus [48 subjects (2.5%)], psoriasis [44 subjects (2.3%)] and upper respiratory tract infection [40 subjects (2.0%)]. The incidence of nasopharyngitis was highest (and the same) in the betamethasone and vehicle groups: 5.8%. The incidence of headache ranged from 2.9% in the vehicle group to 3.8% in the betamethasone group. The incidence of pruritus was highest in the calcipotriol group [77 subjects (7.9%), a possible function of known irritancy of the substance, blunted by the betamethasone in the combination group (incidence of pruritus was the same between the combination and betamethasone groups). The incidence of psoriasis was highest in the calcipotriol group (3.1%) and was similar between the other three treatment groups (2.1 to 2.3%). The incidence of upper respiratory tract infection was highest in the vehicle group (3.5%) and lowest in the calcipotriol group (1.3%).

The incidence of irritation was lowest (and the same) in the combination and betamethasone groups (0.5%) as compared to the calcipotriol and vehicle groups (3.6% and 2.9%, respectively). This is consistent with the irritancy associated with calcipotriol, but could also suggests that the vehicle could have some potential for irritancy.

The most frequently reported adverse drug reaction in subjects treated with the combination product was pruritus. Treatment-related pruritus was reported for 1.8% of subjects in the combination group, 1.7% in the betamethasone group, 7.4% in the

calcipotriol group, and 4.0% in the vehicle group. All other adverse drug reactions in the combination group occurred in ≤0.5% of subjects.

1.3.4 Dosing Regimen and Administration

The recommended dosing is once daily to affected areas on the scalp for up to 8 weeks. The maximum weekly dose should not exceed 100 g. The proposed maximum weekly dose is driven by the calcipotriene component, i.e. this is the maximum weekly dose for products containing calcipotriene.

1.3.5 Drug-Drug Interactions

Drug-drug interaction studies were not done.

1.3.6 Special Populations

The product has not been adequately studied in subjects with renal or hepatic insufficiency. Pregnant and nursing women were excluded from study; however, three confirmed pregnancies occurred in the development program (spontaneous abortion was the outcome for two pregnancies, and delivery of a healthy boy was the outcome for the third). There were no particular concerns identified pertaining to the geriatric age group.

The product has not been studied in the pediatric population. A deferral was issued for study of the product in the age group of 12 to 17 years, and a partial waiver was issued for study of the product in the age group of 0 through 11 years.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

PAREXEL International (Parexel) has submitted a marketing application for a fixed combination suspension product containing the two active ingredients, calcipotriene hydrate 50 mcg/g (a vitamin D analog) and betamethasone dipropionate 0.5 mg/g (a corticosteroid). The combination product is proposed for the once daily topical treatment of psoriasis vulgaris of the scalp (scalp psoriasis), in adults aged 18 years and above.

The new product is not marketed anywhere. However, both active ingredients have been approved individually in various formulations for marketing in the United States. Additionally, the applicant markets a fixed combination ointment product containing the same active ingredients as the new product and at the same concentrations. In the United States, the ointment is marketed under the trade name "Taclonex". In other countries the ointment is marketed under the trade names "Daivobet" or "Dovobet", and the applicant refers to the new product as "Daivobet" in this marketing application (e.g. in data tables). Therefore, references to "Daivobet" in this review refer to the new combination suspension product. Ultimately, however, the applicant has proposed "Taclonex" as the trade name for the new product, i.e. the same name under which the ointment is marketed.

Per p. 14 of the safety summary, the new formulation "has been developed to supplement calcipotriol plus betamethasone dipropionate combination ointment..." Per the "Definition of Terms" provided in the Clinical Overview, calcipotriene is the US Adopted Name (USAN) and calcipotriol is the International Non-Proprietary Name (INN). Therefore, in this review, "calcipotriene" and "calcipotriol" refer to the same substance.

As the marketing application was being prepared, the applicant considered the formulation to be a "gel" and refers to it as such in the submission. However, during the review process, the chemistry manufacturing and controls (CMC) reviewer advised the applicant that based on the product's flow behavior, the product was a liquid and not a semi-solid. Thus, it should be labeled as a suspension, rather than a gel; the applicant agreed. Therefore references to "gel" in the review, e.g. in tables from the application, should be taken to refer to the suspension product.

LEO Pharmaceutical Products Ltd. A/S (Leo) of Ballerup, Denmark is the manufacturer of calcipotriene hydrate contained in the calcipotriene single- ingredient products marketed under the trade name "Dovonex", as well as the fixed combination ointment product marketed as "Taclonex". Parexel is acting as the U.S. agent for Leo. In this review, the term "applicant" refers to Leo.

2.2 Currently Available Treatment for Indications

Currently available treatments for psoriasis of the scalp include corticosteroids (in gel, foam, oil and solution formulations) and calcipotriene (solution formulation).

2.3 Availability of Proposed Active Ingredient in the United States

Calcipotriene hydrate (calcipotriene) is marketed in the United States by Bristol-Meyers Squibb in three formulations under the trade name Dovonex®:

- Dovonex® ointment: approved under NDA 20-723 on December 29, 1993 and indicated for once or twice daily treatment of plaque psoriasis in adults.
- Dovonex® cream: approved under NDA 20-554 on July 22, 1996 and indicated for treatment of plaque psoriasis.
- Dovonex® Scalp Solution: approved under NDA 20-611 on March 3, 1997 and indicated for treatment of chronic, moderately severe scalp psoriasis.

Per the "Drugs @FDA" website, a generic calcipotriene solution has been approved, and the sponsor is Hitech Pharma.

Betamethasone dipropionate (betamethasone) is currently marketed in the United States in a number of formulations (creams, ointments, and lotions) for the treatment of corticosteroid-responsive dermatoses. The initial approval of a product containing this active ingredient appears to have been February 1, 1977, and several products containing the substance have been approved under abbreviated new drug applications. With the antifungal clotrimazole, betamethasone is also currently marketed in combination products (cream and lotion formulations) and is indicated in patients 17 years and older for the topical treatment of certain symptomatic, inflammatory fungal infections of the skin.

2.4 Important Issues With Pharmacologically Related Products

The adverse event profile for each of the active ingredients is well-established. As a vitamin D analog, systemic safety concerns pertaining to calcipotriene relate to those seen with vitamin D toxicity, namely the manifestations of hypercalcemia. Signs and symptoms of hypercalcemia are a function of the extent of the calcium elevation and may include anorexia, nausea, vomiting, constipation, altered mental status, bone pain, and arrhythmias, etc. Irritation has been reported with topical calcipotriene products.

As a topical corticosteroid, safety concerns pertaining to betamethasone relate to the local effects seen with this class of drugs, which include atrophy, telangiectasias, hypopigmentation, and striae. Additionally, should there be sufficient systemic absorption of a topical corticosteroid, manifestations of toxicity could be those seen with systemic administration of corticosteroids, such as hypothalamic-pituitary-adrenal (HPA) axis suppression, cushingoid changes, etc.

2.5 Presubmission Regulatory Activity

The product was developed under IND 67,835.

Pre-IND Meeting: June 10, 2004

Chemistry Manufacturing and Controls (CMC) b(4)

- In the IND submission, the sponsor should justify designating the proposed drug product as a gel formulation. The proposed formulation [redacted]
- During the meeting, the applicant gave their justification for calling the product a "gel". They indicated [redacted] made the finished product a gel. b(4)
- The Agency accepted the applicant's explanation "for the time being" and would await additional information during the IND before ruling on this description. The applicant would provide additional information on the physical characteristics that will support the identification of the dosage form.

Biopharmaceutics:

- Using calcium metabolism/HPA axis assessment endpoints as surrogates for bioavailability was acceptable provided they are properly validated and other direct in vivo methods of assessment are not feasible
- To use calcium homeostasis as a marker for drug absorption, baseline and on-treatment daily calcium balance should be determined for each individual by serum calcium assessments with concomitant timed urinary calcium excretion; because of the unusual nature of this trial, the applicant was encouraged to submit the protocol to the FDA for comment

Clinical

- The applicant proposed to measure serum calcium values in the Phase 3 studies as a surrogate for calcipotriol levels, and to conduct a Phase 1 hypothalamic-pituitary-adrenal (HPA) axis suppression test.
- The applicant was advised to add a 24-hour urine for calcium on the last day of drug exposure; the applicant proposed to incorporate the calcium measures into the HPA axis suppression study. A minimum of 30 evaluable subjects with extensive scalp and body psoriasis would be studied, and subjects would be treated for 4 weeks. It was agreed that weekly serum calcium levels would be obtained and baseline and end-of treatment cosyntropin stimulation testing and 24-hour urine for urinary calcium levels would be done.
- The applicant indicated that they had developed a six-point Investigator's Global Assessment (IGA) scale for the assessment of scalp psoriasis, since there was no

validated scale for such. The scale was intended for use as the primary endpoint in the pivotal trials and was being evaluated in a Phase 2 trial at the time of the Pre-IND meeting. "Controlled disease" was defined as absence of disease or very mild disease on the IGA. The agency found the IGA included in the briefing package to be "reasonable" with the following exceptions:

1. "The sentence 'The disease is controlled.' should be deleted from the Absence of disease category.
2. "Under Very mild disease, the sentence 'The disease is controlled, but not entirely cleared' should be deleted.
3. "Under Very mild disease it should only allow for the presence of minimum erythema."

Additional comments addressed:

- The applicant's plans to conduct the Phase 3 trials in Europe and Canada. The Agency recommended that the applicant study diseased populations reflective of U.S. demographics who receive care consistent with U.S. practice of medicine.
- The Agency inquired about the applicant's plans for pediatric development and the rationale for proposing the product for "adults over 18 years of age."
- Dermal safety studies
- The applicant should seek to study HPA axis suppression in adults and subjects 12 to < 18 years. The applicant stated [redacted] used in the HPA axis testing) and Cortrosyn were the same. b(4)
- The study should be powered to show that the combination dyad product is superior to the monads and to vehicle. To gain approval, replication of superiority of the dyad to the monads may be needed. Comments and commitments by the Division concerning Phase 3 studies will be based on data collected in Phase 2 trial(s). There could be some reduction in the factorial design, based on what is learned in Phase 2.
- HPA axis suppression studies are safety studies; efficacy data from such studies have no regulatory utility.
- Each patient in the HPA axis suppression study must have widespread scalp involvement in addition to other areas of the body.

Biostatistics

- The appropriate dose and treatment regimen should be identified in Phase 2 trials, and Phase 2 trials should include the endpoints that would be considered primary in Phase 3 trials. Estimates of these endpoints from Phase 2 trials could be used to power Phase 3 trials. b(4)
- The applicant indicated that the Phase 3 trials would include co-primary endpoints [redacted] The protocol should provide sufficient detail so that the endpoints and analyses agreed

upon with the Division for registration in the United States are clearly defined and any necessary adjustments for multiplicity are accounted for.

The applicant was advised to request an End-of-Phase 2 meeting. Comments on Phase 1 and Phase 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.

End-of-Phase 2 Meeting: December 1, 2004

Clinical Pharmacology and Biopharmaceutics:

- The applicant again indicated that they would perform a separate HPA axis suppression study. The Agency responded:

"For the HPA axis (s)tudy, it appears that the sponsor is proposing to apply the Dovobet gel to the scalp and the Dovobet ointment to the trunk/limbs concurrently, to the same patient as a once daily application. The sponsor is advised that the use of both products concurrently will depend on the outcome of the HPA axis suppression study and the calcium metabolism evaluation following application of the ointment alone. As an example, if the outcome of the study for the ointment alone is negative then a combination of both the ointment and the gel will provide additional information to make appropriate inferences."

- The applicant had developed an assay to determine the plasma levels of betamethasone and calcipotriol in their toxicokinetic studies. The applicant was encouraged to also assess the plasma levels of the active ingredients in human plasma following maximal use of the product, with this assay method (if feasible). The Agency recommended that the applicant explore the relationship between the plasma levels and the serum cortisol levels, which the applicant stated was their intention to do in an exploratory way during the HPA axis study.
- Serum calcium would be measured in the Phase 3 studies and serum calcium and 24-hour urinary calcium excretion in the HPA axis study. The applicant had proposed that calcium metabolism would be evaluated in 10 of the 30 proposed evaluable subjects and that only subjects on a "Calcium Fixed Diet" would be included in the calcium metabolism evaluation. During the meeting, the applicant stated that all 30 evaluable subjects would be included in the calcium metabolism evaluation and would not be on a calcium restricted diet but an individualized calcium diet (to decrease the variation in baseline calcium).

Clinical

- The skin irritation and sensitization potential study appeared appropriate.
- The Agency had moved toward using the 30-minute post stimulation time-point for evaluating HPA axis suppression; evaluation at the 60-minute time point was not necessary.

- The Agency had moved toward using the absolute serum cortisol value as a marker of HPA axis suppression and would consider a serum cortisol value of 18μg/dL or less after Cortrosyn stimulation at 30 minutes as a sign of HPA axis suppression. Evidence of a normally functioning HPA axis would be a 30-minute post stimulation value of serum cortisol greater than18 μg/dL.
- Subjects with evidence of HPA axis suppression should not receive a follow-up stimulation test prior to 4 weeks after suppression was noted.

The applicant advised that they planned to conduct two international pivotal Phase 3 studies (MBL 0405 and MBL 0406). These studies would compare the combination product with each active component in the product's vehicle, applied once daily to the scalp for up to 8 weeks. Study MBL 0405 INT would also include a vehicle treatment arm. The primary end-point would be the proportion of patients with "Controlled disease" based on the Investigator Global Assessment (IGA) of Disease Severity. The sample size for the two pivotal studies was determined from the results of a Phase 2 proof-of-concept study (MBL 0401 INT) and clinical trials conducted with calcipotriol in a scalp solution..."

- "The FDA does use the IGA as the primary endpoint in these types of trials." Depending on the morphologic descriptors for the category of "clear" and "almost clear", the scale would be dichotomized to success vs. failure (with success being "clear" and "almost clear"). The Agency advised that the IGA scale in the proposed protocol was not adequate or acceptable, e.g. the scale needed morphologic descriptors that described what "moderate" meant. The descriptors should be clear, to reduce investigator variability from site to site. The Agency advised that a scale with severity levels of clear, almost clear, mild, moderate, and severe would be considered. Subjects with "very mild disease" or "almost clear" disease should not have any discrete lesions present.
- The applicant stated that the six-point scale was the one used in the Phase 2 studies. It was agreed that the six-point scale could be used; however, clear distinguishing morphologic descriptors should be used to define each severity level. The Agency was especially interested in seeing a clear difference between the "severe" and "very severe" levels. This could also be supported by clinical photographs.
- Subjects with "mild" disease at baseline would need to achieve "absence of disease" to be considered successes. The Agency suggested that the applicant might want to consider that subjects entering the trial have moderate scalp disease.
- The Agency advised that the scales for the secondary efficacy variables that include the clinical signs of psoriasis should also have morphologic descriptors to accompany each level of severity. These scales should also be dichotomized to success vs. failure a priori in the protocol. Success should be measured via a static assessment and not a change from baseline, as was suggested in the protocol. The Agency has not found secondary endpoints that refer to a change from baseline to be very useful.

- In diseases such as psoriasis, while variables such as "treatment success" and quality of life issues are important, hard efficacy data, the IGA and the secondary endpoints outlined above are reflective of these issues.
- The Agency advised that the applicant might want to consider pruritus severity as a secondary efficacy variable. The applicant declined.
- The applicant was referred to the ICH E5 guideline as the development program for any drug marketed in the United States should include trials that reflect the heterogeneous population of the United States. This could be done by a small U.S. trial or by adding centers in the United States to be certain to capture those populations in the pivotal studies that will be evaluated for efficacy of the drug product. For this product, there should also be representation of different hair textures, styles, grooming practices that may cross cultures.
- The applicant indicated that they planned to conduct a 52-week controlled clinical safety study in 400 subjects with scalp psoriasis treated with the combination product to ensure at least 300 treated subjects for at least 26 weeks. One-year data from at least 100 subjects would also be available. The applicant considered that this study would address the ICH E1A guideline and provide sufficient documentation of long-term safety. The Agency agreed.
- The applicant indicated their plans to request a partial pediatric waiver for children up to 12 years and to perform a post-marketing study in adolescents 12-17 years to investigate efficacy and safety, including HPA axis testing, in this population. The Agency stated this appeared to be a "reasonable approach."
- The agency was uncertain of the regulatory utility of the Skin Atrophy Study as designed. The applicant was requested to define what they hoped to obtain in labeling from the trial. The applicant responded that there would be no labeling claim from this study. b(4)
- The applicant was advised that a single dose UV study in humans is not an adequate surrogate for a preclinical photocarcinogenicity study.
- The Agency invited the applicant to submit the protocols for the HPA axis study and Phase 3 studies to the IND through the 45-day Special Protocol Assessment (SPA) mechanism for agency review, comment and agreement, prior to study initiation (Project Management comment).

Statistical

- The Phase 2 program only assessed the treatment effect using an IGA similar to the one proposed for the Phase 3 studies for the combination product versus betamethasone. Consequently, the information on the IGA success rate for the calcipotriol and vehicle arms is limited. In addition, the applicant proposed to use an unequal randomization scheme (4:4:2:1 for the combination, betamethasone, calcipotriol, and vehicle). Without additional Phase 2 information on the calcipotriol and vehicle success rates, the Phase 3 studies may be underpowered. The applicant was encouraged to conduct a Phase 2 study to estimate the success rates for all treatment arms before proceeding to Phase 3 studies, in order to provide more reliable estimates for sample size calculations.

- The Agency also stated that if the success criteria used in the Phase 2 trials, such as the handling of subjects who discontinue early due to clearance or the final disease state needed for success for subjects with mild baseline disease, differs from the criteria recommended by the Agency for Phase 3 trials, the sample size may need to be re-estimated.
- The applicant was encouraged to include a vehicle arm in both Phase 3 studies to make it easier to interpret the results of the second study. In addition, when all subjects are on an active treatment, there may be a tendency to overestimate response which may make it harder to establish efficacy.
- Secondary endpoints should be limited in number and clinically relevant. If many clinically relevant secondary endpoints are specified, [redacted] may be necessary. The Agency emphasized that any necessary [redacted] must be specified in the protocol as such adjustments cannot be made post hoc. b(4)
- While it was acceptable to discontinue treatment early in subjects who achieve "absence of disease," these subjects should remain in the study and be evaluated for efficacy at Day 56 to ensure continued clearance.
- Due to the large number of centers (approximately 100 per study) and the unequal treatment allocation, the number of subjects per center, particularly on the calcipotriol and vehicle arms, may be small. The applicant was encouraged to design the studies with fewer centers so that each center enrolled an adequate number of subjects per treatment arm, avoiding problems in the analysis due to cells with small frequencies. The protocol might specify an approach for pooling centers in case the actual enrollment is small. The Agency emphasized that a plan for pooling centers, if needed, should be included in the protocol rather than deferred to the blinded data review stage.
- The protocols for the Phase 3 studies should ensure that there is consistency in the evaluation of subjects across different countries.
- The Agency recommended including a significance level for testing treatment by center interaction, such as 0.10 in the protocol. The protocol should include a sensitivity analysis to assess the nature and effect of the treatment by center interaction if it is present. The Agency stated that the test for interaction is used as a guide to identify potential problems due to treatment by center interaction and that interactions should be thoroughly investigated and explained. The sensitivity analyses should be designed to ensure that the study conclusions are not driven by results from extreme centers.

