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RESEARCH**

APPLICATION NUMBER:
NDA 22-185

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

Clinical Pharmacology Review

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| NDA Number | 22-185 |
| Stamped Receipt Date(s) | June 19 th , 2007 |
| Brand Name | Taclonex Scalp [®] Gel |
| Generic Name | Calcipotriene hydrate 0.5 mcg/g (0.005%) and Betamethasone dipropionate 0.5 mg/g (0.05%) |
| Reviewer | Abimbola Adebowale, Ph.D. |
| Team Leader | Lydia Velazquez, Pharm.D. |
| OCP Division | DCP 3 |
| OND division | HFD-540 |
| Applicant | Parexel International, NC 27713 for Leo Pharmaceutical Products Ltd., Denmark |
| Relevant IND(s) | 67,835 |
| Submission Type; Code | Original NDA; 3S |
| Formulation | Gel |
| Indication | Treatment of Psoriasis Vulgaris of the Scalp in Adults aged 18 years and above |

Table of Contents

| | |
|---|----|
| 1. Executive Summary..... | 2 |
| 1.1 Recommendation..... | 2 |
| 1.2 Phase IV Commitment..... | 3 |
| 1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings | 3 |
| 2 QBR | 6 |
| 2.1 General Attributes of the Drug | 6 |
| 2.2 General Clinical Pharmacology..... | 7 |
| 2.3 Intrinsic Factors | 17 |
| 2.4 Extrinsic Factors | 17 |
| 2.5 General Biopharmaceutics..... | 17 |
| 2.6 Analytical..... | 18 |
| 3 Detailed Labeling Recommendations..... | 20 |
| 4 Appendices | 20 |
| 4.1 Consult review (including Pharmacometric Reviews)..... | 20 |
| 4.2 Proposed Package Insert..... | 20 |
| 4.3 Individual Study Reviews..... | 35 |
| 4.4 OCPB Filing Form | 83 |

1. Executive Summary

This application is for Taclonex Scalp[®] gel (also referred to as Daivobet[®] gel), a fixed combination product containing two drug substances calcipotriol 50 mcg/g (equivalent to 52.2 mcg/g calcipotriol hydrate) and betamethasone 0.5 mg/g (equivalent to 0.643 mg/g betamethasone dipropionate). The proposed indication for Taclonex Scalp[®] gel is topical treatment of psoriasis vulgaris of the scalp (also referred to as scalp psoriasis) in adults 18 years of age and older. The gel is intended to be applied to the affected areas of the scalp once daily for up to 8 weeks. The maximum weekly dose should not exceed 100 g.

Taclonex Scalp[®] gel has been developed to complement the existing combination product Taclonex[®] ointment (NDA 21-852, approved on January 9th, 2006), which contains the same drug substances in the same concentrations. Taclonex[®] ointment is indicated for the once daily topical treatment of psoriasis vulgaris on the body in adults 18 years of age and older for up to 4 weeks (compared to 8 weeks that is being proposed for the gel).

In addition, both active ingredients of Taclonex Scalp[®] gel have been marketed individually in the US for several years for the topical treatment of psoriasis or other indications. Calcipotriol has been marketed in the US since 1994 under the trade name Dovonex[®] ointment, cream and scalp solution formulations are available. Betamethasone dipropionate has been available on the US market in several topical formulations from various manufacturers since 1975.

The clinical pharmacology and biopharmaceutics data and information included in this submission (see Section 1.3 below for details) to support the use of Taclonex Scalp[®] gel is discussed in this review. Please note that calcipotriol and calcipotriene are used interchangeably through this review document. Calcipotriol is identical to calcipotriene. Calcipotriol is the International Non-Proprietary Name (INN) and calcipotriene is the US Adopted name (USAN). “Taclonex Scalp[®] gel” and “Daivobet[®] gel” and “Taclonex[®] ointment” and “Daivobet[®] ointment” are also used interchangeably.