Request for Special Protocol Assessment, received March 8, 2005

The protocol for the HPA axis study was submitted for Special Protocol Assessment: protocol MBL 0404 FR was entitled "Effect of Dovobet/Daivobet Gel on the HPA Axis and Calcium Metabolism in Patients with Extensive Scalp Psoriasis."

Clinical comments on the protocol:

product in the NDA. The Agency advised that a final assessment of the dosage form could not be made until the sample had been fully evaluated and the information to be provided in the NDA had been reviewed.

- The proposed draft labeling would be written in US English using the USAN for the active substance "calcipotriene", whereas the remaining eCTD will be written in UK English using the INN "calcipotriol".
- It was agreed that the remaining 44-week data safety data from the study in racial and ethnic subgroups in the United States (MBL 0502 US) would be included in the 120-day safety update, and the final study report would be submitted at the end of 2007.

Note: Because of the nature of the issues raised and discussed at the Pre-NDA meeting regarding the statistical analyses, direct quotes from the minutes (with some formatting changes) are presented below:

Sponsor's Question 11:

"LEO has conducted two large adequate and well-controlled double-blind pivotal studies (MBL 0405 INT and MBL 0406 INT) investigating the efficacy and safety of up to 8 weeks treatment with Taclonex® Scalp gel vs. both betamethasone dipropionate in the gel vehicle and calcipotriol in the gel vehicle in patients with scalp psoriasis. Study MBL 0405 INT also included a gel vehicle control. These studies included 1505 and 1417 patients, respectively. These protocols were amended while the studies were ongoing as a result of the advice given by the FDA at the End of Phase 2 (EOP2) meeting and in context of knowledge gained from the Phase 2 study (MBL 0401 INT). The historical and evidentiary context for this decision is provided in the following paragraphs.

"At the pre-IND meeting held on June 10, 2004, the Investigator's Global Assessment of disease severity (IGA) scale and the success criteria as used in the ongoing Phase 2 study were discussed with the Division. For the two pivotal Phase 3 studies the scale was adjusted according to the FDA's comments. The IGA scale consists of six disease severity levels: 'absence', 'very mild', 'mild', 'moderate', 'severe', and 'very severe'. At the pre-IND meeting, the primary response criterion for the Phase 3 studies (patients with 'absence of disease' or 'very mild disease' at week 8 according to the IGA) was also discussed. Since the FDA did not comment on the proposed success criteria at the meeting, LEO inferred that the proposed definition of the success criteria was acceptable to the FDA.

"The statistical design of the Phase 3 studies included power calculations which were based on the results of the Phase 2 study. The first Phase 2 study results were available on August 2, 2004, and these results were used to design the Phase 3 study protocols. Importantly, the assumptions used in the power calculations were based on primary efficacy success criteria of 'absence of disease' or 'very mild disease', as presented by LEO at the pre-IND meeting.

"The IND was submitted on August 31, 2004, and the EOP2 meeting request was submitted on October 5, 2004. LEO had originally fully intended to start the two pivotal Phase 3 studies after the EOP2 meeting with the FDA.

"However, the EOP2 meeting occurred later than LEO had intended. And although the FDA was able to grant the meeting within the PDUFA timeline, LEO decided that it was necessary to start the studies before the EOP2 meeting in order to meet the seasonal requirements for the disease. Even so, the first patients were enrolled in Phase 3 studies only 2 weeks prior to the EOP2 meeting. The decision to start was based on the following considerations:

- "A delay in study start would imply a risk of not being able to complete enrollment for the studies before the summer period, during which it is known that a higher degree of spontaneous improvement in disease severity may occur due to sunlight and ambient humidity, making the evaluation of drug effects more difficult.
- "The IGA scale on which the primary endpoint was based had been discussed with the FDA at the Taclonex® Scalp gel pre-IND meeting on June 10, 2004, and LEO subsequently modified the IGA to be fully consistent with the FDA comments.
- "At the pre-NDA meeting for Taclonex® Ointment held on May 10, 2004, the FDA did not raise any objections to the pivotal study which employed a design similar to that of the two pivotal Taclonex® Scalp gel studies, including definition of the primary endpoint.

"Therefore, LEO did not expect that major comments to the study designs would be raised by the FDA at the EOP2 meeting.

"At the EOP2 meeting held on December 1, 2004, the six-point IGA rating scale of disease severity was reconfirmed from the pre-IND meeting; however, the FDA stated to LEO for the first time that patients with 'mild disease' severity at baseline would have to achieve 'absence of disease' on the IGA scale in order to be considered a success, a two-level decrease in severity. As stated in the EOP2 minutes: *'If the Sponsor is going to allow patients with mild disease into the trial at baseline, those patients would have achieve an "absence of disease" on the IGA scale in order to be considered a success'.* LEO realized that this request would reduce the power of the Phase 3 studies.

"Accordingly, *'the Division suggested that the sponsor may want to consider that patients who enter the trial have moderate disease of the scalp'.* LEO recognized that the Division was providing a solution to protect the power of the ongoing Phase 3 studies. Thus, it was necessary to amend the ongoing protocols, and the Sponsor promptly implemented this solution through the release of protocol amendments on January 20, 2005 (IND No. 67,835 Amendment Serial No. 010), only one month after receiving the final meeting minutes from the FDA. At the time these protocol amendments were issued, only 57 patients with "mild disease" had entered and 14 of these had left the studies (MBL 0405 INT and MBL 0406 INT). These studies, of course, remained double-blinded, from study start to completion.

"Is there any additional information that LEO can provide to the FDA regarding the chronology, and the Sponsor's decision-making process for the protocol amendments, which incorporated the FDA's solution to protect the power of the studies?

"**Agency response:**

- "It should be noted that the intention of the comment about redefining treatment success criteria or changing enrollment criteria was meant to provide a clinically relevant definition of treatment success and not to 'protect the power of the study'.
- "It is not clear if the sponsor communicated with the Agency at the End of Phase 2 Meeting held on 12/01/2004 the two Phase 3 trials were initiated approximately 2 week prior to the meeting. As such, the sponsor was taking the risk of initiating the Phase 3 trials prior to Agency comments about the Phase 3 trials which subsequently raised issues about the appropriate patient population, definition of treatment success, and impacts these may have on the power of the study.
- At the End of Phase 2 Meeting, the Division advised the sponsor to re-estimate the sample size calculations based upon changes in the definition of treatment success or possible changes in patient population. However given that the sponsor modified the patient population, it is not clear if such a calculation was performed and if this impacted the original sample size calculations. Further, if such a re-estimation was performed it does not appear that it was shared with the Agency for comment.

"The sponsor clarified that sample size was not re-estimated because mild patients constituted a small proportion of the population.

"**Sponsor's Question 12:**

"In the Phase 3 protocols for the two pivotal studies (MBL 0405 INT and MBL 0406 INT) originally submitted to the IND, the measure of the success efficacy endpoint included patients with 'mild disease' but defined success as 'absence of disease' or 'very mild disease'. For ease of discussion, this will be referred to as the 'Sponsor Original Analysis'.

"At the End of Phase 2 (EOP2) meeting held on December 1, 2004, the FDA stated that patients with "mild disease" severity at baseline would have to achieve 'absence of disease' on the IGA scale in order to be considered a success, a two-level decrease in severity. This will be referred to as the 'FDA Analysis'.

"As described in Question 11, amendments to both protocols were issued on January 20, 2005, which effected the exclusion of patients with 'mild disease'. However, a number of patients with 'mild disease' severity entered the studies before the amendments were fully implemented at all study sites. The last authority approval of the amendments was on April 28, 2005.

"The protocol-specified analysis of the two pivotal studies ('Sponsor Original Analysis') includes patients with 'mild disease', and does not address FDA's request at the EOP2 meeting that patients with 'mild disease' achieve absence of disease in order to be considered a success. LEO promptly amended the protocols to incorporate the FDA solution of exclusion of 'mild patients'. Since it was the Sponsor's intention to exclude the 'mild patients', LEO will perform an analysis ('Sponsor Amended Analysis') which the Sponsor believes to be fully consistent with both the 'Sponsor Original Analysis' and

the 'FDA Analysis'. For this analysis, only patients with at least 'moderate disease' will be included, and patient success will require that patients achieve an IGA rating of "absence of disease" or 'very mild disease', which means that all patients will experience at least a two-step decrease in the IGA scale.

"In fact, the exclusion of 'mild disease' patients from the 'Sponsor Original Analysis' would result in an analysis identical to the 'FDA Analysis' since the 'Sponsor Original Analysis' and the 'FDA Analysis' only differ in respect of the evaluation of patients with 'mild disease'.

"LEO will conduct these two additional analyses (the 'FDA Analysis' and the 'Sponsor Amended Analysis') and include them in the NDA together with the protocol specified analysis ('Sponsor Original Analysis'). These three analyses are collectively essential for the complete assessment of the efficacy of Taclonex® Scalp gel.

"Agency's Response:

"The sponsor's proposal of submitting 3 alternative analyses following the completion of the Phase 3 trials and un-blinding of the data raise concern about the multiplicity adjustment and the appropriate patient population to be analyzed. The Agency has several comments about such analyses.

- "As communicated to the sponsor at the End of Phase 2 Meeting, subjects that were enrolled as mild and almost clear at the end of treatment do not necessarily reflect a clinical benefit. Thus, the 'Sponsor's Original Analysis' might not be acceptable for establishing the efficacy.
- "By changing the baseline disease severity as measured by the subjective primary endpoint after already accruing subjects, it is not clear how such a change was implemented (protocol amendment, communication with investigators) and how it impacted the conduct of the trial and consequently the assessment of efficacy.
- "At this time, the appropriate approach for efficacy assessment will be a review issue.
- "In addition to the sponsor's proposed three analyses, please incorporate an indicator variable to denote which subjects enrolled prior to the protocol amendment and those enrolled after – note that this should be in addition to dates of enrollment.

Additional Discussion

- The applicant indicated that they were conducting a clinical study in the United States including 177 African-American and Hispanic patients (MBL 0502 US) to comply with the ICHE5 guideline. The applicant would include 8 weeks safety and efficacy results in the NDA to support the 8-week treatment claim proposed in the product label. The Agency agreed.
- The applicant should submit all post-marketing use of Taclonex ointment worldwide and especially in the United States.

2.6 Other Relevant Background Information

The sponsor included the implementation procedures for the amendments to the protocols for the pivotal studies in Module 5: "Report on Implementation of Amendments to MBL 0405 INT and MBL 0406 INT." Per the report, implementation was according to the applicant's standard operating procedure for amending study protocols. Procedures included:

- "Protocol amendments will have to be approved by LEO management and the International Co-ordinating Investigator (ICI).
- "The protocol amendment will then have to be approved by Ethics Committees (EC) or the Competent Authorities where required, in the country where the study is conducted.
- "All investigators for each centre will have to sign an implementation form (standard form appended to the I-SOP B3) stating that he/she acknowledges receipt of the Protocol Amendment and will implement all changes outlined in the amendment and inform his/her staff involved in the study and any changes it may lead to in the staff's study-related duties/responsibilities.

Two educational meetings were held to facilitate the implementation of the amendments (one with the International Co-ordinating Investigators and one with the national clinical trial managers).

Comment: The applicant appears to have taken reasonable steps to implement the amendments.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

From Section 3.2.P.1, the composition of the to-be-marketed product is:

Name of Components	Quantity per g	Function	Reference to Quality Standard(s)
Drug Substance(s)			
Calcipotriol (as Hydrate)	50 mcg [1)]	Drug Substance	Ph.Eur. (2284) / LEO
Betamethasone Dipropionate	0.643 mg [2)]	Drug substance	Ph.Eur. (0809) / USP
Excipients			
Paraffin, Liquid [3)]			Ph.Eur. (0239) / USP
PPG-15 Stearyl Ether [4)]			LEO
Castor Oil, Hydrogenated [5)]			Ph.Eur. (1497) / NF

b(4)

The product contains two drug substances in a fixed combination: Calcipotriol hydrate 50 mcg/g on the anhydrous basis and betamethasone dipropionate 0.643 mg/g. Per the

applicant, a thin oily layer may occur on the top surface on standing. Therefore, the bottle is to be shaken before use.

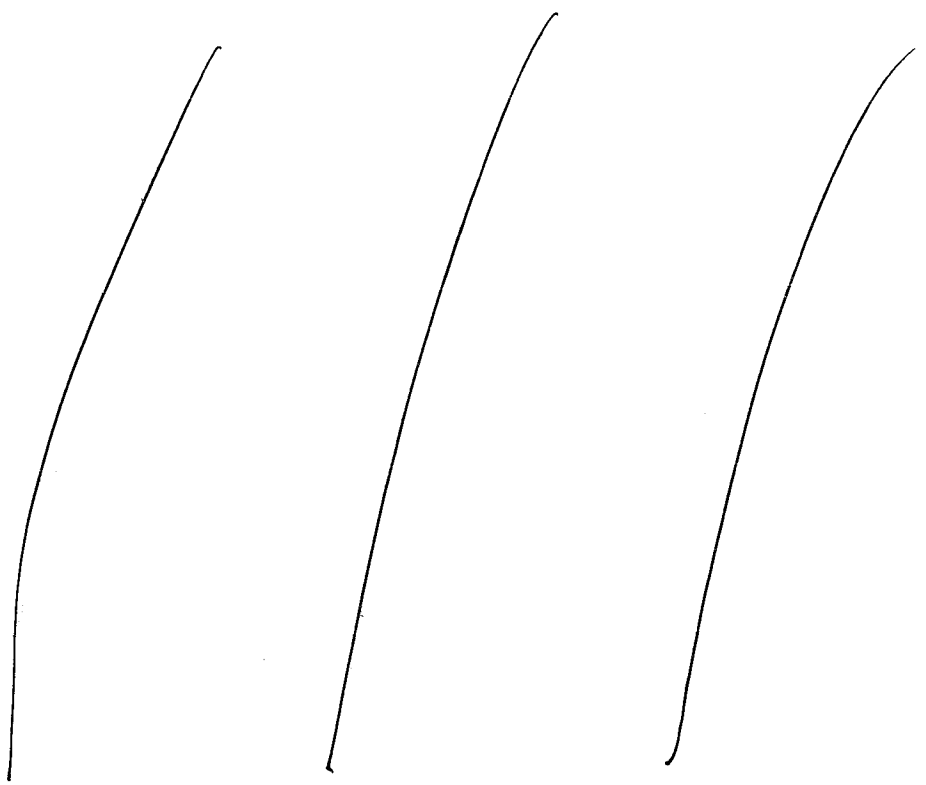
During the review cycle, the CMC reviewer informed the applicant that their product should be labeled as a suspension, rather than a gel, since the flow behavior of the product makes it a liquid and not a semi-solid. The applicant agreed to this during teleconference held on December 10, 2007. During the same teleconference, the applicant was requested to address the issue of ——— , in the in-use stability study, and the applicant provided a synopsis of the studies conducted to test the ——— ——— and the applicant was requested to formally submit the data. The CMC reviewer determined that the applicant adequately addressed this issue. b(4)

3.2 Animal Pharmacology/Toxicology

The pharmacology/ toxicology reviewer concluded that, "The clinical formulation of the drug product and the individual components of the product have been adequately evaluated for safety and the database supports the safety of the proposed use of the product."

The pharmacology/ toxicology reviewer recommended the following wording for the label

Pregnancy: b(4)



[redacted] b(4)

Per the pharmacology/ toxicology review, the applicant has committed to evaluate the carcinogenicity of calcipotriene in a two-year oral study in rats (post-approval).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

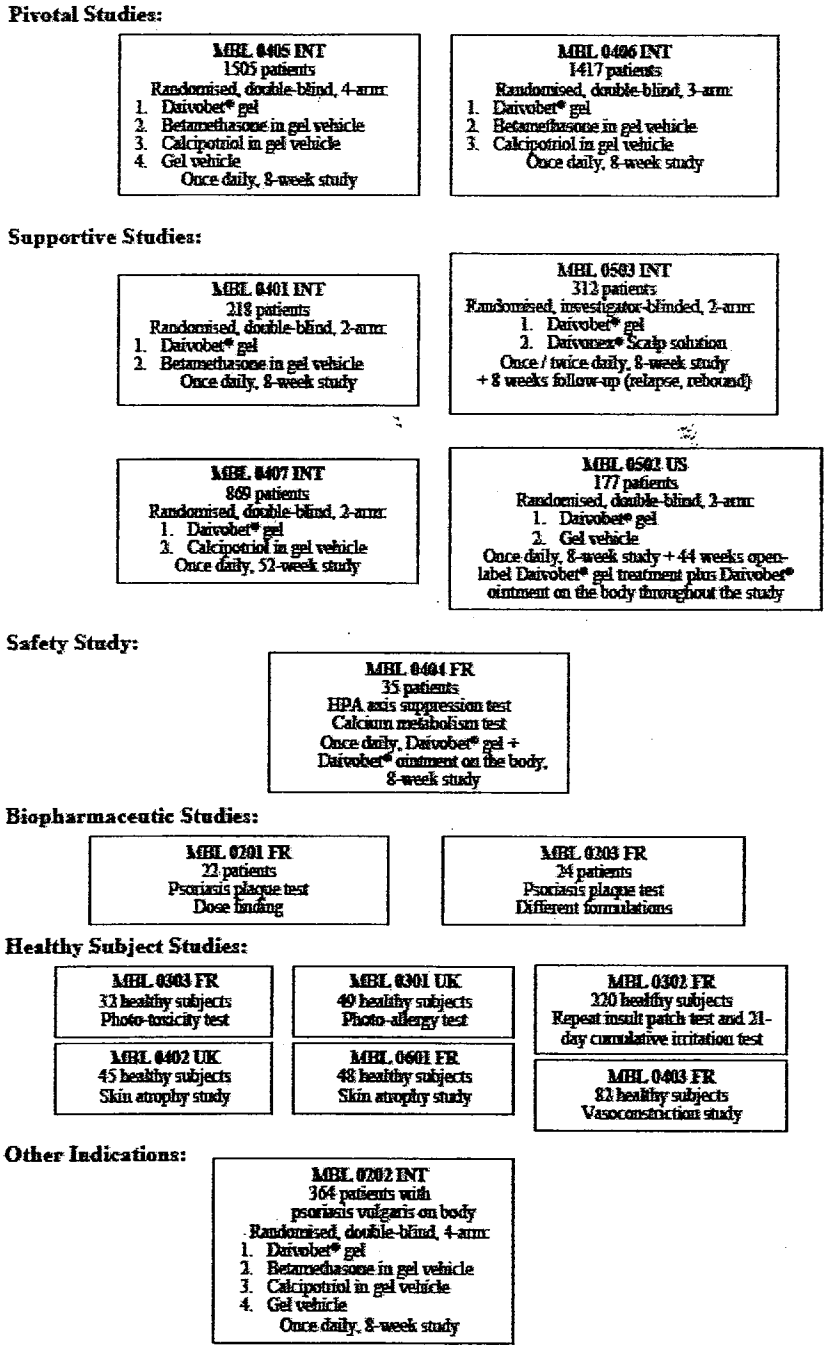
The source of the clinical data was that collected in the applicant's development program.

4.2 Tables of Clinical Studies

The clinical development program includes 16 studies: ten studies were conducted in subjects with psoriasis and six studies were conducted in healthy subjects without psoriasis.

The remainder of this page is left intentionally blank.

Applicant Figure 1: Overview of the Clinical Development Program table from p. 12 of overview:



4.3 Review Strategy

The review of efficacy was based primarily on data from the two pivotal studies (MBL 0405 INT and MBL 0406 INT), each of which was designed to be address CFR 300.50.

Supportive evidence of efficacy was provided from four studies that included controlled (active or vehicle), 8-week treatment periods, i.e. the treatment duration proposed for marketing studies:

- MBL 0502 US: a Phase 3 study conducted in the United States in African-American and Hispanic subjects to address ICHE5 (vehicle-controlled)
- MBL 0503 INT: a Phase 3 study which compared the applicant's product to Dovonex scalp solution (this study also assessed for relapse and rebound; per Section 4.2.3 of the Clinical Overview, [redacted] b(4)
- MBL 0407 INT: Phase 3 long-term safety study, the first 8 weeks of which were controlled and in which the applicant's product was compared to calcipitriol in the applicant's vehicle.
- MBL 0401 INT: Phase 2 proof-of concept study which compared the applicant's product to betamethasone dipropionate in the applicant's vehicle.

The review of safety was primarily based on data from the clinical trials described above, as well as data from special safety studies conducted by the applicant.

4.4 Data Quality and Integrity

Division of Scientific Investigations inspections were not requested. The applicant's analyses were reviewed, and independent analyses were performed by the review team.

4.5 Compliance with Good Clinical Practices

Per Section 1.7 of the Clinical Overview, the applicant asserts that, "All studies were conducted in accordance with Good Clinical Practice and with the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments."

4.6 Financial Disclosures

The applicant submitted a completed FDA Form 3454. The applicant stated that they acted with "due diligence" to obtain the required information from clinical investigators. Pertaining to the pivotal trials, there were no financial disclosures for any of the investigators who completed the disclosure forms.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The systemic bioavailability of the active ingredients in the applicant's product was assessed using exploratory pharmacokinetics in study MBL 0404 FR (the HPA axis study). Based on the results from this study, the clinical pharmacology/biopharmaceutics reviewer proposed that the following wording be included in the pharmacokinetics section of the label:

Taclonex Scalp® topical suspension:
"The systemic effect of Taclonex Scalp® topical suspension in extensive psoriasis was investigated in the study described above ' b(4) . In this study, the serum levels of calcipotriene and betamethasone dipropionate and their major metabolite were measured after 4 and 8 weeks of once daily application of Taclonex Scalp® gel on the scalp in combination with Taclonex® ointment on the body. Calcipotriene and betamethasone dipropionate were below the lower limit of quantification in all serum samples of the 34 patients evaluated.

"However, one major metabolite of calcipotriene (MC1080) was quantifiable in 10 of 34 (29.4%) patients at week 4 and in five of 12 (41.7%) patients at week 8. The major metabolite of betamethasone dipropionate, betamethasone 17-propionate (B17P) was also quantifiable in 19 of 34 (55.9%) patients at week 4 and seven of 12 (58.3%) patients at week 8. The serum concentrations for MC1080 ranged from 20-75 pg/mL b(4) The clinical significance of this finding is unknown."

5.2 Pharmacodynamics

The systemic pharmacodynamics of the active ingredients in the applicant's product were indirectly assessed using surrogate parameters (serum calcium in studies MBL 0405 INT, MBL 0406 INT and MBL 0502 US and HPA axis testing and serum and urinary calcium measurements in study MBL 0404 FR). See Sections 7.1.7.1 and 7.1.12.

Local pharmacodynamic effects were assessed in two studies which will not be further discussed as they are not of regulatory utility for this application:

- MBL 0403 FR: vasoconstrictor assay
- MBL 0402 UK and MBL 0601 FR skin atrophy studies b(4)

5.3 Exposure-Response Relationships

Exposure-response work was primarily limited to evaluation of different combinations of concentrations of the active ingredients: study MBL 0201 FR evaluated six concentrations applied once daily for three weeks. The early development program appears to have devoted less effort to the evaluation of frequency and duration of treatment, with each of these elements apparently being extrapolated to the applicant's product based on dosing of other products:

- The frequency of once daily dosing appears to have been based on the dosing of the applicant's ointment product (i.e. once daily) which contains the same active ingredients at the same concentrations. Per Section 4.2.1 of the Clinical Overview, the treatment duration of eights week "was selected based on the results of the Phase 2 proof-of-concept study (MBL 0401 INT), which showed a continuous improvement in mean values up to week 8 and a statistically significant difference from betamethasone dipropionate in the gel vehicle after up to 8 weeks treatment.
- "The treatment duration in the Phase 2 study was initially selected based on experience from clinical practice and previous studies of other products in scalp psoriasis, indicating that a treatment period of up to 8 weeks would generally be required for a recalcitrant disease like scalp psoriasis."

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The product is proposed for the once daily topical treatment of psoriasis vulgaris of the scalp (scalp psoriasis), in adults aged 18 years and above.

6.1.1 Methods

The applicant conducted two pivotal trials: MBL 0405 INT and MBL 0406 INT. They submitted data from four additional trials that included controlled (active or vehicle), 8-week treatment periods as being supportive of efficacy, i.e. the treatment duration proposed for marketing studies:

- MBL 0502 US: a Phase 3 study conducted in the United States in African-American and Hispanic subjects to address ICHE5 (vehicle-controlled)
- MBL 0503 INT: a Phase 3 study which compared the applicant's product to Dovonex scalp solution (this study also assessed for relapse and rebound; per Section 4.2.3 of the Clinical Overview, b(4)
- MBL 0407 INT: Phase 3 long-term safety study, the first 8 weeks of which were controlled and in which the applicant's product was compared to calcipitriol in the applicant's vehicle.

- MBL 0401 INT: Phase 2 proof-of concept study which compared the applicant's product to betamethasone dipropionate in the applicant's vehicle.

These six studies constitute the "controlled studies."

6.1.2 General Discussion of Endpoints

The primary efficacy criterion was the proportion of subjects who achieved "Controlled disease" (defined as "Absence of disease" or "Very mild disease") according to an investigator's global assessment (IGA) of disease severity at Week 8 (end of treatment). This endpoint was discussed at the Pre-IND meeting, and the Agency found the applicant's proposed IGA scale to be generally acceptable (with recommendations for minor changes; see Section 2.5). The acceptability of assessment of primary efficacy on an IGA was discussed at the End-of-Phase 2 meeting, although the Phase 3 trials were already underway at the time of that meeting.

Secondary response criteria included:

- Total sign score at week 8
- Score for scaliness, redness and thickness at week 8
- Patients with "Controlled disease" ("Absence of disease" or "Very mild disease") according to investigator's global assessment of disease severity at week 2 and 4.
- Patients with "Treatment success" ("Almost clear" or "Cleared") according to patient's overall assessment of disease severity at week 8. The patient's overall assessment of treatment response is in this way dichotomized as a static end point.

6.1.3 Study Design

Both pivotal studies were international (conducted in Canada and Europe), multi-center, randomized, and double-blind. Study MBL 0405 INT (0405) was active and vehicle controlled. Specifically, the treatment arms were: the applicant's product, betamethasone in the applicant's vehicle (betamethasone), calcipotriol in the applicant's vehicle (calcipotriol), and vehicle. Study MBL 0406 INT (0406) did not include a vehicle arm (i.e. active controls only), but was otherwise identical in design to 0405 in regard to Inclusion and Exclusion Criteria, clinical assessments, efficacy assessments, etc.

MBL 0405 INT: Calcipotriol plus Betamethasone Dipropionate Gel Compared to Betamethasone Dipropionate in the Gel Vehicle, Calcipotriol in the Gel Vehicle and the Gel Vehicle alone in Scalp Psoriasis

Main objective: To compare the efficacy and safety of once daily treatment for up to 8 weeks of the combination product with betamethasone dipropionate in the product vehicle (betamethasone), calcipotriol in the product vehicle (calcipotriol) and the product vehicle in subjects with scalp psoriasis

Study Design: international (Europe and Canada), multi-center, prospective, randomized, double-blind, 4-arm, parallel group

Methodology: Subjects with scalp psoriasis were randomized to one of the four treatment groups: the combination product, betamethasone, calcipotriol or vehicle (4:4:2:1). Subjects were treated with study product once daily for up to 8 weeks. Study visits occurred on Days 0, 7, 14, 28, 42 and 56. Two 50 gram bottles of study products were dispensed on Days 0 and 7, and four bottles of product were dispensed on Days 14, 28, and 42 (i.e. two bottles per week). Safety and efficacy assessments were performed at each study visit after Day 0.

Main Inclusion Criteria:

1. Scalp psoriasis amenable to topical treatment with a maximum of 100 g of medication per week.
2. Clinical signs of psoriasis vulgaris on trunk and/or limbs, or earlier diagnosed with psoriasis vulgaris on trunk and/or limbs.
3. Extent of scalp psoriasis involving more than 10% of the total scalp area (see scale below)
4. Investigator's assessment of clinical signs of the scalp of at least 2 in one of the clinical signs, erythema, thickness and scaliness, and at least 1 in each of the other two clinical signs (see scale below)
5. Disease severity on the scalp graded as Moderate, Severe or Very severe according to the investigator's global assessment of disease severity (see scale below)
6. Aged 18 years or above

Exclusion Criteria:

1. PUVA or Grenz ray therapy within 4 weeks prior to randomization
2. UVB therapy within 2 weeks prior to randomisation
3. Systemic treatment with biological therapies (marketed or not marketed), with a possible effect on scalp psoriasis (e.g., alefacept, efalizumab, etanercept, infliximab) within 6 months prior to randomization
4. Systemic treatment with all other therapies than biologicals, with a possible effect on scalp psoriasis (e.g., corticosteroids, vitamin D analogues, retinoids, immunosuppressants) within 4 weeks prior to randomisation
5. Any topical treatment of the scalp (except for medicated shampoos and emollients) within 2 weeks prior to randomisation
6. Topical treatment of the face, trunk and/or limbs with very potent WHO group IV corticosteroids within 2 weeks prior to randomisation
7. Planned initiation of, or changes to concomitant medication that could affect scalp psoriasis (e.g., beta blockers, anti-malaria drugs, lithium) during the study
8. Current diagnosis of erythrodermic, exfoliative or pustular psoriasis
9. Patients with any of the following conditions present on the scalp area: Viral lesions, fungal and bacterial skin infections, parasitic infections and atrophic skin

10. Known or suspected abnormality of the calcium homeostasis associated with clinically
    significant hypercalcaemia
11. Known or suspected severe renal insufficiency or severe hepatic disorders
12. Planned exposure to sun during the study, that may affect scalp psoriasis
13. Known or suspected hypersensitivity to component(s) of the Investigational Products
14. Current participation in any other interventional clinical study
15. Patients who have received treatment with any non-marketed drug substance (i.e., an agent which has not yet been made available for clinical use following registration) within a month prior to randomization
16. Previously randomized and having received at least one treatment application in this study
17. Patients known or suspected of not being able to comply with a trial protocol (e.g., due to alcoholism, drug dependency or psychotic state)
18. Females who are pregnant, or of child-bearing potential and wishing to become pregnant during the study, or are breast feeding
19. Females of child-bearing potential with positive pregnancy test at Visit 1 (all females of child-bearing potential must have a pregnancy test at Visit 1 and should furthermore be willing to use an adequate method of contraception during the study)

Comment: *The WHO classification for topical corticosteroids (Exclusion Criterion #6) ranks topical corticosteroids from "weak" (Group I) to "very potent" (Group IV). In the United States, corticosteroids are ranked in the reverse order on scales that have approximately 7 levels, with the highest potency products being in Class 1 and the lowest potency products in Class 7. Betamethaosone dipropionate is in Class III ("potent") on the WHO scale and in Class 1 on the scale used in the United States.*

At each study visit, the investigator assessed:

1. **global disease severity** of the scalp psoriasis at each study visit according to the following scale:

- Absence of disease: No evidence of redness, no evidence of thickness and no evidence of scaliness on the scalp.
- Very mild disease: The overall clinical picture consists of lesions with the presence of minimum erythema.
- Mild disease: The overall clinical picture consists of lesions with light red coloration, slight thickness and a fine, thin scale layer.
- Moderate disease: The overall clinical picture consists of lesions with red coloration, a moderate thickness and a moderate scaled layer.
- Severe disease: The overall clinical picture consists of lesions with red coloration, severe thickness and a severe, coarse thick scale layer.
- Very severe disease: The overall clinical picture consists of lesions with red coloration, very severe thickness and a very severe, coarse thick scale layer.

2. **the extent of scalp psoriasis:** 0 = no involvement; 1 = < 10%; 2 = 10 – 29%; 3 = 30 – 49%; 4 = 50 – 69%; 5 = 70 – 89%; 6 = 90 – 100%

3. **clinical signs (redness, thickness and scaliness)** 0 = no signs; 1 = slight signs; 2 = moderate signs; 3 = severe signs; 4 = very severe signs
The sum of the three scores (redness, thickness and scaliness) totals from 0 to 12.

The primary efficacy criterion was the proportion of patients who achieved "Controlled disease" at Week 8. "Controlled disease" was defined as "Absence of disease" or "Very mild disease" according to the investigator's global assessment of disease severity above, and the outcomes were compared between the treatment groups.

Subjects graded to have "Absence of disease" according to the investigator's global assessment of disease severity on Days 7 through 42 were to attend all visits until Day 56. Study products were dispensed and treatment restarted as needed (based on the subjects' judgment).

Secondary efficacy criteria were:

- Total sign score at week 8
- Score for scaliness, redness and thickness at week 8
- Patients with "Controlled disease" ("Absence of disease" or "Very mild disease") according to investigator's global assessment of disease severity at week 2 and 4.
- Patients with "Treatment success" ("Almost clear" or "Cleared") according to patient's overall assessment of disease severity at week 8. The patient's overall assessment of treatment response is in this way dichotomised as a static end point.

Safety evaluations included:

- the absolute change in Total Serum Calcium, Serum Albumin and Albumin Corrected Serum Calcium from baseline to Day 28
- Any reported adverse events
- Any reported adverse drug reactions

MBL 0406 INT: Calcipotriol plus Betamethasone Dipropionate Gel Compared to Betamethasone Dipropionate in the Gel Vehicle, and Calcipotriol in the Gel Vehicle in Scalp Psoriasis

The design of this study was virtually identical to 0405, with the main difference being that this study did not include a vehicle arm, i.e. it was a 3-arm study evaluating the combination product, betamethasone and calcipotriol (2:2:1 randomization ratio). The study enrolled the same patient population, conducted the same study assessments employing the same scales, and the same efficacy criteria and assessments.

6.1.4 Efficacy Findings

For both pivotal studies, generally only outcomes for subjects who had at least moderate disease at enrollment/baseline are considered, (termed "amended analysis"; also see regulatory history in Section 2.5). Under the applicant's original analysis, subjects

with mild disease at baseline would have been considered successes if they improved to very mild disease at primary efficacy assessment (i.e. achieved only a one-grade improvement), and the reviewer does not consider this to be a convincing demonstration of efficacy.

Statistical Review Table 4 Subject Disposition-Study 0405

	Taclonex ($N = 541$)	Betamethasone ($N = 556$)	Calcipotriene ($N = 272$)	Vehicle ($N = 136$)
Completed all trial visits	434 (80.2)	473 (85.1)	210 (77.2)	106 (77.9)
Efficacy prior to week 8†	47 (8.7)	37 (6.7)	5 (1.8)	0 (0.0)
Discontinued*	60 (11.1)	46 (8.3)	57 (21.0)	30 (22.1)
Exclusion criteria emerged	3 (0.6)	3 (0.5)	2 (0.7)	3 (2.2)
Unacceptable adverse event(s)	8 (1.5)	6 (1.1)	20 (7.4)	7 (5.1)
Unacceptable treatment efficacy	2 (0.4)	9 (1.6)	19 (7.0)	16 (11.8)
Lost to follow-up	16 (3.0)	9 (1.6)	7 (2.6)	0 (0.0)
Voluntary (and no other reason)	10 (1.8)	10 (1.8)	10 (3.7)	3 (2.2)
Other	23 (4.3)	14 (2.5)	8 (2.9)	7 (5.1)

† Subjects had a treatment response prior to Week 8 and thus did not have a week 8 visit.

* Subjects can have more than one reason for discontinuation.

Source: Table 2 of the Sponsor's Study Report; results reproduced by reviewer.

Statistical Review Table 8 Subject Disposition-Study 0406

	Taclonex® scalp suspension ($N = 568$)	Betamethasone ($N = 563$)	Calcipotriene ($N = 286$)
Completed all trial visits	469 (82.6)	465 (82.6)	244 (85.3)
Efficacy prior to week 8†	51 (9.0)	32 (5.7)	4 (1.4)
Discontinued*	48 (8.5)	66 (11.7)	38 (13.3)
Exclusion criteria emerged	2 (0.4)	4 (0.7)	0 (0.0)
Unacceptable adverse event(s)	4 (0.7)	7 (1.2)	8 (2.8)
Death	0 (0.0)	0 (0.0)	1 (0.3)
Unacceptable treatment efficacy	7 (1.2)	9 (1.6)	8 (2.8)
Lost to follow-up	12 (2.1)	17 (3.0)	6 (2.1)
Voluntary (and no other reason)	9 (1.6)	6 (1.1)	4 (1.4)
Other	16 (2.8)	25 (4.4)	15 (5.2)

† Subjects had a treatment response prior to Week 8 and thus did not have a week 8 visit.

* Subjects can have more than one reason for discontinuation.

Source: Table 2 of the Sponsor's Study Report; results reproduced by reviewer.