1.1 Recommendation (s):

The pharmacokinetic data obtained following topical application of Taclonex Scalp[®] gel on the scalp in combination with Taclonex[®] ointment to the body of patients with psoriasis vulgaris indicated that the serum concentrations of calcipotriene and betamethasone dipropionate obtained were below the lower limit of quantification in all the serum samples collected. In addition, one of the major metabolites of calcipotriene and betamethasone dipropionate respectively, could be measured in a few plasma samples for some of the patients.

For the hypothalamic-pituitary-adrenal (HPA) axis assessment as a measure of the systemic exposure of betamethasone, the data obtained following topical application of Taclonex Scalp[®] gel on the scalp in combination with Taclonex[®] ointment to the body of patients with psoriasis for 4 to 8 weeks demonstrated that a total of six of 32 patients (four at week 4, one at week 8 and one both at weeks 4 and 8) showed adrenal suppression as indicated by a serum cortisol value ≤ 18 mcg/dL, 30 minutes post-stimulation. The applicant has incorporated the findings of this study in their label.

For the effect on calcium metabolism assessment as a measure of the systemic exposure of calcipotriene, the individual data indicated that there was an increase in urinary calcium excretion in a total of two of 32 patients (one at week 4 and one at week 8), following topical application of Taclonex Scalp[®] gel on the scalp in combination with Taclonex[®] ointment to the body of patients with psoriasis for 4 to 8 weeks. In addition, an increase in albumin-corrected serum calcium was **b(4)** observed in 5 of 1085 (0.5 %) patients treated with Taclonex Scalp[®] gel for 4 weeks.

Based on the data submitted the applicant has met the requirements outlined in 21CFR 320 and, their application is acceptable from a clinical pharmacology and biopharmaceutics perspective. We recommend that the labeling changes included in the product package insert (see section 4.2) be conveyed to the applicant.

1.2 Phase IV Commitments: Not Applicable

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings:

Introduction:

The clinical pharmacology program consisted of 8 studies as follows: (1) Study # MBL 0404 FR: HPA axis and calcium metabolism study in patients with plaque psoriasis (2) Study # MBL 0403 FR: vasoconstriction study in healthy subjects (3) Study # MBL 0402 FR: atrophy study in healthy subjects (4) Study # MBL 0601 FR: atrophy study in healthy subjects (5) MBL 0201 FR,; clinical psoriasis plaque test. In addition, serum calcium was also measured in three Phase 3 studies; MBL 0405 INT, MBL 0406 INT and MBL 0502 US

The 5 studies reviewed were MBL 0404 FR, MBL 0403 FR and the serum calcium measurements in the three Phase 3 studies MBL 0405 INT, MBL 0406 INT and MBL 0502 US because they assessed the systemic bioavailability of the active constituents in Taclonex Scalp[®] gel. In MBL 0404 FR systemic bioavailability was assessed using exploratory pharmacokinetics and, indirectly assessed using surrogate parameters (serum calcium and hypothalamic-pituitary-adrenal (HPA) axis testing). The use of these surrogate parameters is based on adrenal suppression and hypercalcemia being known as the main pharmacological effects that result from systemic exposure following topical use of calcipotriol and betamethasone dipropionate. The serum calcium measurements in three Phase 3 studies; MBL 0405 INT, MBL 0406 INT and MBL 0502 US was also assessed as a measure of the systemic bioavailability of calcipotriene. Study # MBL 0403 FR (vasoconstriction study) assessed the corticosteroid potency of betamethasone dipropionate in Daivobet[®] gel in accordance with the FDA guidance entitled: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence

The atrophy studies (MBL 0402 FR and MBL 0601 FR) and the clinical psoriasis plaque test MBL 0201 FR were not reviewed because these studies are considered clinical studies with clinical endpoints and they are being reviewed by the clinical reviewer

Systemic Exposure:

The systemic exposure of Taclonex Scalp[®] gel was investigated in study MBL 0404 FR. This study was conducted in patients (N=35) with extensive psoriasis on both scalp (at least 30% of scalp) and body (15%-30% of BSA) who were treated with Daivobet[®] gel on the scalp and Daivobet[®] ointment on the body. Patients were initially treated for 4 weeks with Taclonex Scalp[®] gel on the scalp and Daivobet[®] ointment on the body. If the scalp psoriasis was cleared at that point, the patient left the study. If signs of scalp psoriasis were still present, the patient continued using Taclonex Scalp[®] gel once daily on the scalp for another 4 weeks, and used Daivobet[®] ointment as required on the body during that period. HPA axis suppression, serum calcium and exploratory pharmacokinetics of calcipotriol and betamethasone dipropionate and one of their respective major metabolites (MC1080 and betamethasone 17 dipropionate) were evaluated in this study. It should be noted that since the patients in this study applied Daivobet[®] gel to psoriasis lesions on the scalp and Daivobet[®] ointment to psoriasis lesions on the body, it is not possible to evaluate the single effect of Daivobet[®] gel applied to the scalp. Therefore this study only provides information on the maximum combined systemic exposure of the two products.

Effects on calcium metabolism: The evaluation of calcium metabolism in study MBL 0404 FR consisted of measurements of serum calcium and 24-hour urinary calcium excretion at baseline, week 4 and week 8. There were no patients with a serum calcium value above the upper reference limit at any time-point during study MBL 0404 FR when measurements were made. Mean serum calcium did not change over the study period. The 24-hour urinary calcium excretion is known to be a more sensitive measure of calcium metabolism than serum calcium and was therefore also investigated in this study. No trend in increasing mean values of urinary calcium excretion during the study was observed. However, two patients with a possible clinically significant increase in urinary calcium excretion were identified following an evaluation of the individual data. The applicant stated that the changes in both patients were considered most likely due to random biological variation in calcium metabolism and none were of clinical concern, therefore the overall conclusion by the applicant was that no clinically relevant changes in calcium metabolism were observed in the study.

However, the albumin-corrected serum calcium values that were obtained from the three Phase 3 studies (MBL 0405 INT, MBL 0406 INT; and MBL 0502 US) also indicated that there were 5 of 1085 (0.5 %) patients shifting from a normal value at baseline to a value above the reference limit when Daivobet[®] gel was applied once daily for up to 4 weeks for treating scalp psoriasis. Please note that the applicant also concluded that no clinically relevant changes in calcium metabolism were observed in the study.

Reviewer's Comments: This reviewer believes that the information on the increase observed in the urinary calcium excretion for the two patients should be mentioned in the label. This is further supported by the observed cases of an increase in albumin-corrected serum calcium in the Phase 3 studies.

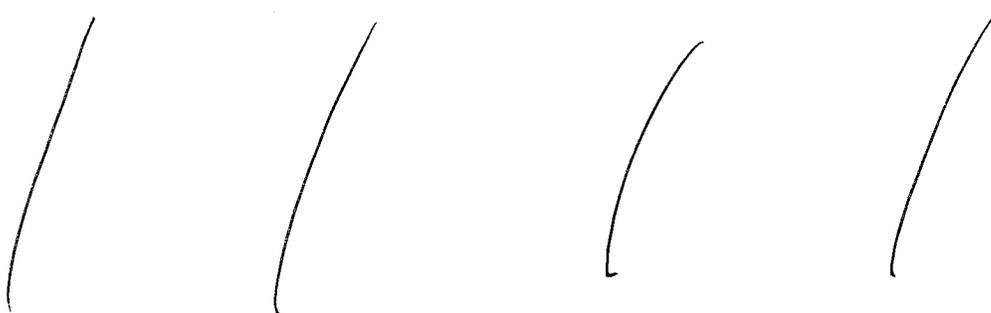
Effects on the HPA axis: The HPA axis testing in study MBL 0404 FR was conducted by means of administration of a standard dose (250 mg intravenously) of _____ (tetracosactide, synthetic adrenocorticotrophic hormone [ACTH]) test, at baseline, week 4 and week 8. The primary response criterion for evaluation of a normal HPA axis function was that the serum cortisol level 30 minutes after _____ injection should be > 18 mcg/dL (i.e. the FDA criterion). In addition, the serum

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cortisol level 60 minutes after injection and the incremental rise from time zero to 30 and 60 minutes, respectively, were used as secondary criteria by the applicant.