Applicant Table 6: Baseline Demographics by study for the controlled studies

	MBL 0405 INT		MBL 0406 INT		MBL 0502 US		MBL 0503 INT		MBL 0401 INT		MBL 0407 INT		All studies	
Age (years)														
Median	50.0		49.0		44.0		51.0		49.0		48.0		49.0	
Mean	49.1		48.3		44.7		51.0		48.4		48.6		48.7	
SD	15.9		16.3		13.0		15.4		15.5		15.0		15.7	
Minimum	17		18		18		18		17		18		17	
Maximum	97		92		76		91		84		96		97	
Number	1505		1415		177		312		218		869		4496	
Age group n %														
≤35 years	350	23.3	358	25.3	45	25.4	59	18.9	47	21.6	181	20.8	1040	23.1
36 to 50 years	424	28.2	394	27.8	76	42.9	92	29.5	68	31.2	286	32.9	1340	29.8
51 to 64 years	462	30.7	389	27.5	44	24.9	95	30.4	69	31.7	257	29.6	1316	29.3
≥65 years	269	17.9	274	19.4	12	6.8	66	21.2	34	15.6	145	16.7	800	17.8
Sex n %														
Male	674	44.6	634	44.8	112	63.3	134	42.9	98	45.0	383	44.1	2035	45.3
Female	831	55.2	781	55.2	65	36.7	178	57.1	120	55.0	486	55.9	2461	54.7
Race n %														
Caucasian /White	1450	96.3	1376	97.2	72	40.7	309	99.0	213	97.7	840	96.7	4260	94.8
African-American/Black	9	0.6	6	0.4	78	44.1	0	0.0	2	0.9	4	0.5	99	2.2
Oriental/Asian	34	2.3	18	1.3	0	0.0	1	0.3	2	0.9	20	2.3	75	1.7
Other	12	0.8	15	1.1	27	15.3	2	0.6	1	0.5	5	0.6	62	1.4

Applicant Table 7: Baseline Disease Characteristics by study and all efficacy studies

	MBL 0405 INT		MBL 0406 INT		MBL 0502 US		MBL 0503 INT		MBL 0401 INT		MBL 0407 INT		All studies	
Duration of history of psoriasis[1] (years)														
Median	13.0		12.0		9.5		15.0		10.0		15.0		12.0	
Mean	16.5		15.9		10.8		18.7		14.6		17.5		16.3	
SD	13.5		13.4		8.9		14.5		13.9		13.6		13.5	
Minimum	0		0		1		0		0		1		0	
Maximum	72		70		50		70		65		72		72	
Number	1505		1414		176		312		218		869		4494	
Investigator's global assessment of disease severity n %														
Mild	98	6.5	135	9.5	0	0.0	0	0.0	32	14.7	0	0.0	265	5.9
Moderate	846	56.2	759	53.6	142	80.2	177	56.7	118	54.1	480	55.2	2522	56.1
Severe	475	31.6	453	32.0	33	18.6	112	35.9	64	29.4	331	38.1	1468	32.7
Very severe	86	5.7	68	4.8	2	1.1	23	7.4	4	1.8	58	6.7	241	5.4
TSS														
Median	6.0		7.0		6.0		7.0		7.0		NA[2]		7.0	
Mean	6.8		6.9		6.3		7.3		6.8		NA[2]		6.8	
SD	1.8		1.8		1.7		1.9		1.6		NA[2]		1.8	
Minimum	4		3		4		4		4		NA[2]		3	
Maximum	12		12		11		12		12		NA[2]		12	
Number	1505		1415		177		312		218		NA[2]		3627	
Extent of scalp psoriasis n %														
<10%	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	0.1
10 to 29%	519	34.5	490	34.6	100	56.5	130	41.7	87	39.9	325	37.4	1651	36.7
30 to 49%	394	26.2	396	28.0	30	16.9	65	20.8	41	18.8	206	23.7	1132	25.2
50 to 69%	211	14.0	228	16.1	20	11.3	39	12.5	37	17.0	138	15.9	673	15.0
70 to 89%	209	13.9	165	11.7	12	6.8	45	14.4	36	16.5	102	11.7	569	12.7
90 to 100%	169	11.2	136	9.6	15	8.5	33	10.6	17	7.8	98	11.3	469	10.4

1) In study MBL 0401 INT, duration of history of scalp psoriasis was recorded
2) NA- not applicable. In study MBL 0407 INT TSS was not recorded

From Applicant Table 14: "Controlled disease" at week 8 by study, treatment group and pooled treatment group: intent-to-treat population

Study Investigators global assessment of disease severity	Daivobet® gel Number of ptt	%	Betamethasone gel Number of ptt	%	Calcipotriol gel Number of ptt	%	Gel vehicle Number of ptt	%
MBL 0405 INT								
CONTROLLED DISEASE	346	70.0	335	63.1	94	36.7	25	19.8
NON-CONTROLLED DISEASE	148	30.0	196	36.9	162	63.3	101	80.2
TOTAL	494	100.0	531	100.0	256	100.0	126	100.0
Lower 95% CL (controlled)		66.0		59.0		30.8		12.9
Upper 95% CL (controlled)		74.1		67.2		42.6		26.8
MBL 0406 INT								
CONTROLLED DISEASE	344	67.2	308	59.6	103	41.0		
NON-CONTROLLED DISEASE	168	32.8	209	40.4	148	59.0		
TOTAL	512	100.0	517	100.0	251	100.0		
Lower 95% CL (controlled)		63.1		55.3		35.0		
Upper 95% CL (controlled)		71.3		63.8		47.1		

The results of the statistical reviewer's analyses were consistent with the applicant's "amended" analyses. From the statistical review:

From Table 5 of the statistical review: Analysis Study 0405

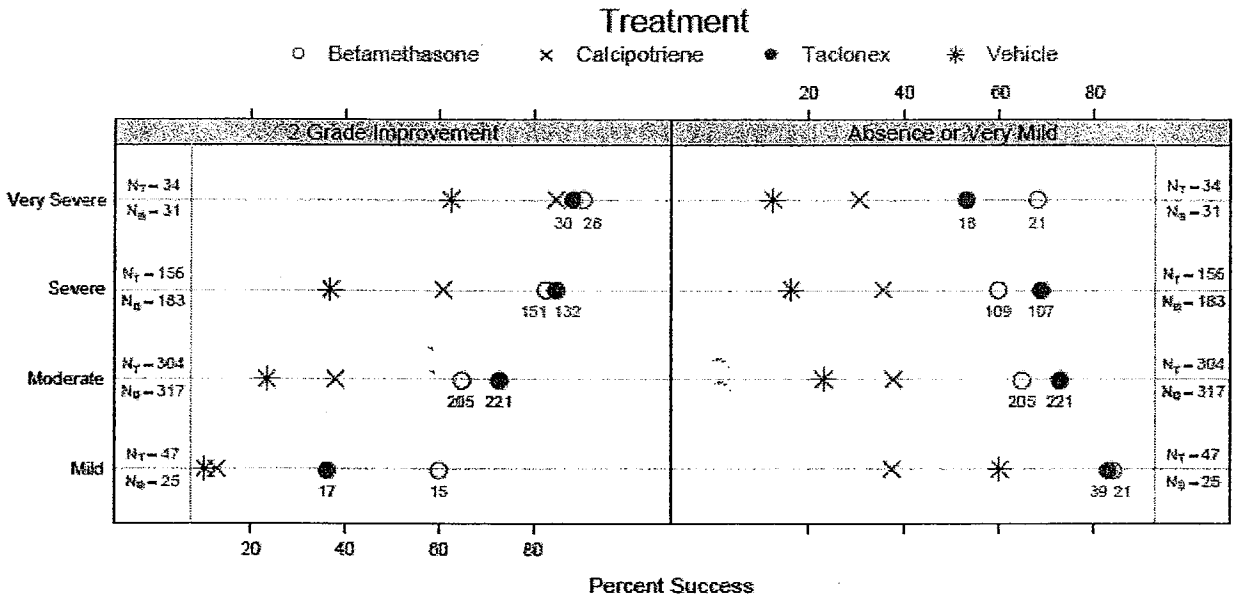
	Combination	Betamehasone	Calcipotriene	Vehilce
Sample Size	494	531	256	126
Success (%)	346 (70.0)	335 (63.1)	94 (36.7)	25 (19.8)
p-value[2]	-	0.0205	< .001	< .001

From Table 9 of statistical review: Analysis Study 0406

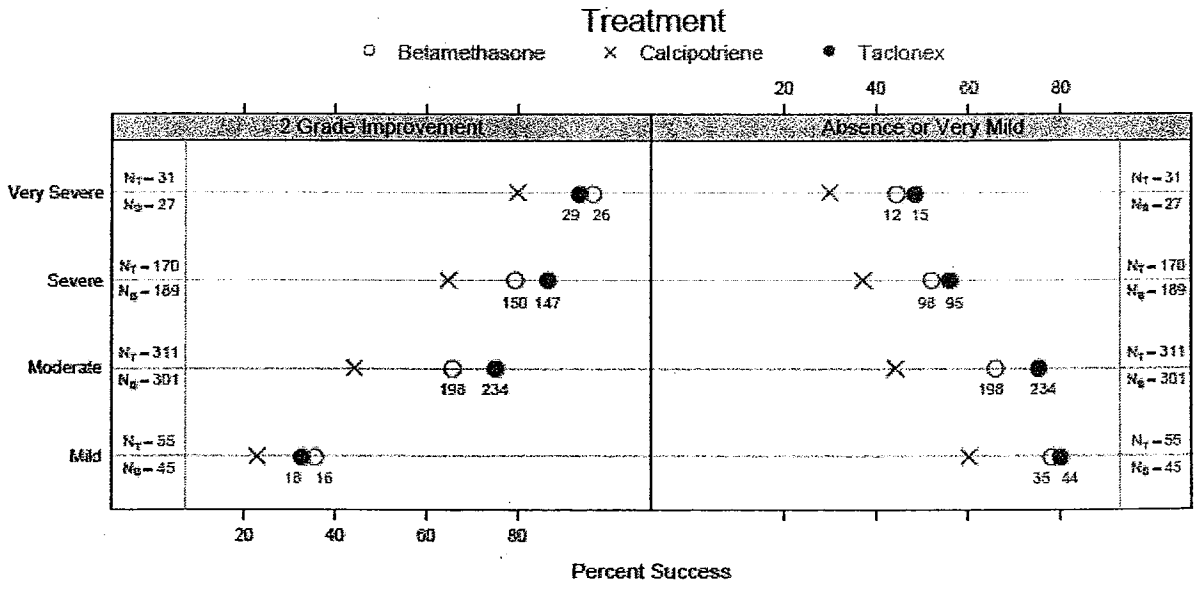
	Combination	Betamehasone	Calcipotriene
Sample Size	512	517	251
Success (%)	344 (67.2)	308 (59.6)	103 (41.0)
p-value[1]	-	0.0089	< .001

The applicant's combination product was shown to be superior to all comparators in both pivotal trials. Each active ingredient was adequately shown to contribute to efficacy.

Efficacy According to Baseline IGA Score Study 0405



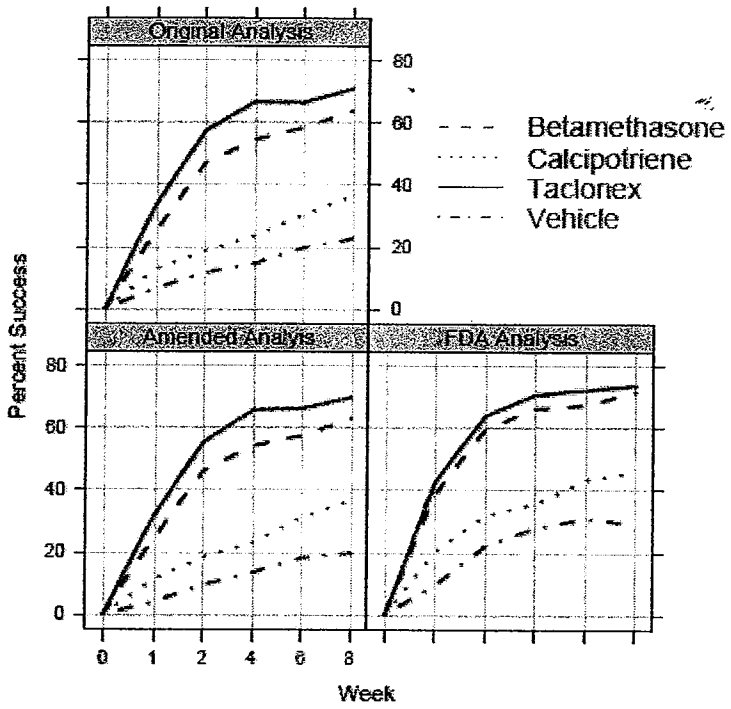
Efficacy According to Baseline IGA Score Study 0406



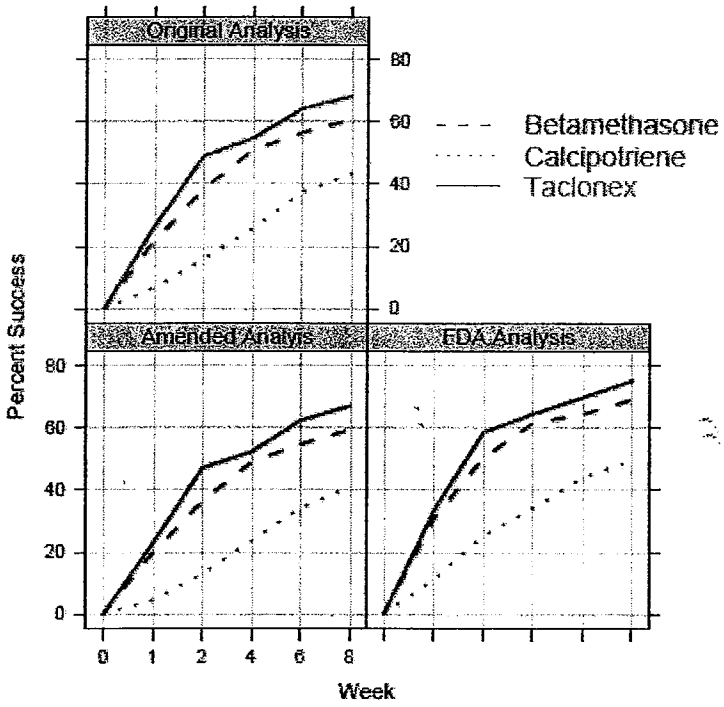
When baseline disease was considered, superiority over all comparators in the proportion of subjects who achieved "absence" or "very mild disease", (i.e. "Controlled disease") was demonstrated in both studies only for baseline disease of "moderate" to "severe" severity. The combination product was not superior to betamethasone in study 0405 for subjects with baseline disease of "mild" or "very severe" severity, and thus the contribution of calcipotriene to efficacy was not demonstrated for subjects in these two categories.

Secondary endpoint

Figure 3: Efficacy Across Time (Study 405)



Efficacy Across Time (Study 406)



In both pivotal studies, the percentage of subjects with controlled disease by Week 2 was highest in subjects treated with the combination product.

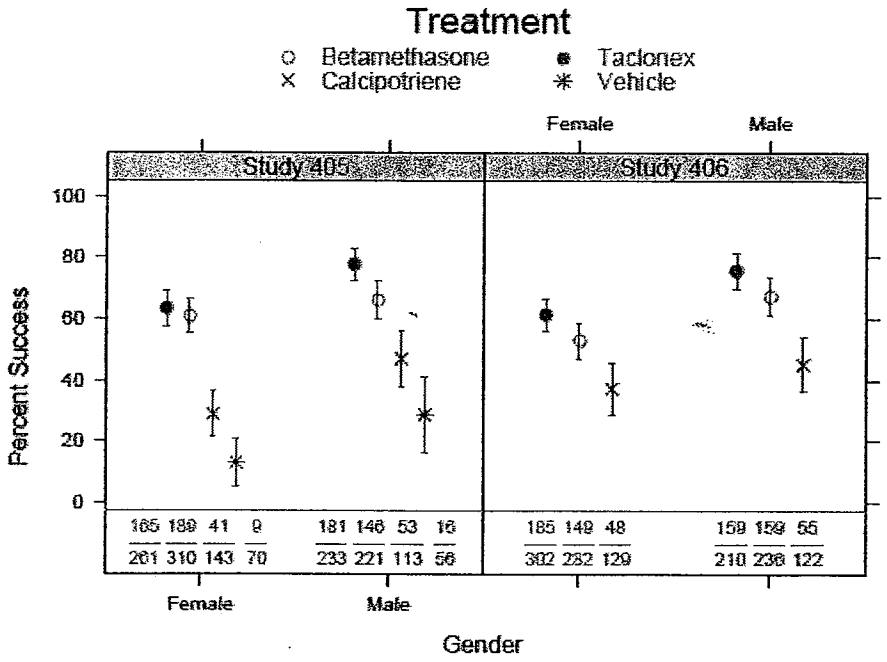
Efficacy by Subgroups

The statistical reviewer considered efficacy by subgroup for the pivotal trials and considered only those subjects who had disease of moderate severity at baseline. The applicant considered efficacy by subgroup for the all of the controlled studies, i.e. they pooled the numbers.

This review will present the graphs from the statistical review, and the applicant's findings will be described in narrative.

Gender

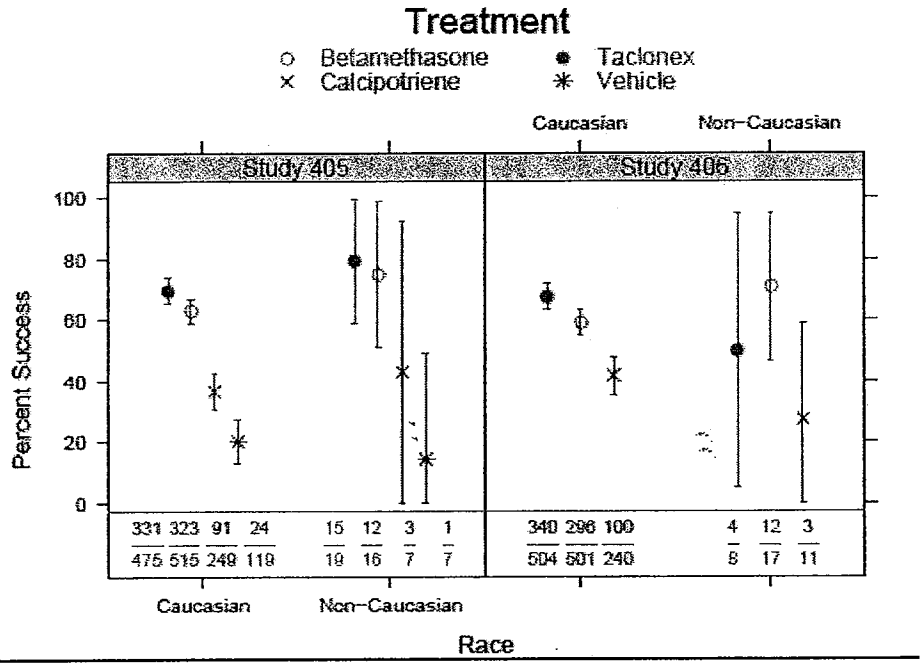
Statistical Review Figure 10: Efficacy Results According to Gender



The applicant's product was superior to all comparators in both pivotal studies in both genders. Males had a higher percentage of success in both studies. Both males and females showed a greater response rate with the combination product compared to the other treatment groups.