Of the 35 patients included in the study, three had 30-minute serum cortisol levels less than 18 mcg/dL at baseline and were excluded from the per protocol analysis set. Based on the primary response criterion, a total of six of the 32 patients in the per protocol population (four at week 4, one at week 8 and one both at weeks 4 and 8) showed evidence of adrenal suppression (i.e. a serum cortisol value less than 18 mcg/dL, 30 minutes after injection). However, in all patients the serum cortisol levels 60 minutes (second criteria) after injection were > 18 mcg/dL.

b(4)



b(4)

Pharmacokinetic data: In Study MBL 0404 FR, pharmacokinetic analysis was conducted at week 4 and week 8. Blood samples were collected at the following times 0 (before initiation of the application of the gel and ointment) and then at 1, 2, 3, 5 and 7 hours post-dosing. Serum samples were analyzed for calcipotriol and one of its' major metabolites, MC1080 and betamethasone dipropionate and one of its major metabolites, betamethasone 17-propionate (B17P). The pharmacokinetic data indicated that the serum concentrations of calcipotriene and betamethasone dipropionate were below the lower limit of quantification (LOQ = 50 pg/mL and 30 pg/mL, respectively) in all serum samples. However, one major metabolite of calcipotriene (MC1080) and one major metabolite of betamethasone (betamethasone 17 dipropionate B17P) could be measured in a few samples for some of the patients. MC1080 was quantifiable in 10 of 34 (29.4%) patients at week 4 and in five of 12 (41.7%) patients at week 8. Betamethasone 17-propionate was 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 (LOQ 20 pg/mL) ranged from 20-75 pg/mL and for betamethasone 17-propionate (LOQ 30 pg/mL) the serum concentrations ranged from 30-170 pg/mL. No pharmacokinetic parameters could be calculated because several patients had values below or close to the LOQ, such that full PK profiles could not be obtained.

Reviewer's Comments: The data obtained for B17P should be interpreted with caution and may not be reliable due to the highly variable long term stability data (differences ranging from -24 % to 208 %) observed between concentration values obtained before (Day 0) and after storage of serum samples for up to 23 days.

Corticosteroid Potency

A vasoconstriction study (MBL 0403 FR) was conducted in order to determine the corticosteroid potency of betamethasone dipropionate in Taclonex Scalp[®] gel. The comparator chosen was Diprosone[®] ointment, a formulation of betamethasone 0.5 mg/g (as dipropionate) marketed in the

USA. The US approved product information for Diprosone[®] classifies the ointment in the high range of potency. The study was designed as a bioequivalence study conducted according to the vasoconstrictor assay as described in the FDA guideline on *in vivo* bioequivalence of topical dermatologic corticosteroids. The results of the study demonstrated that Taclonex Scalp[®] gel was not bioequivalent to Diprosone[®] ointment in that Taclonex Scalp[®] gel induced less skin blanching than Diprosone[®] ointment. Based on the results of the vasoconstriction study, the potency of betamethasone dipropionate in Taclonex Scalp[®] gel is not expected to exceed that of a highly potent corticosteroid.

Signatures:

Abimbola Adebawale, Ph.D., Senior Clinical Pharmacology Reviewer, DCP 3

Lydia Velazquez, Pharm.D., Team Leader, DCP 3

2. QBR

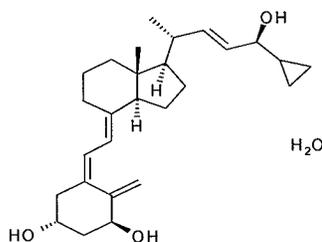
2.1 General Attributes

Physicochemical Properties of the active drug substances, calcipotriene hydrate and betamethasone dipropionate in Taclonex Scalp[®] Gel

Calcipotriene hydrate: It is a white to almost white crystalline compound.