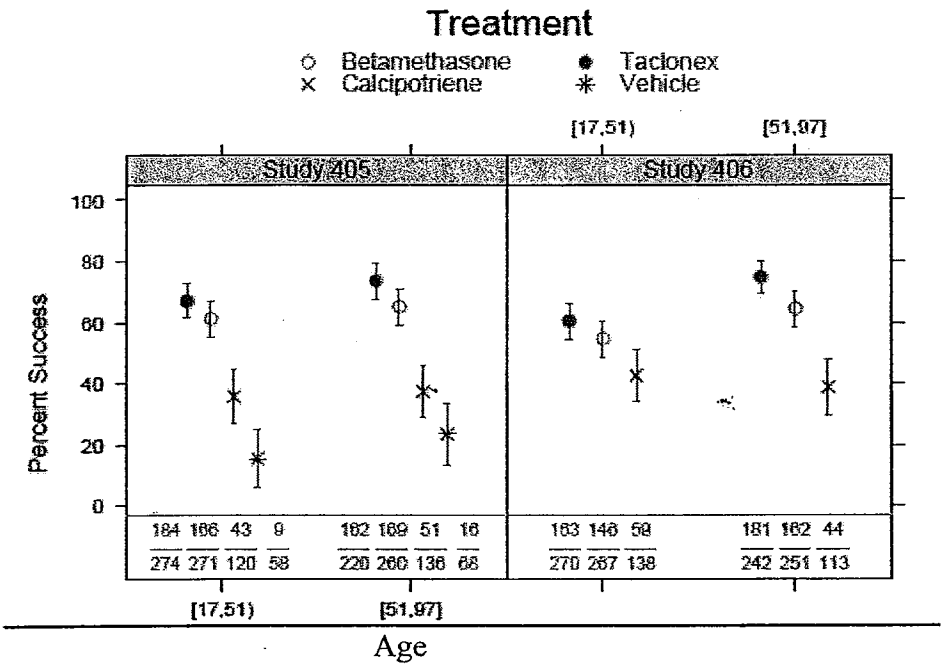
APPEARS THIS WAY
ON ORIGINAL

Statistical Review Figure 11: Efficacy Results According to Race



The statistical reviewer dichotomized into the categories "Caucasian" and "Non-Caucasian" because of the paucity of non-Caucasian subjects in the pivotal studies. There were too few non-Caucasian subjects in the pivotal trials to permit meaningful conclusions regarding outcomes in this subgroup in the pivotal trials. The applicant considered outcomes by the following categories: "Caucasian/White", "African-American/Black", "Hispanic/Latino", "Asian/Oriental," and "Other." (Most African-American/Black subjects were from study MBL 0502 US, conducted to address ICH E5.) The percentage of subjects treated with the combination product who achieved "controlled disease" was generally similar to the results in the pivotal trials, ranging from 61.8% in the "Other" group to 78.3% in the African-American/Black group. However, for these same two groups, the contribution of calcipotriene to efficacy was not demonstrated (i.e. the combination was not superior to betamethasone).

Statistical Review Figure 12: Efficacy Results According to Age



The applicant's product was superior to all comparators in the percentage of subjects who achieved success in the age categories considered in the statistical review, i.e. subjects 17-51 years and subjects 51 to 97 years. The statistical reviewer dichotomized into these categories based on the split of the overall median age in the two pivotal studies (50 years old). The applicant considered different age categorizations (< 35, 36 to 50, 51 to 64, and > 65 years), and similar outcomes were seen, i.e. their product was superior to comparators in all age categories evaluated.

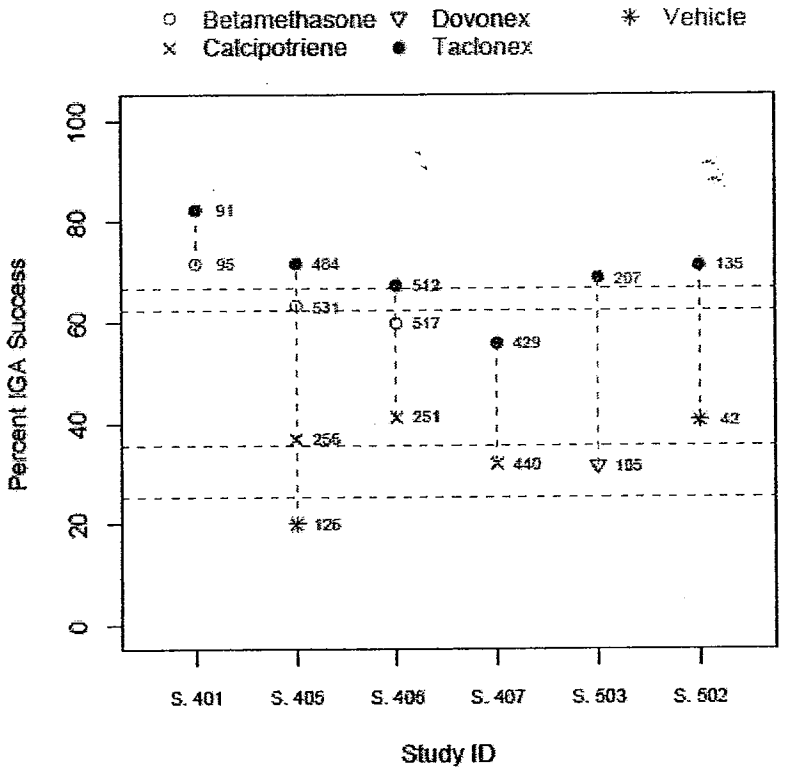
SUPPORTIVE EVIDENCE OF EFFICACY

Supportive evidence of efficacy was provided from four studies that included controlled, 8-week treatment periods, i.e. the treatment duration proposed for marketing studies:

- MBL 0502 US: conducted in the United States in African-American and Hispanic subjects to address ICH E5; the first 8 weeks were vehicle-controlled
- MBL 0503 INT: Phase 3 study which compared the applicant's product to Dovonex scalp solution (this study also assessed for relapse and rebound; per Section 4.2.3 of the Clinical Overview, [redacted] b(4)
- MBL 0401 INT: Phase 2 proof-of concept study which compared the applicant's product to betamethasone dipropionate in the applicant's vehicle.

- MBL 0407 INT: Phase 3 long-term study, the first 8 weeks of which were controlled and the applicant's product was compared to calcipitriol in the applicant's vehicle.

Statistical Review Figure 14: Efficacy Summary for all Controlled Trials



The combination product was superior to comparator in each of the supportive studies.

APPEARS THIS WAY
ON ORIGINAL

6.1.5 Clinical Microbiology

The product is not an antimicrobial.

6.1.6 Efficacy Conclusions

The applicant conducted two adequate and well-controlled pivotal trials. Efficacy of the combination product was adequately demonstrated in both pivotal trials. The combination product was superior to all comparators in each study for the proportion of subjects with "Controlled Disease" at Week 8, as assessed on a static global severity scale. ("Controlled Disease" was defined as subjects with "absence of disease" or "very mild disease" at efficacy assessment.) The degree of superiority was statistically significant for all comparisons in both pivotal trials.

Both pivotal trials were appropriately designed to allow for demonstration of the contribution to efficacy for each of the active ingredients in the fixed combination product. Each active ingredient was adequately shown to contribute to efficacy, and thus 21 CFR 300.50 was adequately addressed. The combination product was superior to each monad and to vehicle in MBL 0405 INT, and the combination product was superior to each active comparator in MBL 0406 INT.

Supportive evidence of efficacy was provided from four additional trials which included once daily treatment for 8 weeks under controlled conditions (i.e. the 8-week period included a control of some sort, active or vehicle): MBL 0502 US, MBL 0503 INT, MBL 0401 INT, and MBL 0407 INT. The combination product was superior to comparator in each of the supportive studies.

When baseline disease was considered, superiority over all comparators in the proportion of subjects who achieved "absence" or "very mild disease", (i.e. "Controlled disease") was demonstrated in both studies only for "moderate" to "severe" baseline. The combination product was not superior to betamethasone in study 0405 for subjects with "mild" or "very severe" baseline disease, and thus the contribution of calcipotriene to efficacy was not demonstrated for subjects in these two categories.

In both pivotal studies, the percentage of subjects with controlled disease by Week 2 was highest in subjects treated with the combination product.

The applicant had adequately demonstrated that their combination product is effective in the treatment of moderate to severe psoriasis of the scalp.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

1.1.3 Integrated analyses of safety

The applicant based the integrated analyses of safety on studies which included treatment regimens of once daily for eight weeks. The eight-week treatment periods were controlled (active and/or vehicle) in these studies, thus the studies grouped for the safety review are referred to as the "controlled studies." The review of the integrated analyses of safety will focus primarily on the controlled studies as these included treatment regimens that are the same as proposed for the market; those studies are:

- MBL 0405 INT pivotal
- MBL 0406 INT pivotal
- MBL 0502 US race/ethnicity US (first 8 week were vehicle-controlled)
- MBL 0503 INT (8 week double-blind treatment phase)
- MBL 0407 INT long-term safety study (first 8 weeks; calcipotriol in vehicle control)
- MBL 0401 INT (Phase 2 proof-of-concept; betamethasone in vehicle control)

The "safety analysis set" includes all randomized subjects who applied study treatment and for whom the "presence or confirmed absence of AEs" was available.

Although MBL 0502 US and MBL 0407 INT were both 52 weeks in duration, the latter is the designated long-term safety study. MBL 0502 US was conducted to address ICH E5.

Special safety studies are discussed in Section 7.1.12, and those studies are:

- MBL 0404 FR (assessment of effects on the HPA axis and calcium metabolism)
- MBL 0301 UK photo-allergy
- MBL 0302 FR repeat insult/21-day cumulative irritancy
- MBL 0303 UK photo-toxicity

The applicant pooled data from studies MBL 0405 INT, MBL 0406 INT and MBL 0502 US for assessment of impact of treatment on calcium metabolism (serum albumin-corrected calcium), although these data were collected only for the first four weeks of treatment in the pivotal trials and would therefore not be supportive of the proposed duration of treatment of eight weeks.

Deaths, serious adverse events, discontinuations due to adverse events and clinically important adverse events were considered from all clinical studies.

The review will generally not consider events that occurred in the Daivonex solution group. b(4) References to "betamethasone" and "calcipotriol" in the following discussion refer to the substance in the applicant's vehicle (unless otherwise indicated).

7.1.1 Deaths

Four deaths were reported out of 5330 subjects (0.08%) in the development program. The applicant considered none of the deaths to be related to study treatment, and the reviewer concurs. Discussion of the deaths follows:

Subject MBL0406 4406 DE065

This was an 88-year-old female in the calcipotriol group in the pivotal trial MBL 0406 INT. She was hospitalized with pneumonia and stroke. Death was due to pneumonia which was considered to be unrelated to study treatment.

Subject MBL0407 7898 DE109

This was a 67-year-old who received treatment with the combination product in the long-term study MBL 0407 INT. The subject developed septic shock with cardiopulmonary insufficiency, renal insufficiency and "liver insufficiency" after hemicolectomy surgery for a benign stenosing caecal tumor. The subject died from surgical complications.

MBL0407 7663 FR181

This was a 33-year-old female who received treatment with calcipotriol in vehicle in the long-term study MBL 0407 INT. The subject was under the care of a cardiologist for an unspecified genetic cardiomyopathy. Her father was reported to have the same condition and had a
defibrillator. The subject reportedly discontinued her medications without consulting her cardiologist. She went into ventricular fibrillation and ultimately died due to a cardiac arrest.

MBL0502 4401 US037

This was a 59-year-old male who was treated with the vehicle on the scalp and Daivobet®
ointment on the body on January 11, 2006. From March 8, 2006, he switched to treatment with
the combination product on the scalp (Daivobet® ointment was continued on the body). He completed the study on ——— and was in motor vehicle accident on the same day. He died of injuries sustained in the accident. b(6)

7.1.2 Other Serious Adverse Events

The incidence of serious adverse events was generally similar across treatment groups in the controlled scalp studies. One serious adverse event was considered possibly related to study treatment:

Subject MBL 0407 7912 DE008

This was a 39-year old female who was treated with calcipotriol in vehicle. She experienced moderate sinus tachycardia. She had a history of diabetes, hypertension, hyperlipoproteinemia,
obesity and thyroid adenoma, conditions for which she was taking multiple medications. While under treatment with the study product, she began to experience drowsiness, vertigo and shivering. An electrocardiogram showed sinus tachycardia, which resolved on 27-JUN-2006. Echocardiography showed "good" left ventricular function and hypertrophy of the cardiac septum. The event was considered to be of moderate intensity.

The following is the breakdown of the occurrence of serious adverse events in the controlled studies:

- in the combination group, 13 of 1,953 subjects (0.7%) had a total of 17 serious adverse events
- in the betamethasone group, 6 of 1,214 subjects (0.5%) had a total of 6 serious adverse events
- in the calcipotriol group, 12 of 979 subjects (1.2%) had a total of 17 serious adverse events
- in the vehicle group, 1 of 173 subject (0.6%) had one serious adverse event

No one serious adverse event was reported by more than one subject in the combination group. For subjects treated with the combination product, most serious adverse events were in the "injury poisoning and procedural complications" system organ class (SOC), and four subjects reported five events in this SOC. The events were hand fracture, joint injury, road traffic accident, tibia fracture, wrist fracture, concussion, and contusion. The next most common SOCs in which serious adverse events were reported for subjects treated with the combination gel was "infections and infestations" and "nervous system disorders," three events were reported by three and two subjects, respectively. In the "infections and infestations" SOC, the events were cellulitis, groin abscess and pneumonia. In the "nervous system disorders" SOC, the events were cerebrovascular accident, convulsion and syncope.

No correlation with treatment group was identified in the occurrence of serious adverse events.

Applicant's Table 60: Serious adverse events by primary SOC and preferred term for the "controlled scalp studies"

Primary System Organ Class[1] Preferred Term[2]	Daivobet® gel (n=1953) Number of Patients	%	Betamethasone gel (n=1214) Number of Patients	%	Calcipotriol gel (n=979) Number of Patients	%	Gel vehicle (n=173) Number of Patients	%	Daivonex® scalp solution (n=104) Number of Patients	%
Infections and infestations										
Cellulitis	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0
Groin abscess	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Pneumonia	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0
Appendicitis	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Arthritis infective	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Erysipelas	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Lower respiratory tract infection	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Total number of adverse events	3		3		3		0		0	
Total number of patients with adverse events[3]	3	0.2	3	0.2	3	0.3	0	0.0	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)										
Anal cancer	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Benign colonic neoplasm	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Total number of adverse events	2		0		0		0		0	
Total number of patients with adverse events[3]	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Metabolism and nutrition disorders										
Diabetes mellitus inadequate control	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Total number of adverse events	0		0		1		0		0	
Total number of patients with adverse events[3]	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Nervous system disorders										
Cerebrovascular accident	1	0.1	0	0.0	2	0.2	0	0.0	0	0.0
Convulsion	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Syncope	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Neuromuscular blockade	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Sleep apnoea syndrome	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Total number of adverse events	3		1		3		0		0	
Total number of patients with adverse events[3]	2	0.1	1	0.1	3	0.3	0	0.0	0	0.0
Cardiac disorders										
Atrial fibrillation	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Cardiac arrest	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Cardiac failure congestive	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0

Primary System Organ Class[1] Preferred Term[2]	Daivobet® gel (n=1953) Number of Patients	%	Betamethasone gel (n=1214) Number of Patients	%	Calcipotriol gel (n=979) Number of Patients	%	Gel vehicle (n=173) Number of Patients	%	Daivonex® scalp solution (n=104) Number of Patients	%
Total number of adverse events	0		0		3		0		0	
Total number of patients with adverse events[3]	0	0.0	0	0.0	3	0.3	0	0.0	0	0.0
Vascular disorders										
Circulatory collapse	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Deep vein thrombosis	0	0.0	0	0.0	2	0.2	0	0.0	0	0.0
Total number of adverse events	1		0		2		0		0	
Total number of patients with adverse events[3]	1	0.1	0	0.0	2	0.2	0	0.0	0	0.0
Respiratory, thoracic and mediastinal disorders										
Pulmonary hypertension	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Total number of adverse events	0		0		1		0		0	
Total number of patients with adverse events[3]	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Gastrointestinal disorders										
Diverticulitis	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Total number of adverse events	1		0		0		0		0	
Total number of patients with adverse events[3]	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Skin and subcutaneous tissue disorders										
Hand dermatitis	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Psoriasis	0	0.0	0	0.0	0	0.0	1	0.6	0	0.0
Total number of adverse events	0		0		1		1		0	
Total number of patients with adverse events[3]	0	0.0	0	0.0	1	0.1	1	0.6	0	0.0
Musculoskeletal and connective tissue disorders										
Musculoskeletal pain	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0

Arthropathy	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Total number of adverse events	1		1		0		0		0	
Total number of patients with adverse events[1]	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0
Renal and urinary disorders										
Urinary incontinence	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Total number of adverse events	0		0		1		0		0	
Total number of patients with adverse events[1]	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
General disorders and administration site conditions										
Chest pain	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Fatigue	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
[illegible]										
General disorders and administration site conditions										
Total number of adverse events	0		0		1		0		0	
Total number of patients with adverse events[1]	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Injury, poisoning and procedural complications										
Hand fracture	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Joint injury	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Road traffic accident	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Tibia fracture	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Wrist fracture	1	0.1	0	0.0	0	0.0	0	0.0	1	1.0
Concussion	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Contusion	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Skin laceration	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Total number of adverse events	5		1		0		0		3	
Total number of patients with adverse events[1]	4	0.2	1	0.1	0	0.0	0	0.0	1	1.0
Surgical and medical procedures										
Bone lesion excision	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Total number of adverse events	1		0		0		0		0	
Total number of patients with adverse events[1]	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Overall Totals										
Total number of adverse events	17		5		17		1		3	
Total number of patients with adverse events[1]	13	0.7	5	0.5	12	1.2	1	0.6	1	1.0

1) Coded according to MedDRA version 6.1.
2) A single patient could appear in more than one category.

APPEARS THIS WAY
ON ORIGINAL

Other Serious Adverse Events

As of the cut-off date for the submission (April 1, 2007), seven serious adverse events had been reported beyond the initial eight weeks of treatment from the then ongoing study MBL 0502 US (race/ethnicity). The events that occurred during the initial eight weeks of this study were discussed under "controlled scalp studies."

Subject MBL0502 4401 US037; Event: Death due to Road traffic accident

This subject has been previously discussed. He died on the day he completed the study.

Subject MBL0502 4509 US038; Event: Pyelonephritis acute

The subject was a 25-year-old female who received vehicle on the scalp and Daivobet® ointment on the body on 20 February 2006. From 17 April 2006, she switched to treatment with the combination product on the scalp while Daivobet® ointment was continued on the body. The patient was hospitalized with fever, chills and left-sided abdominal pain on [redacted] and ultimately diagnosed with acute pyelonephritis. Treatment with investigational products was continued. She was treated and was discharged on 02 [redacted] Causal relationship to the investigational products was assessed as not related. b(6)

MBL0502_4900_US042;Event: Deep vein thrombosis

The subject was a 55-year-old male who started therapy with the combination product on the scalp and Daivobet® ointment on the body on 23 May 2006. He had a history of diabetes mellitus and hyperthyroidism. He was hospitalized for deep vein thrombosis on [redacted] He was treated with anticoagulants and recovered. Treatment with investigational products was continued. Causal relationship to the investigational products was assessed as not related. b(6)

MBL0502_5304_US046; Events: Loss of consciousness, Mental status changes

The subject was a 69-year-old male who started treatment with the combination product on the scalp and Daivobet® ointment on the body on 26 June 2006. He had a history of laryngeal cancer with laryngectomy, gallstones, prostate cancer, seizures, arthritis, alcohol abuse and chronic sinusitis. Investigational products were stopped on 09 September 2006. The subject was hospitalized on [redacted] due to loss of conciousness and altered mental status secondary to alcohol abuse. Additional findings were uncontrolled hypertension, normocytic anemia and gastroesophageal reflux disease. He recovered, was discharged and resumed treatment with investigational products on [redacted] . Causal relationship to the investigational products was assessed as not related. b(6)

MBL0502_4706_US040 Event: Pancreatitis

The subject was a 63-year-old female who started treatment with the combination product on the scalp and Daivobet® ointment on the body on 20 May 2006. She had a history of headache, vaginal polyps, and knee surgery. She was hospitalized on [redacted] b(6) due to pancreatitis. Treatment with investigational products was continued. The subject was hospitalized for 4 days and discharged with the outcome reported as "not recovered." Causal relationship to the investigational products was assessed as not related.

MBL0502_4905_US042 Event: Knee arthroplasty

The subject was a 47-year-old male who started treatment with the combination product on the scalp and Daivobet® ointment on the body on 23 June 2006. He had a history of diabetes mellitus, arthritis, and hypertension. He was hospitalized on [redacted] b(6) for a total right knee replacement. Treatment with the investigational product was continued. He was discharged on [redacted] Causal relationship to the investigational products was assessed as not related.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In the controlled scalp studies, the incidence of dropouts was highest in the vehicle group
[33 of 173 subjects (19%)], and the most common reason in this group was "Unacceptable treatment efficacy" [16 subjects (9%)]. The incidence of dropouts was lowest in the combination gel group [158 of 1953 subjects (8%)], and the most common reason in this group was "Other."[52 subjects (3%)]. Eighteen subjects who discontinued for "Other" cited cosmetic unacceptability ("greasiness" was the most frequently specified reason). The following table presents the overall profile of dropouts from the controlled scalp studies:

Applicant's Table 3: Subject disposition for the "controlled scalp studies"; safety analysis set

APPEARS THIS WAY
ON ORIGINAL

Reason for withdrawal	Dafvobet® gel (n=1953)		Betamethasone gel (n=1214)		Calcipotriol gel (n=979)		Gel vehicle (n=173)		Daivonex® scalp solution (n=104)	
	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%
Unacceptable treatment efficacy	17	0.9	20	1.6	44	4.5	16	9.2	5	4.8
Unacceptable adverse event(s)	19	1.0	15	1.2	55	5.6	7	4.0	9	8.7
Exclusion criteria emerging during study	7	0.4	9	0.7	10	1.0	3	1.7	0	0.0
Lost to follow up	44	2.3	22	1.8	21	2.1	2	1.2	0	0.0
Death	1	0.1	0	0.0	2	0.2	0	0.0	0	0.0
Voluntary	25	1.3	11	0.9	12	1.2	2	1.2	2	1.9
Other reason(s)	52	2.7	36	3.1	44	4.5	9	5.2	5	4.8
Total number of reasons for withdrawal[1]	165		115		188		39		21	
Total number of withdrawn subjects	158	8.1	107	8.8	161	16.4	33	19.1	19	18.3
Total number of subjects completing treatment period[2]	1795	91.9	1107	91.2	618	63.6	140	80.9	85	81.7

1) Patients may have had more than one reason for withdrawal.
2) A completer is defined as a patient who does not have a reason for withdrawal stated (except completion or absence of disease). For study MRL 0503 INT all patients who were qualified to enter the observation phase (i.e. were 'Controlled' according to Investigator's global assessments of treatment efficacy at week 8) are defined as completers.

7.1.3.2 Adverse events associated with dropouts

In the controlled scalp studies, adverse events were recorded as the reason for withdrawal for 19 subjects (1.0%) in the combination group, 15 (1.2%) in the betamethasone group, 55 (5.6%) in the calcipotriol group, and 7 (4.0%) in the vehicle group.

Nausea and pruritus were the most common adverse events that led to withdrawal in the combination group, three subjects each (0.2%). Psoriasis led to the withdrawal of two subjects in the combination group (0.1%). All other adverse events that led to withdrawal in the combination group were reported by one subject each.

At the systems organ class level, the most common adverse events leading to withdrawal in the combination group were in the skin and subcutaneous tissues category, and 14 such events were reported for 12 subjects (0.6%). The numbers of subjects who withdrew due to skin and subcutaneous tissue disorders were:

- 12 (0.6%) in the combination group
- 9 (0.7%) in the betamethasone group
- 49 (5.0%) in the calcipotriol group
- 7 (4.0%) in the gel vehicle group.

The following table presents all adverse events that lead to discontinuation.

Applicant Table 62: Adverse events leading to discontinuation by primary SOC and preferred term for the controlled scalp studies (safety analysis set)

Primary System Organ Class[1] Preferred Term[2]	Dafvobet® gel (n=1953)		Betamethasone gel (n=1214)		Calcipotriol gel (n=979)		Gel vehicle (n=173)		Daivonex® scalp solution (n=104)	
	Number of Patients	%	Number of Patients	%	Number of Patients	%	Number of Patients	%	Number of Patients	%

Infections and infestations										
Folliculitis	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Arthritis infective	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Furuncle	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Total number of adverse events	1		2		0		0		0	
Total number of patients with adverse events[1]	1	0.1	2	0.2	0	0.0	0	0.0	0	0.0
Metabolism and nutrition disorders										
Hypercalcaemia	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Total number of patients with adverse events[1]	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Psychiatric disorders										
Depression	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Total number of adverse events	1		0		0		0		0	
Total number of patients with adverse events[1]	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Nervous system disorders										
Burning sensation	1	0.1	2	0.2	8	0.8	0	0.0	0	0.0
Headache	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0
Tremor	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Syncope	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Total number of adverse events	3		3		9		0		0	
Total number of patients with adverse events[1]	3	0.2	3	0.2	9	0.9	0	0.0	0	0.0
Eye disorders										
Eye irritation	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0
Eye swelling	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Eyelid oedema	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Total number of adverse events	2		0		2		0		0	
Total number of patients with adverse events[1]	2	0.1	0	0.0	2	0.2	0	0.0	0	0.0
Gastrointestinal disorders										
Nausea	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0
Vomiting	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Total number of adverse events	4		0		0		0		0	
Total number of patients with adverse events[1]	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0
Skin and subcutaneous tissue disorders										
Pruritus	3	0.2	3	0.2	16	1.6	2	1.2	2	1.9
Psoriasis	2	0.1	2	0.2	5	0.5	2	1.2	0	0.0
Dermatitis	1	0.1	0	0.0	0	0.0	0	0.0	1	1.0
Dermatitis acneiform	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Dermatitis contact	1	0.1	0	0.0	3	0.3	1	0.6	1	1.0
Dry skin	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0
Erythema	1	0.1	0	0.0	10	1.0	0	0.0	2	1.9
Face oedema	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0
Rash	1	0.1	0	0.0	3	0.3	0	0.0	0	0.0
Rash papular	1	0.1	0	0.0	2	0.2	1	0.6	0	0.0
Skin irritation	1	0.1	1	0.1	13	1.3	1	0.6	3	2.9
Alopecia	0	0.0	2	0.2	0	0.0	0	0.0	0	0.0
Eczema	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Hand dermatitis	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Skin burning sensation	0	0.0	2	0.2	2	0.2	0	0.0	0	0.0
Skin inflammation	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Total number of adverse events	14		11		58		7		9	
Total number of patients with adverse events[1]	12	0.6	9	0.7	49	5.0	7	4.0	9	8.7
Musculoskeletal and connective tissue disorders										
Arthralgia	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Psoriatic arthropathy	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Total number of adverse events	0		1		1		0		0	
Total number of patients with adverse events[1]	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0
General disorders and administration site conditions										
Pain	1	0.1	0	0.0	1	0.1	1	0.6	0	0.0
Application site dermatitis	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Oedema	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Secretion discharge	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Swelling	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Total number of adverse events	1		1		4		1		0	
Total number of patients with adverse events[1]	1	0.1	1	0.1	3	0.3	1	0.6	0	0.0
Injury, poisoning and procedural complications										
Joint injury	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Thermal burn	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Wrist fracture	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Total number of adverse events	1		0		2		0		0	
Total number of patients with adverse events[1]	1	0.1	0	0.0	2	0.2	0	0.0	0	0.0
Overall Totals										
Total number of adverse events	27		19		76		8		9	
Total number of patients with adverse events[2]	19	1.0	15	1.2	55	5.6	7	4.0	9	8.7

1) Coded according to MedDRA version 6.1.
2) A single patient could appear in more than one category.

7.1.3.3 Other significant adverse events

Also, please see Sections 7.1.7 and 7.1.12 for discussion of systemic safety.

Local Adverse Events Potentially Reflecting Use of a Topical Corticosteroid

There were no reports of atrophy, striae or hypertrichosis in the controlled scalp studies in any treatment group. There were no reports of lesional/perilesional hypopigmentation. There were two reports of telangiectasia in subjects treated with the combination product, both in the long-term study

- one subject was reported to have telangiectasia on an ear; this event was considered not related to study treatment.
- a second subject had telangiectasia on the scalp, but "distant" from the treated areas; this event was considered possibly related to study treatment (reported at 36 weeks).

Lesional/perilesional infections of any type were reported for 20 (1.0%) subjects in the combination group, 16 (1.3%) in the betamethasone group and 8 (0.8%) in the calcipotriol in the group. The lesional/perilesional infections were folliculitis, lice infestation and "rash pustular." Lesional/perilesional or treatment related folliculitis was reported for 11 (0.6 %) subjects in the combination group, 12 (1.0%) in the betamethasone group and 4 (0.4%) in the calcipotriol vehicle group. "Rash pustular" was reported for 2 (0.1%) subjects in the combination group and 2 (0.2%) in the betamethasone vehicle group. Possibly treatment related skin infections were herpes simplex, otitis externa and furuncle. Herpes simplex was reported for 2 (0.1%) subjects in the combination group and 2 (0.2%) in the calcipotriol group. Otitis externa was reported for 2 (0.1%) subjects in the combination group. Furuncle was reported for 1 (0.1%) subject in the betamethasone group.

Eye disorders/eye infections

The liquid nature of the product could make for possible eye exposures. The incidence of adverse events coded to the eye disorders primary system organ class was similar between the combination and betamethasone groups, higher in the calcipotriol group and highest in the vehicle group. The respective incidences were 0.9%, 0.8%, 1.9%, and 2.9%.

Table 66: Number and percentage of patients reporting at least one adverse event in the eye disorders primary system organ class in the 'controlled scalp studies': safety analysis set

Primary System Organ Class[1] Preferred Term[1]	Daivobet® gel (n=1953)		Betametha-sone gel (n=1214)		Calcipotriol gel (n=979)		Gel vehicle (n=173)		Daivonex® scalp solution (n=104)	
	Pats	%	Pats	%	Pats	%	Pats	%	Pats	%
Eye disorders										
Eye disorder	3	0.2	1	0.1	1	0.1	0	0.0	0	0.0
Eye irritation	3	0.2	3	0.2	3	0.3	0	0.0	0	0.0
Vision blurred	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0
Conjunctivitis	2	0.1	2	0.2	3	0.3	1	0.6	0	0.0
Conjunctival haemorrhage	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Conjunctivitis allergic	1	0.1	1	0.1	1	0.1	0	0.0	0	0.0
Eye movement disorder	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Eye pain	1	0.1	0	0.0	0	0.0	2	1.2	0	0.0
Eye pruritus	1	0.1	0	0.0	1	0.1	0	0.0	0	0.0
Eye swelling	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Iritis	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Keratoconjunctiv-itis sicca	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Blepharitis	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0
Dermatitis eyelid	0	0.0	0	0.0	2	0.2	0	0.0	0	0.0
Entropion	0	0.0	0	0.0	0	0.0	1	0.6	0	0.0
Erythema of eyelid	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0
Eye discharge	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Eye redness	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Eyelid oedema	0	0.0	0	0.0	3	0.3	1	0.6	0	0.0
Eyelids pruritus	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Lacrimation increased	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Meibomianitis	0	0.0	0	0.0	0	0.0	1	0.6	0	0.0
Ocular discomfort	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Periorbital haematoma	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0
Vitreous detachment	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Number of AEs	19		10		22		6		0	
Number of pats with AEs	18	0.9	10	0.8	19	1.9	5	2.9	0	0.0

1) Coded according to MedDRA version 6.1.

7.1.4 Other Search Strategies

See Sections 7.1.3.3 and 7.1.5.6.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events information was collected by non-leading questioning of study subjects and by recording changes not reported by the study subjects but observed by the investigator.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Events were coded according to MeDRA version 6.1, and categorization appeared to be appropriate.

7.1.5.3 Incidence of common adverse events

For the "controlled scalp studies", the four most common adverse events in the combination gel group were nasopharyngitis [79 subjects (4.0%)], headache [66 subjects (3.4%)], pruritus [48 subjects (2.5%)], psoriasis [44 subjects (2.3%)] and upper respiratory tract infection [40 subjects (2.0%)]. The incidence of nasopharyngitis was highest (and the same) in the betamethasone and vehicle groups: 5.8%. The incidence of headache ranged from 2.9% in the vehicle group to 3.8% in the betamethasone group. The incidence of pruritus was highest in the calcipotriol group [77 subjects (7.9%), a possible function of known irritancy of the substance, blunted by the betamethasone in the combination group (incidence of pruritus was the same between the combination and betamethasone groups). The incidence of psoriasis was highest in the calcipotriol group (3.1%) and was similar between the other three treatment groups (2.1 to 2.3%). The incidence of upper respiratory tract infection was highest in the vehicle group (3.5%) and lowest in the calcipotriol group (1.3%).

The incidence of irritation was lowest (and the same) in the combination and betamethasone
groups (0.5%) as compared to the calcipotriol and vehicle groups (3.6% and 2.9%, respectively). This is consistent with the irritancy associated with calcipotriol, but could also suggests that the vehicle could have some potential for irritancy.

7.1.5.4 Common adverse event tables

Events that occurred at ≥1% of subjects treated with the combination product in the controlled studies are presented in the following table.

The remainder of this page is left intentionally blank.

Table 19: Events that occurred at ≥1% of subjects by primary SOC and preferred term

Primary System Organ Class[1] Preferred Term[1]	Daivobet® gel (n=1953) Number of Patients	%	Betamethasone gel (n=1214) Number of Patients	%	Calcipotriol gel (n=979) Number of Patients	%	Gel vehicle (n=173) Number of Patients	%	Daivonex® scalp solution (n=104) Number of Patients	%
Infections and infestations										
Cystitis	2	0.1	2	0.2	0	0.0	0	0.0	1	1.0
Viral pharyngitis	1	0.1	0	0.0	0	0.0	0	0.0	1	1.0
Psychiatric disorders										
Depression	4	0.2	0	0.0	3	0.3	0	0.0	1	1.0
Insomnia	4	0.2	2	0.2	0	0.0	0	0.0	1	1.0
Anxiety	2	0.1	5	0.4	2	0.2	0	0.0	1	1.0
Nervous system disorders										
Headache	66	3.4	46	3.8	29	3.0	5	2.9	1	1.0
Dizziness	10	0.5	4	0.3	4	0.4	1	0.6	1	1.0
Burning sensation	8	0.4	6	0.5	19	1.9	0	0.0	1	1.0
Tension headache	2	0.1	0	0.0	0	0.0	0	0.0	1	1.0
Transient ischaemic attack	1	0.1	0	0.0	0	0.0	0	0.0	1	1.0
Eye disorders										
Eye pain	1	0.1	0	0.0	0	0.0	2	1.2	0	0.0
Ear and labyrinth disorders										
Vertigo	2	0.1	3	0.2	2	0.2	1	0.6	1	1.0
Vascular disorders										
Hypertension	10	0.5	3	0.2	1	0.1	1	0.6	2	1.9
Respiratory, thoracic and mediastinal disorders										
Cough	8	0.4	8	0.7	4	0.4	4	2.3	0	0.0
Rhinitis	5	0.3	4	0.3	2	0.2	3	1.7	0	0.0
Nasal congestion	2	0.1	2	0.2	0	0.0	0	0.0	1	1.0
Postnasal drip	0	0.0	0	0.0	0	0.0	1	0.6	1	1.0
Gastrointestinal disorders										
Diarrhoea	14	0.7	4	0.3	6	0.6	2	1.2	0	0.0
Dyspepsia	4	0.2	7	0.6	5	0.5	0	0.0	1	1.0
Gastritis	3	0.2	2	0.2	1	0.1	0	0.0	1	1.0
Skin and subcutaneous tissue disorders										
Pruritus	49	2.5	30	2.5	77	7.9	10	5.8	6	5.8
Psoriasis	44	2.3	25	2.1	30	3.1	4	2.3	3	2.9
Erythema	10	0.5	5	0.4	29	3.0	1	0.6	7	6.7
Skin irritation	10	0.5	6	0.5	35	3.6	5	2.9	5	4.8
Dermatitis	8	0.4	1	0.1	3	0.3	1	0.6	1	1.0
Alopecia	7	0.4	7	0.6	3	0.3	2	1.2	0	0.0
Dermatitis contact	6	0.3	1	0.1	8	0.8	1	0.6	2	1.9
Eczema	5	0.3	4	0.3	8	0.8	0	0.0	1	1.0
Dry skin	4	0.2	4	0.3	10	1.0	0	0.0	2	1.9
Skin burning sensation	3	0.2	3	0.2	8	0.8	0	0.0	2	1.9
Rosacea	2	0.1	2	0.2	4	0.4	0	0.0	1	1.0
Scab	1	0.1	0	0.0	0	0.0	1	0.6	1	1.0
Seborrhoeic dermatitis	1	0.1	0	0.0	5	0.5	0	0.0	2	1.9
Musculoskeletal and connective tissue disorders										
Back pain	21	1.1	14	1.2	7	0.7	1	0.6	3	2.9
Arthralgia	19	1.0	11	0.9	8	0.8	0	0.0	2	1.9
Neck pain	1	0.2	4	0.3	3	0.3	0	0.0	1	1.0
General disorders and administration site conditions										
Pain	6	0.3	3	0.2	7	0.7	3	1.7	0	0.0
Influenza like illness	4	0.2	3	0.2	2	0.2	0	0.0	1	1.0
Application site burning	2	0.1	1	0.1	3	0.3	0	0.0	5	4.8
Fatigue	2	0.1	4	0.3	7	0.7	0	0.0	1	1.0
Xerosis	1	0.1	2	0.2	0	0.0	0	0.0	1	1.0
Application site warmth	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Oedema	0	0.0	0	0.0	1	0.1	0	0.0	1	1.0
Investigations										
Biopsy breast	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Injury, poisoning and procedural complications										
Contusion	4	0.2	1	0.1	0	0.0	0	0.0	1	1.0
Post procedural pain	4	0.2	2	0.2	3	0.3	0	0.0	1	1.0
Limb injury	2	0.1	2	0.2	1	0.1	1	0.6	2	1.9
Muscle strain	2	0.1	1	0.1	0	0.0	2	1.2	1	1.0
Skin laceration	1	0.1	1	0.1	0	0.0	0	0.0	1	1.0
Wrist fracture	1	0.1	0	0.0	1	0.1	0	0.0	1	1.0
Soft tissue injury	0	0.0	0	0.0	0	0.0	0	0.0	2	1.9
Surgical and medical procedures										
Tooth extraction	0	0.0	1	0.1	3	0.3	0	0.0	2	1.9

1) Coded according to MedDRA version 6.1.