Molecular Formula: C₂₇H₄₀O₃, H₂O, **Molecular Weight:** 430.6

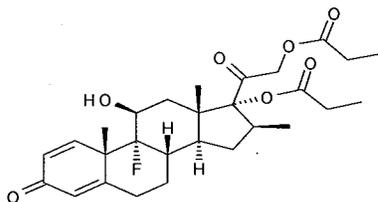
Structural Formula:



Betamethasone dipropionate: It is a white to almost white odorless powder

Molecular Formula: C₂₈H₃₇FO₇, **Molecular Weight:** 504.6

Structural Formula:



Mechanism of Drug Action

Calcipotriene hydrate is a synthetic vitamin D₃ analogue and, betamethasone dipropionate is a synthetic corticosteroid. Taclonex Scalp[®] gel combines the pharmacological effects of calcipotriene hydrate and betamethasone dipropionate. The possibility of a beneficial effect of combining vitamin D₃ analogues and topical corticosteroids has been suggested because of their different modes of action. It is believed that the vitamin D₃ analogue may reduce the daily amount of steroid used and, the duration of steroid exposure, decreasing the risk of steroid-related adverse effects such as skin atrophy, and telangiaectasia. Likewise, the anti-inflammatory effect of the corticosteroid may serve to decrease the skin irritation frequently associated with the vitamin D₃ analogues.

Calcipotriene:

The mechanism of action of calcipotriene is similar to that of the active form of vitamin D₃, 1, 25 (OH)₂ D₃ (calcitriol). Calcipotriene, like calcitriol, acts by binding to the vitamin D receptor and regulating various genes. Calcitriol is known to be involved in the regulation of calcium homeostasis. Additionally, calcitriol has been shown to inhibit proliferation and induce differentiation of keratinocytes, and modulate the immune response in skin tissue. Calcipotriene is believed to have the same effects as calcitriol on the skin, but with minimal effects on calcium metabolism, possibly due to the fact that it is rapidly metabolized to less active metabolites in the liver.

Betamethasone dipropionate:

Corticosteroids have a broad mechanism of action. They inhibit the synthesis of many inflammatory cytokines, the production of prostaglandins and nitric oxide, and the expression of adhesion molecules. Betamethasone dipropionate is believed to have anti-inflammatory and antipruritic actions that are characteristic of corticosteroids.

Therapeutic Indications and Proposed Dosing Regimen

Taclonex Scalp[®] gel is indicated for the topical treatment of psoriasis vulgaris on the scalp in adults aged 18 years and above. It is recommended to be applied to the affected areas on the scalp once daily for up to 8 weeks. The maximum weekly dose should not exceed 100 g.

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2.2 General Clinical Pharmacology

Q. *What were the design features of the clinical pharmacology and clinical studies used to support efficacy and safety?*

Figure 1 Overview of the Clinical Development Program

Pivotal Studies:

MBL 0405 INT
1505 patients
Randomised, double-blind, 4-arm:
1. Daivobet® gel
2. Betamethasone in gel vehicle
3. Calcipotriol in gel vehicle
4. Gel vehicle
Once daily, 8-week study

MBL 0406 INT
1417 patients
Randomised, double-blind, 3-arm:
1. Daivobet® gel
2. Betamethasone in gel vehicle
3. Calcipotriol in gel vehicle
Once daily, 8-week study

Supportive Studies:

MBL 0401 INT
218 patients
Randomised, double-blind, 2-arm:
1. Daivobet® gel
2. Betamethasone in gel vehicle
Once daily, 8-week study

MBL 0503 INT
312 patients
Randomised, investigator-blinded, 2-arm:
1. Daivobet® gel
2. Daivonex® Scalp solution
Once / twice daily, 8-week study
+ 8 weeks follow-up (relapse, rebound)