7.1.5.5 Identifying common and drug-related adverse events

"Adverse drug reactions" were those adverse events for which the investigator had not excluded a causal relationship to study product. The most frequently reported adverse drug reaction in subjects treated with the combination product was pruritus. Treatment-related pruritus was reported for 1.8% of subjects in the combination group, 1.7% in the betamethasone group, 7.4% in the calcipotriol group, and 4.0% in the vehicle group. All other adverse drug reactions in the combination group occurred in ≤0.5% of subjects, and the events are presented in the table below.

Table 22: Adverse drug reactions occurring in ≥1% of patients by primary SOC and preferred term for the .controlled scalp studies

	Daivobet® gel (n=1953)		Betamethasone gel (n=1214)		Calcipotriol gel (n=979)		Gel vehicle (n=173)		Daivonex® scalp solution (n=104)	
Primary System Organ Class[1] Preferred Term[1]	Number of Patients	%	Number of Patients	%	Number of Patients	%	Number of Patients	%	Number of Patients	%
Infections and infestations										
Folliculitis	10	0.5	12	1.0	3	0.3	0	0.0	0	0.0
Nervous system disorders										
Headache	10	0.5	13	1.1	2	0.2	2	1.2	0	0.0
Burning sensation	8	0.4	6	0.5	19	1.9	0	0.0	1	1.0
Respiratory, thoracic and mediastinal disorders										
Nasal congestion	0	0.0	1	0.1	0	0.0	0	0.0	1	1.0
Skin and subcutaneous tissue disorders										
Pruritus	36	1.8	21	1.7	72	7.4	7	4.0	6	5.8
Erythema	9	0.5	4	0.3	26	2.7	1	0.6	6	5.8
Skin irritation	9	0.5	6	0.5	31	3.2	4	2.3	5	4.8
Alopecia	5	0.3	6	0.5	3	0.3	2	1.2	0	0.0
Dermatitis	4	0.2	0	0.0	3	0.3	1	0.6	1	1.0
Dry skin	4	0.2	3	0.2	9	0.9	0	0.0	1	1.0
Eczema	3	0.2	0	0.0	7	0.7	0	0.0	1	1.0
Skin burning sensation	3	0.2	3	0.2	8	0.8	0	0.0	2	1.9
Dermatitis contact	2	0.1	0	0.0	4	0.4	1	0.6	2	1.9
General disorders and administration site conditions										
Pain	6	0.3	1	0.1	6	0.6	3	1.7	0	0.0
Application site burning	2	0.1	1	0.1	3	0.3	0	0.0	5	4.8
Application site warmth	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Oedema	0	0.0	0	0.0	1	0.1	0	0.0	1	1.0

1) Coded according to MedDRA version 6.1.

7.1.5.6 Additional analyses and explorations

Cutaneous adverse events occurring ≤ 2 cm from the border of a treated lesion were classified as "lesional/perilesional." A total of 111 lesional/perilesional adverse events were reported in the combination group, 74 in the betamethasone group, 168 in the calcipotriol in the group, and 22 in the vehicle group.

The most common lesional/perilesional adverse event in the combination group was pruritus (2.0%). All other lesional/perilesional adverse events in the combination group were reported by ≤0.4% of subjects. The following table summarizes lesional/perilesional events reported by at least 1% of patients in any treatment group in the controlled scalp studies:

Table 24: Lesional/perilesional adverse events on the scalp occurring in ≥1% of patients by primary SOC and preferred term for the controlled scalp studies

	Daivobet® gel (n=1953)		Betamethasone gel (n=1214)		Calcipotriol gel (n=979)		Gel vehicle (n=173)		Daivonex® scalp solution (n=104)	
Primary System Organ Class[1] Preferred Term[1]	Number of Patients	%	Number of Patients	%	Number of Patients	%	Number of Patients	%	Number of Patients	%
Nervous system disorders										
Burning sensation	6	0.3	5	0.4	16	1.6	0	0.0	1	1.0
Skin and subcutaneous tissue disorders										
Pruritus	39	2.0	20	1.6	64	6.5	9	5.2	5	4.8
Skin irritation	7	0.4	2	0.2	22	2.2	3	1.7	4	3.8
Alopecia	3	0.2	6	0.5	3	0.3	2	1.2	0	0.0
Dermatitis contact	2	0.1	0	0.0	1	0.1	1	0.6	1	1.0
Skin burning sensation	2	0.1	3	0.2	4	0.4	0	0.0	2	1.9
General disorders and administration site conditions										
Pain	4	0.2	1	0.1	4	0.4	3	1.7	0	0.0
Application site burning	2	0.1	1	0.1	3	0.3	0	0.0	5	4.8
Application site warmth	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0
Injury, poisoning and procedural complications										
Skin laceration	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0

1) Coded according to MedDRA version 6.1.

Most lesional/perilesional adverse events were reported as mild or moderate intensity. A total of 12 adverse events of severe intensity were reported in the combination group (10.8%), three in the betamethasone group (4.1%), 37 in the calcipotriol in the gel vehicle group (22.0%), three in the gel vehicle group (13.6%). The most common severe lesional/perilesional adverse event in the combination group was pruritus (three reports). In the combination group, there was one report each of severe burning sensation, skin irritation, skin burning sensation and pain. Lesional/perilesional adverse events reported by ≥1% of patients in any treatment group are presented in the following table:

Table 25: Intensity of lesional/perilesional adverse events on the scalp occurring in ≥1% of patients by primary SOC and preferred term for the 'controlled scalp studies': safety analysis set

	Daivobet® gel (n=1953)			Betamethasone gel (n=1214)			Calcipotriol gel (n=979)			Gel vehicle (n=173)			Daivonex® scalp solution (n=104)		
Primary System Organ Class[1] Preferred Term[1]	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Nervous system disorders															
Burning sensation	2	3	1	3	1	1	6	4	6	0	0	0	1	0	0
Skin and subcutaneous tissue disorders															
Pruritus	28	8	3	15	5	0	23	25	16	2	5	2	2	1	2
Skin irritation	4	2	1	1	1	0	12	9	1	2	1	0	0	2	2
Alopecia	1	2	0	4	1	1	3	0	0	1	1	0	0	0	0
Dermatitis contact	1	1	0	0	0	0	1	0	0	0	1	0	0	0	1
Skin burning sensation	0	1	1	2	1	0	1	3	0	0	0	0	1	1	0
General disorders and administration site conditions															
Pain	1	2	1	1	0	0	2	1	1	1	1	1	0	0	0
Application site burning	1	1	0	1	0	0	2	1	0	0	0	0	4	1	0
Application site warmth	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Injury, poisoning and procedural complications															
Skin laceration	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

MBL 0407 INT: "Long-term treatment of Scalp Psoriasis with Calcipotriol plus Betamethasone dipropionate gel"

Main objective: To study the safety of calcipotriol plus betamethasone dipropionate gel for long term treatment of scalp psoriasis (up to 52 weeks)

Study design: international, multi-center, prospective, randomized, double-blind, active-control, 2-arm, parallel group, 52 week safety study.

Methodology: Subjects with scalp psoriasis (of at least moderate severity) were randomized to receive once daily treatment for up to 52 weeks with either

- the combination product [calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate)] or
- calcipotriol 50 mcg/g in the same vehicle

Study visits were every 4 weeks between weeks 0 and 52, and safety and efficacy assessments occurred at each study visit. Subjects whose scalp psoriasis cleared at any time during the study will remained in the study but discontinued treatment. Treatment was to be resumed should at a on an as needed basis. A maximum of 100 g of study treatment per week was allowed. The global severity scale was the same as was used in the pivotal trials.

Safety was assessed by collection of adverse event data (including adverse drug reactions) and adverse events of concern associated with long-term corticosteroid use on the scalp and recording of reasons for withdrawal from the study.

The primary end points/response criteria were

- Incidence of adverse drug reactions of any type
- Incidence of adverse events of concern associated with long-term corticosteroid use on the scalp.

Secondary end points/response criteria: The incidence of subjects with "satisfactorily controlled disease" at each visit (defined as "Absence of disease", "Very mild disease" or Mild disease").

Comment: Although not found specified in the protocol, the study report included an analysis of the percentage of patients with "Controlled disease" ("Absence of disease" or "Very mild disease") according to the Investigator's Global Assessment of disease severity at Week 8).

The remainder of this page is left intentionally blank.

APPEARS THIS WAY
ON ORIGINAL

Disposition

The "safety analysis set" comprised all subjects who received any treatment with trial medication and "for whom the presence or confirmed absence" of adverse events was available. The safety analysis set consists of 850 subjects: 419 in the combination group and 431 in the calcipotriol in the vehicle group

Applicant's Table 4: Subject disposition for the MBL 0407 INT; safety analysis set

	All patients (safety) (n=850)		DAIVOBET gel (n=419)		Calcipotriol gel (n=431)	
Reason for withdrawal	Number of patients	%	Number of patients	%	Number of patients	%
Unacceptable adverse event(s)	53	6.2	9	2.1	44	10.2
Death	2	0.2	1	0.2	1	0.2
Unacceptable treatment efficacy	65	7.6	14	3.3	51	11.8
Exclusion criteria emerging during study	20	2.4	5	1.2	15	3.5
Lost to follow-up	42	4.9	20	4.8	22	5.1
Other reason(s)	67	7.9	21	5.0	46	10.7
Voluntary	33	3.9	16	3.8	17	3.9
Total number of reasons for withdrawal[1]	282		86		196	
Total number of withdrawn patients (%)	248	(29.2)	82	(19.6)	166	(38.5)

1) A patient may have had more than one reason for withdrawal
Source: MBL 0407 INT Clinical Study Report, Table 2

The incidence of dropouts was higher for subjects in the calcipotriol group [166 of 431 subjects (39%)], and the most common reasons for withdrawal were "Unacceptable treatment efficacy" and "Other" [51 subjects (11.8%) and 46 subjects (10.7%), respectively]. The incidence of dropouts in the combination group was 19.2% (82 of 419 subjects), and the most common reasons or withdrawal were "Other" and "Lost to follow-up" [21 subjects (5.0%) and 20 subjects (4.8%), respectively].

ADVERSE EVENTS (long-term safety study)

Two deaths occurred in this study and neither was considered to be related to study treatment. See Section 7.1.1 for discussion of the deaths.

Serious Adverse Events

Nineteen of 419 subjects (4.5%) in the combination group experienced serious adverse events, and 34 events were reported. None of these events were considered related to study treatment. In the calcipotriol group, 22 of 431 subjects (5.1%) experienced serious adverse events, and 35 events were reported, all but one of which were considered unrelated to study treatment. The lone exception was the report of sinus tachycardia previously discussed (the event occurred during the first eight weeks of treatment).

Applicant's Table 61: Serious adverse events by primary SOC and preferred term for the long-term controlled study (MBL 0407 INT): safety analysis set

SOC[1,2] & Preferred term[2]	DAIVOBET gel (n=419) Number of patients	%	Calcipotriol gel (n=431) Number of patients	%
Blood and lymphatic system disorders				
Anaemia	0	0.0	1	0.2
Cardiac disorders				
Arrhythmia	0	0.0	1	0.2
Atrial fibrillation	1	0.2	1	0.2
Cardiac arrest	0	0.0	1	0.2
Cardiac failure congestive	0	0.0	1	0.2
Myocardial ischaemia	0	0.0	1	0.2
Sinus tachycardia	0	0.0	1	0.2
Tachycardia	1	0.2	0	0.0
Eye disorders				
Eye irritation	1	0.2	0	0.0
Eye pain	1	0.2	0	0.0
Photophobia	1	0.2	0	0.0
Visual acuity reduced	1	0.2	0	0.0
Gastrointestinal disorders				
Abdominal pain	0	0.0	1	0.2
Gastric ulcer	1	0.2	0	0.0
Small intestinal obstruction	1	0.2	0	0.0
Tooth fracture	1	0.2	0	0.0
Upper gastrointestinal haemorrhage	1	0.2	0	0.0
Vomiting	1	0.2	0	0.0
General disorders and administration site conditions				
General physical health deterioration	0	0.0	1	0.2
Malaise	0	0.0	1	0.2
Pyrexia	1	0.2	0	0.0
Hepatobiliary disorders				
Cholecystitis	0	0.0	2	0.5
Cholelithiasis	0	0.0	2	0.5
Infections and infestations				
Appendicitis	1	0.2	0	0.0
Cellulitis	2	0.5	0	0.0
Hepatitis A	0	0.0	1	0.2
Meningitis	1	0.2	0	0.0
Pneumonia	1	0.2	0	0.0

Table is continued on the next page.

SOC[1,2] & Preferred term[2]	DAIVOBET gel (n=419) Number of patients	%	Calcipotriol gel (n=431) Number of patients	%
Injury, poisoning and procedural complications				
Concussion	1	0.2	0	0.0
Facial bones fracture	0	0.0	1	0.2
Joint sprain	0	0.0	1	0.2
Lower limb fracture	1	0.2	1	0.2
Meniscus lesion	0	0.0	1	0.2
Road traffic accident	0	0.0	1	0.2
Upper limb fracture	1	0.2	0	0.0
Metabolism and nutrition disorders				
Diabetes mellitus inadequate control	0	0.0	1	0.2
Musculoskeletal and connective tissue disorders				
Arthralgia	1	0.2	0	0.0
Intervertebral disc disorder	0	0.0	1	0.2
Localised osteoarthritis	0	0.0	1	0.2
Myalgia	1	0.2	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Benign colonic neoplasm	1	0.2	0	0.0
Gastrointestinal neoplasm	0	0.0	1	0.2
Prostatic adenoma	1	0.2	0	0.0
Tongue neoplasm malignant stage unspecified	0	0.0	1	0.2
Nervous system disorders				
Cerebrovascular accident	0	0.0	1	0.2
Headache	2	0.5	0	0.0
Loss of consciousness	1	0.2	0	0.0
Sleep apnoea syndrome	0	0.0	1	0.2
Transient ischaemic attack	0	0.0	2	0.5
Psychiatric disorders				
Depression	1	0.2	0	0.0
Mental disorder	1	0.2	0	0.0
Renal and urinary disorders				
Renal colic	1	0.2	0	0.0
Urinary incontinence	0	0.0	1	0.2
Reproductive system and breast disorders				
Cervical dysplasia	1	0.2	0	0.0
Respiratory, thoracic and mediastinal disorders				
Pulmonary hypertension	0	0.0	1	0.2
Skin and subcutaneous tissue disorders				
Hand dermatitis	0	0.0	1	0.2

Surgical and medical procedures				
Bone lesion excision	1	0.2	0	0.0
Cholecystectomy	0	0.0	2	0.5
Joint arthroplasty	1	0.2	0	0.0
Osteotomy	1	0.2	0	0.0
Thyroidectomy	0	0.0	1	0.2
Total number of adverse events[3]	34		35	
Total number of patients (%)[4]	19	4.5	23	5.1

1) System Organ Class
2) Classification according to the MedDra 6.1
3) Different adverse events within the same class and involving the same patient have been counted as one. A single patient could appear in multiple classes.
4) All patients with at least one event whichever its frequency

Common Adverse Events

The most common adverse events reported in the combination group and calcipotriol group (and the respective incidences), were psoriasis (11.9%; 10.0%), nasopharyngitis (11.5%;
10.0 %), pruritus (4.5%; 11.4%), and headache (6.2 %; 9.8%). The overall profile of adverse events was similar to that observed in the "controlled scalp studies."

Table 30: Adverse events occurring in ≥2% of patients by primary SOC and preferred term for the long-term controlled study: safety analysis set

SOC[1],[2] & Preferred term[2]	Daivobet® gel (n=419)		Calcipotriol gel (n=431)	
	Number of patients	%	Number of patients	%
Gastrointestinal disorders				
Diarrhoea	8	1.9	11	2.6
Infections and infestations				
Bronchitis	13	3.1	10	2.3
Folliculitis	9	2.1	4	0.9
Influenza	13	3.1	16	3.7
Nasopharyngitis	48	11.5	43	10.0
Sinusitis	10	2.4	15	3.5
Upper respiratory tract infection	22	5.3	10	2.3
Musculoskeletal and connective tissue disorders				
Arthralgia	18	4.3	13	3.0
Back pain	8	1.9	12	2.8
Nervous system disorders				
Burning sensation	5	1.2	13	3.0
Headache	26	6.2	38	8.8
Respiratory, thoracic and mediastinal disorders				
Cough	5	1.2	9	2.1
Pharyngolaryngeal pain	4	1.0	15	3.5
Skin and subcutaneous tissue disorders				
Alopecia	6	1.4	9	2.1
Eczema	6	1.4	9	2.1
Erythema	11	2.6	15	3.5
Pruritus	19	4.5	49	11.4
Psoriasis	50	11.9	43	10.0
Skin irritation	9	2.1	27	6.3

1) System Organ Class

2) Classification according to MedDra 6.1

Source: MBL 0407 INT Clinical Study Report, Table 28

The incidences for adverse drug reactions was lower for subjects treated with the combination product compared to subjects treated with calcipotriol:

Table 32: Adverse drug reactions occurring in ≥2% of patients by primary SOC and preferred term for the long-term controlled study: safety analysis set

SOC[1,2] & Preferred term[2]	Daivobet® gel (n=419)		Calcipotriol gel (n=431)	
	Number of patients	%	Number of patients	%
Nervous system disorders				
Burning sensation	4	1.0	12	2.8
Skin and subcutaneous tissue disorders				
Erythema	9	2.1	14	3.2
Pruritus	15	3.6	43	10.0
Psoriasis	10	2.4	9	2.1
Skin irritation	6	1.4	24	5.6

1) System Organ Class

2) Classification according to the MedDRA 6.1

Source: MBL 0407 INT Clinical Study Report, Table 22

A total of 62 lesional/perilesional adverse events were reported in the combination group
and 152 in the calcipotriol group. Pruritus was the only lesional/perilesional adverse event reported at an incidence of ≥2.0% in the combination group (4.3%). In the calcipotriol group, pruritus (10.0%), skin irritation (3.9%), burning sensation (2.6%) and erythema (2.1%) were reported at an incidence ≥2.0%.

Table 33: Lesional/perilesional adverse events on the scalp occurring in ≥2% of patients by primary SOC and preferred term for the long-term controlled study safety analysis set

SOC[1,2] & Preferred term[2]	Daivobet® gel (n=419)		Calcipotriol gel (n=431)	
	Number of patients	%	Number of patients	%
Nervous system disorders				
Burning sensation	3	0.7	11	2.6
Skin and subcutaneous tissue disorders				
Erythema	5	1.2	9	2.1
Pruritus	18	4.3	43	10.0
Skin irritation	5	1.2	17	3.9

1) System Organ Class
2) Classification according to MedDra 6.1
Source: MBL 0407 INT Clinical Study Report, Table 34

Adverse Events: 0-6 months

There were 350 subjects in the combination group and 295 in the calcipotriol group with at least 6 months of exposure to study product. The most frequently reported adverse events by preferred term were nasopharyngitis, headache and psoriasis which occurred at similar incidences in both groups.

The percentage of subjects reporting adverse drug reactions was lower in the combination group (11.4%) compared with the calcipotriol group (22.4%). In the combination group, Adverse drug reactions reported during this period were erythema, pruritus, skin burning sensation, and skin irritation, and none were reported at an incidence > 2.0% (0 to 1.7%) for the combination group. Skin burning sensation was not reported for the combination group. All of these reactions were reported at an incidence ≥2% in the calcipotriol group (2.0-6.8%). Pruritus was the most commonly reported adverse drug reaction in both treatment groups: 1.7% in the combination group and 6.8% in the calcipotriol group.

The percentage of subjects reporting lesional/perilesional adverse events on the scalp during this period was lower in the combination group (8.0%) compared with the calcipotriol group (14.9%). A total of 33 lesional/perilesional adverse events on the scalp were reported for
subjects with a minimum of 6 months exposure in the combination group and 71 in the calcipotriol group. Pruritus (2.3%) was the only lesional/perilesional adverse event on

the scalp reported during months 0-6 at an incidence of ≥2.0% in the combination group for patients exposed for at least 6 months.

Adverse Events: 0-12

There were 281 patients in the combination group and 235 in the calcipotriol in vehicle group with at least 12 months exposure. The most frequently reported adverse events were nasopharyngitis, psoriasis and headache, all of which occurred with similar incidence in the two treatment groups, occurring with higher incidence (10.2%) compared with the combination group (2.8%). The following adverse events were reported by ≥2.0% of subjects exposed for at least 12 months: nausea, asthenia, ear infection, gastroenteritis, pharyngitis, pain in extremity, pain of skin, skin burning sensation, urticaria and hypertension. Asthenia and skin burning sensation were not reported in the combination group.

The percentage of subjects reporting adverse drug reactions was lower in the combination group (15.7%) compared with the calcipotriol group (26.4%). Adverse drug reactions reported during this period were erythema, pain of skin, pruritus, psoriasis, and skin irritation. In the combination group, pruritus and psoriasis were the only reactions that occurred with an incidence >2%, and these reactions were both reported for 2.1% of subjects. The most common adverse drug reactions in the calcipotriol group were pruritus (8.9%) and skin irritation (3.4%). The corresponding incidences for these reactions in the combination group were 2.1% and 1.1%, respectively.

A total of 35 lesional/perilesional adverse events were reported for subjects with a minimum of 12 months exposure in the combination gel group and 72 in the calcipotriol group. The percentage of subjects reporting lesional/perilesional adverse events on the scalp was lower in the combination group (10.0%) compared with the calcipotriol group (18.3%). Pruritus was the only lesional/perilesional adverse event that occurred in the combination group at an incidence ≥2.0% (reported for 2.5% of subjects). The most common lesional/perilesional adverse events on the scalp in the calcipotriol group were pruritus (8.9%), alopecia (2.6%) and skin irritation (2.1%).

Adverse events associated with long-term corticosteroid use

The applicant convened a body of three independent dermatologists to identify adverse events that might be reflective of long-term corticosteroid use. The body reviewed blinded data, and concluded that there was no increase in the percentage of subjects events of interest were similar in nature and frequency for the two treatment groups. Events that were reported by more than one subject in either group were:

- rosacea, folliculitis and perioral dermatitis in the combination gel group (all reported by 0.7% of subjects) and
- rosacea (1.2%), folliculitis (0.7%) and acne (0.5%) in the calcipotriol group.

There was one case each of "rash pustular" and acne in the combination group. There were no reports of skin atrophy or striae.

7.1.6 Less Common Adverse Events

The most frequently reported adverse drug reaction in the controlled studies for subjects treated with the combination product was pruritus. Treatment-related pruritus was reported for 1.8% of subjects in the combination group, 1.7% in the betamethasone group, 7.4% in the calcipotriol group, and 4.0% in the vehicle group. All other adverse drug reactions in the combination group occurred in ≤0.5% of subjects, and the events (by preferred term) were follicultis, headache, erythema, and skin irritation (all at 0.5%); burning sensation (0.4%); alopecia and pain (both at 0.3%); dermatitis, dry skin, eczema, and skin burning sensation (all at 0.4%); dermatitis contact and application site burning (both at 0.1%).

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Assessment of effects on calcium metabolism was done, routine hematologic and chemistry parameters were evaluated in MBL 0404 FR (HPA axis study)

The applicant took varied approaches to the assessment of calcium in the development program:

- Albumin-corrected calcium was measured only through four weeks of treatment in the pivotal studies, MBL 0405 INT and MBL 0406 INT.
- Albumin-corrected calcium was assessed through Week 52 in study MBL 0502 US (at Weeks 0, 2, 4, 12, 24, 40 and end of study); subjects in this study used the combination product on their scalp and Taclonex ointment on psoriasis lesions on the body.
- 24-hour urinary calcium excretion was assessed only in study MBL 0404 FR (HPA axis study). Serum calcium was also assessed, but albumin was not; subjects in this study used the combination product on their scalp and Taclonex ointment on psoriasis lesions on the body.

<u>Albumin-corrected calcium</u>

Assessment of calcium metabolism in MBL 0405 INT and MBL 0406 INT does not reflect the potential impact on calcium metabolism from a full treatment course of eight weeks, since the assessment was done at the mid-point of treatment, i.e. at Week 4. These data would therefore not support the safety of an eight-week treatment course. Data were pooled from MBL 0405 INT, MBL 0406, INT and the first four weeks of MBL 0502 US. The mean changes observed were similar for all treatment groups: mean changes were between -0.02 and -0.01 mmol/L. Some subjects shifted from normal at baseline to high at Week 4 in all treatment groups: 5 (0.5%) in the combination group, 5

(0.5%) in the betamethasone group, 2 (0.4%) in the calcipotriol group and 1 (0.7%) in the vehicle group.

Table 67: Albumin corrected calcium at baseline, Week 4, and change from baseline for the 'controlled scalp studies': safety analysis set

Albumin corrected calcium (mmol/L)	Daivobet® gel (n=1953)	Betamethasone gel (n=1214)	Calcipotriol gel (n=979)	Gel vehicle (n=173)
Baseline				
Median	2.38	2.40	2.40	2.36
Mean	2.39	2.40	2.40	2.36
SD	0.11	0.12	0.12	0.11
Minimum	2.05	1.40	1.82	2.16
Maximum	3.07	2.85	2.73	2.73
Number	1215	1096	547	171
Week 4				
Median	2.35	2.38	2.37	2.32
Mean	2.36	2.38	2.38	2.34
SD	0.11	0.11	0.11	0.11
Minimum	2.07	2.10	1.98	2.08
Maximum	3.07	2.87	2.73	2.73
Number	1085	979	473	154
Change from baseline				
Median	-0.02	-0.02	-0.02	-0.00
Mean	-0.02	-0.02	-0.02	-0.01
SD	0.09	0.08	0.09	0.08
Minimum	-0.36	-0.32	-0.35	-0.30
Maximum	0.42	0.31	0.54	0.20
Number	1083	973	473	152

Table 69: Patients receiving Daivobet® gel with shifts from 'normal' at baseline to 'high' at Week 4 in the 'controlled scalp studies': safety set

Unique Subject Identifier	Age (years)	Sex	Visit	Albumin corrected calcium[1] (mmol/L)	Reference range Lower	Upper
MBL0405_2622_UK752	56	Male	Week 0	2.60	2.25	2.64
			Week 1	2.53	2.25	2.64
			Week 4	2.75 H	2.25	2.64
			Week 4 R	2.60	2.25	2.64
MBL0406 5214 UK775	43	Male	Week 0	2.55	2.26	2.67
			Week 4	2.70 H	2.26	2.67
			Week 6	2.58	2.26	2.67
MBL0406_5225_UK604	70	Male	Week 0	2.62	2.25	2.64
			Week 1	2.44	2.25	2.64
			Week 4	2.70 H	2.25	2.64
MBL0406_5316_UK521	57	Male	Week 0	2.63	2.25	2.64
			Week 1	2.48	2.25	2.64
			Week 4	2.66 H	2.25	2.64
MBL0502_4126_US034	60	Female	Week 0	2.50	2.12	2.56
			Week 1	2.52	2.12	2.56
			Week 4	2.58 H	2.12	2.56

R represents a repeat or follow-up sample.

Comment: Hypercalcemia between 2.63 and 3 mmol per L may be considered mild and levels in this range may not make for any symptoms.

Hypercalcemia and "increased blood calcium" reported as adverse events

Two subjects had hypercalcemia reported as an adverse event:

- one subject in the combination group (MBL0406 5214 UK775) and

- one subject in the betamethasone group (MBL0405 2373 SE020).

For each of these subjects, the adverse event of hypercalcemia was considered mild and possibly related to study treatment.

"Blood calcium increased" was reported for two subjects in the combination group (MBL0405 2622 UK752 and MBL0406 5291 UK558) and one subject in the betamethasone group (MBL0406 4036 BE034). For subject MBL0406 5291 UK558, the albumin corrected serum calcium was within the reference range throughout the study. These adverse events in the combination group were reported as mild and possibly related to treatment. For the
subject in the betamethasone group, the adverse event was reported as severe and not assessable with regard to relationship to study treatment.

The albumin corrected serum calcium values for these subjects are provided in the following table:

Table 65: Albumin adjusted calcium for patients with adverse events of hypercalcaemia or increased blood calcium in the 'controlled scalp studies': safety analysis set

Patient	Treatment	Age years	Sex	Visit	Albumin corrected calcium (mmol/L)	Reference range lower	upper
MBL0406 5214 UK775	Daivobet® gel	43	Male	Week 0	2.55	2.26	2.67
				Week 4	2.70 H	2.26	2.67
				Week 6	2.58	2.26	2.67
MBL0406 5291 UK558	Daivobet® gel	73	Female	Week 0	2.44	2.25	2.64
				Week 1	2.63	2.25	2.64
				Week 4	2.57	2.25	2.64
				Week 0	2.54	2.25	2.64
MBL0406 4036 BE034	betamethasone	54	Female	Week 1	2.73 H	2.26	2.67
				Week 0	2.73 H	2.26	2.67
				Week 1	2.59	2.26	2.67
MBL0405 2373 SE020	betamethasone	50	Female	Week 1 R	2.68 H	2.26	2.67
				Week 1 R	2.72 H	2.26	2.67
				Week 0	2.74 H	2.26	2.67
				Week 1	2.60	2.25	2.64
				Week 4	2.53	2.25	2.64
MBL0405 2622 UK752	Daivobet® gel	56	Male	Week 4 R	2.75 H	2.25	2.64
					2.60	2.25	2.64

R represents a repeat or follow-up sample.

Other individual cases

One subject (60-year-old female case report number MBL0405 1229) was discontinued from study at Week 4 due to hypercalcemia (the reviewer did not find the calcium value for this time point). However, this subject had an elevated level at baseline of 3.07 mmol/l. Two weeks after discontinuation of treatment the calcium level was higher still at 3.13 mmol/l. She used 13.28 g of the combination product in Week 1, 14.08g in Week 2, 43.06 g during Weeks 3 and 4, and the week between Week 4 (Visit 4) and withdrawal the subject used 38.46 g of the combination product. Thus, it appears that this subject may have had some underlying aberration of calcium metabolism.

24-hour urinary calcium excretion

These data were collected in study MBL 0404 FR, and subjects were treated with the new combination product to scalp lesions and Taclonex ointment to body lesions. Two

subjects had elevated 24-hour urinary calcium excretion, one of whom had a baseline value that was above the upper limit of the reference range (2.50 to 6.25 mmol/24h for females and 2.50 to 7.50 mmol/24 h for males):

- Subject MBL0404 0037 DE117 was a 44-year-old female who had a high 24-hour urine calcium excretion of 13.74 mmol (reference range 2.50 to 6.25 mmol/24h) at baseline. At Week 4, this had increased to 16.80 mmol. This subject used an average weekly amount of 48.0 g suspension and 57.8 g ointment (average total weekly amount of medication 105.8 g) between baseline and Week 4. Headache was the only adverse event reported for this subject, and the investigator considered the event to be unrelated to study medication . The subject left the study at Week 4 as the scalp psoriasis had cleared.
- Subject MBL0404 0044 DE117 was a 32 year-old-male who had a normal 24-hour urine calcium excretion of 6.40 mmol (reference range 2.50 to 7.50 mmol/24h) at baseline and 4.54 mmol at Week 4. At Week 8, the value increased to 10.37 mmol. This subject used an average weekly amount of 10.4 g suspension and 53.6 g ointment (average total weekly amount of medication 64.0 g) between baseline and Week 4, and an average weekly amount of 23.0 g suspension and 50.0 g ointment (average total weekly amount of medication 72.9 g) between Week 5 and Week 8. Adverse events reported for this subject were "intermittent heartburn" and "feeling of pressure renal region," and the investigator considered both events to be unrelated to study medication.

The mean change in 24-hour urinary calcium from baseline to Week 4 was −0.89 mmol/24h (95% confidence interval −1.44 to −0.35) and to Week 8 was 0.33 mmol/24h (95% confidence interval −0.92 to 1.58).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See Section 7.1.7.1.

7.1.7.3 Standard analyses and explorations of laboratory data

See Section 7.1.7.1 and 7.1.12.

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations were preformed.

7.1.7.5 Special assessments

See Section See Section 7.1.7.1 and 7.1.12.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs data were not pooled but were presented in the individual study reports. These data were collected as described below

- Blood pressure was measured at baseline, Weeks 2, 4, 6, 8 and every four weeks thereafter through Week 52 in MBL 0502 US (subjects were treated with either the combination product or vehicle through Week 8, and this phase was double-blinded; all received the combination product from Week 9)
- Blood pressure and pulse rate were measured at baseline, Weeks 4 (if subject left study) or Week 8 in study MBL 0404 FR (in this open-label study, subjects were treated with the new combination product and the approved combination ointment product, i.e. Taclonex ointment, to scalp and body lesions, respectively).
- Blood pressure and pulse rate were measured at baseline and Week 3 in MBL 0302 FR (cumulative irritancy/sensitization study).

There were no clinically relevant changes in mean blood pressures any of the studies.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See Section 7.1.8.1

7.1.8.3 Standard analyses and explorations of vital signs data

MBL 0502 US

In the combination group, the mean change from baseline to end of the double-blind phase (Week 8) in systolic blood pressure was -2.5 mmHg (range: -43.0 to 25.0) and from baseline to the end of the study was -3.0 mmHg (range: -34.5 to 60.0). In the gel vehicle/combination (8/44 weeks) group, the corresponding figures were -5.4 mmHg (range: -47.5 to 31.5), and -2.7 (range: -34.0 to 18.0).

In the combination group, the mean change from baseline to end of the double-blind phase (Week 8) in the diastolic blood pressure, was-2.3 mmHg (range: -34.5 to 25.0) and from baseline to the end of the study (Week 52) was -3.0 mmHg. (range: -32.0 to 21.0). In the vehicle/combination group (8/44 weeks) group, the mean corresponding figures were -5.6 mmHg (range: -32.0 to 22.0) and -2.1 mmHg (range: -22.0 to 22.0).

MBL 0404 FR

The mean systolic pressure at baseline and the end of the study (Week 8) was 132.6 (range: 96 to 185) and 126.3 (range: 99 to 160), respectively. The mean change from baseline was -6.3 (range: -55 to 50).

The mean diastolic pressure at baseline and the end of the study was 77.7 (range: 57 to 105) and 76.6 (range: 58 to 98), respectively. The mean change from baseline was -1.1 (range:

-35 to 30).

MBL 0302 FR

(See Section 7.1.12 for discussion of study design). The mean systolic pressure at baseline and the end of the study (Week 3) for subjects in Treatment Group A (combination product to site 1 and vehicle to site 2) was 121.9 (range: 95 to 177) and 118.4 (range: 87 to 180), respectively. The mean systolic pressure at baseline and the end of the study for subjects in Treatment Group B (gel to site 1 and combination product to site 2) was 122.7 (range: 100 to 161) and 120.8 (range: 96 to 149), respectively.

The mean diastolic pressure at baseline and the end of the study (Week 3) for subjects in Treatment Group A was 67.9 (range: 43 to 106) and 66.4 (range: 46 to 108), respectively. The mean diastolic pressure at baseline and the end of the study for subjects in Treatment Group B was 69.1 (range: 51 to 94) and 66.5 (range: 40 to 97), respectively.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were preformed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were done in study MBL 0404 FR (HPA axis study) at baseline and the end of study.

Preclinical Results

Calcipitriol and betamethasone were tested separately in the safety pharmacology studies. The following information is from the applicant's Nonclinical Overview:

The possible effects of calcipotriol on blood pressure, heart rate, body temperature and electrocardiogram were evaluated after a single oral administration to conscious dogs. In the first part of the study, animals were orally dosed with the control or calcipotriol at doses of 0.5, 1.5 and 5.0 µg/kg p.o., at a volume of 0.5 ml/kg. Telemetric measurements of arterial blood pressure, heart rate and electrocardiogram started at least 24 hours before test article administration and were continued for 24 hours following dosing using an ART™ acquisition system. In the second part of the study, the animal was dosed with calcipotriol by oral route at a dose of 5 µg/kg. A 6 lead electrocardiograms (Leads I, II, III, aVL, aVR, and aVF) and clinical observation was done before dosing, and at 45 and 90 minutes post-treatment. Under the conditions of study, calcipotriol administrated by the oral route at doses of 0.5, 1.5 and 5 µg/kg did not induce any statistically significant change in the parameters monitored, including cardiac conduction times. No changes in

the 6-lead electrocardiogram and no clinical signs were observed after dosing with calcipotriol.

The possible effects of betamethasone dipropionate on blood pressure, heart rate, body temperature and electrocardiogram after single oral administration to conscious dogs were evaluated. As with the calcipotriol, the betamethasone was evaluated in a two-part study. Telemetric measurements were taken after dosing of 0.2, 0.6 and 2.0 mg/kg. A 6 lead electrocardiogram was done after dosing of 2.0 mg/kg. Under the conditions of study, betamethasone dosed at 0.2, 0.6 and 2.0 mg/kg did not induce any statistically significant change in the parameters monitored, including cardiac conduction times statistically significant changes in QT interval, corrected for heart rate using Sarma's method, were observed at doses of 0.2 mg/kg (24 hours post-dosing) and 2 mg/kg (16 and 24 hours post-dosing). These effects were not dose dependant, and not attributed to a pharmacologically relevant effect of betamethasone dipropionate on the duration of ventricular repolarization.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See Section 7.1.9.1

7.1.9.3 Standard analyses and explorations of ECG data

The mean change in the PR interval was 1.6 ms. The mean change in the QRS was 0.3 ms. The mean change in the QT and QTC were -2.1 and -1.3 ms, respectively. These changes were not considered to be clinically significant.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were preformed.

7.1.10 Immunogenicity

This section is not applicable. The product is not a therapeutic protein.

7.1.11 Human Carcinogenicity

The following wording is found in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" of marketed products containing calcipotriene:

"When calcipotriene was applied topically to mice for up to 24 months at dosages of 3, 10 and 30 μg/kg/day (corresponding to 9, 30 and 90 μg/m2/day), no significant changes in tumor incidence were observed when compared to control.In a study in which albino hairless mice were exposed to both UVR and topically applied calcipotriene, a reduction in the time required for UVR to induce the formation of skin tumors was observed (statistically significant in males only), suggesting that calcipotriene may enhance the effect of UVR to induce skin tumors. Patients that apply Dovonex® to exposed portions