MBL 0407 INT
869 patients
Randomised, double-blind, 2-arm:
1. Daivobet® gel
2. Calcipotriol in gel vehicle
Once daily, 52-week study

MBL 0502 US
177 patients
Randomised, double-blind, 2-arm:
1. Daivobet® gel
2. Gel vehicle
Once daily, 8-week study + 44 weeks open-label Daivobet® gel treatment plus Daivobet® ointment on the body throughout the study

Safety Study:

MBL 0404 FR
35 patients
HPA axis suppression test
Calcium metabolism test
Once daily, Daivobet® gel +
Daivobet® ointment on the body,
8-week study

Biopharmaceutic Studies:

MBL 0201 FR
23 patients
Psoriasis plaque test
Dose finding

MBL 0203 FR
24 patients
Psoriasis plaque test
Different formulations

Healthy Subject Studies:

MBL 0303 FR
33 healthy subjects
Photo-toxicity test

MBL 0301 UK
49 healthy subjects
Photo-allergy test

MBL 0302 FR
220 healthy subjects
Repeat insult patch test and 21-day cumulative irritation test

MBL 0402 UK
45 healthy subjects
Skin atrophy study

MBL 0501 FR
48 healthy subjects
Skin atrophy study

MBL 0403 FR
82 healthy subjects
Vasoc constriction study

Other Indications:

MBL 0202 INT
364 patients with
psoriasis vulgaris on body
Randomised, double-blind, 4-arm:
1. Daivobet® gel
2. Betamethasone in gel vehicle
3. Calcipotriol in gel vehicle
4. Gel vehicle
Once daily, 8-week study

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Biopharmaceutics Studies:

As shown in the table above, two clinical psoriasis plaque test studies were conducted to address dose-response (MBL 0201 FR) and formulation development (MBL 0203 FR). These were intra-individual comparisons in patients with psoriasis vulgaris on the body and compared several different dose combinations or formulations. These studies included formulations very similar to the Daivobet® gel formulation to be marketed, but not the exact formulation (Please see sections on exposure-response for efficacy and safety below). All clinical studies, except these two biopharmaceutics studies, however, were conducted using the Daivobet® gel formulation to be marketed.

Reviewer's comments: This reviewer did not review these studies because the formulations used are different from the to-be-marketed formulations and, they are also clinical studies that involve clinical endpoints and are therefore being reviewed by the clinical reviewer.

Pharmacodynamic studies

Three studies investigated the pharmacodynamic properties of Daivobet® gel in healthy subjects. A vasoconstriction study (MBL 0403 FR) evaluated the corticosteroid potency of betamethasone dipropionate in Daivobet® gel relative to that of a betamethasone dipropionate product (Diprosone® ointment). Two atrophy studies, MBL 0402 UK and MBL 0601 FR, compared the atrophogenic potential of Daivobet® gel with that of the gel vehicle and Diprosone® ointment.

Reviewer's Comments: This reviewer only reviewed study # MBL 0403 FR, the vasoconstriction study since it is a bioequivalence study conducted according to FDA guidance for topical dermatologic corticosteroids. Please see clinical review for the review of the atrophogenic potential studies.

Q. What is the basis of selecting the clinical/pharmacodynamic response endpoints?Clinical End Points:

For the pivotal clinical study, the primary endpoint was the Percentage of patients classified as “controlled disease” (absence of disease or very mild disease according to the Investigator’s Global Assessment of Disease Severity IGA) at the end of treatment (i.e. 8 weeks). The IGA was the primary efficacy assessment for the integrated analysis of efficacy (IGA) and the The Investigator's Global Assessment of Disease Severity (IGA) was made using a 6-point scale as follows:

Table 1:

| Scale | Description |
|---------------------|---|
| Absence of disease | The disease is controlled. No evidence of redness, no evidence of thickness, and no evidence of scaling |
| Very mild disease | The disease is controlled but not entirely cleared. The overall clinical picture consists of lesions with some discoloration with absolutely minimal thickness, i.e. the edges of the lesion(s) can just be felt. |
| 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, somewhat coarse scale layer. |
| Severe disease | The overall clinical picture consists of lesions with very red coloration, severe thickness and a severe, coarse thick scale layer |
| Very severe disease | The overall clinical picture consists of lesions with extreme deep red coloration, very severe thickness and very severe, coarse thick scale layer. |

Pharmacodynamic Endpoints:

The applicant used the effects on calcium homeostasis and, HPA axis suppression for the assessment of systemic absorption of calcipotriene and betamethasone dipropionate respectively, in patients with psoriasis. Because of its pharmacological action on calcium metabolism which is

mediated through its binding to vitamin D receptors, serum and urine calcium levels can be used to assess the extent of systemic absorption of calcipotriene. In addition, hypercalcemia is one of the systemic related adverse events (AE) associated with calcitriol and some of its analogues. Therefore, the calcemic activity of calcipotriene was evaluated in a number of the Phase 3 studies by measuring albumin-corrected serum calcium.

The pharmacologic basis for HPA axis monitoring as an assessment of betamethasone dipropionate systemic absorption is the suppression of the HPA axis through negative feed-back. This results in a decrease in cortisol response from the adrenals in response to adrenocorticotrophic hormone (ACTH) stimulation. The applicant also evaluated the vasoconstrictive action (i.e. skin blanching) of betamethasone dipropionate in Daivobet[®] gel to determine its steroid potency.

Q. What are the characteristics of the exposure-response relationships for safety and efficacy?

The sponsor did not conduct any dose-finding studies with the final to be marketed formulation of Daivobet[®] gel. The applicant stated that the concentrations of calcipotriol and betamethasone dipropionate in Daivobet[®] gel were chosen based on:

- The concentrations of calcipotriol and betamethasone dipropionate in marketed single component products (Daivonex[®] and various products containing betamethasone dipropionate, respectively). These products have been used extensively as monotherapy worldwide over many years for treating psoriasis vulgaris, and their safety profiles are well established
- The concentrations of calcipotriol and betamethasone dipropionate used in the combination product, Daivobet[®] ointment, which has been marketed since 2001 in the EU and since 2006 in the US.

In addition, the applicant stated that the selection of the concentrations of calcipotriol and betamethasone dipropionate in Daivobet[®] gel was supported by a clinical psoriasis plaque test in patients with psoriasis vulgaris on the body. In this study the antipsoriatic effect of six different dose combinations of calcipotriol (0, 25 and 50 mcg/g) and/or betamethasone (0, 0.25 and 0.50 mg/g; as dipropionate) in a gel formulation compared to vehicle and Daivobet[®] ointment over a period of 3 weeks was investigated in 22 psoriasis patients. The final Daivobet[®] gel formulation was subsequently improved compared to the gel formulations used in this study. Results were based on visual scoring of erythema, scaling and infiltration on the test sites, as well as sonographic measurements of skin thickness. The applicant stated that the results showed a tendency towards a dose-response relationship for calcipotriol and betamethasone dipropionate, supporting a dose of calcipotriol 50 mcg/g plus betamethasone dipropionate 0.5 mg/g. However, the study design did not allow for clear separation of response to the doses tested. Please refer to clinical review for further details.

Q. What is the systemic absorption of calcipotriol and betamethasone from Taclonex gel?

Study MBL 0404 evaluated the systemic absorption of calcipotriol and betamethasone dipropionate in Taclonex gel. This study investigated systemic absorption in three ways:

- assessment of systemic effects of calcipotriene on calcium metabolism
- assessment of systemic effects of betamethasone dipropionate on the HPA axis
- measurement of calcipotriol and betamethasone dipropionate and their metabolites in serum.

The evaluations of calcium metabolism, adrenal function and pharmacokinetics indicated that there was some degree of systemic exposure of calcipotriene and betamethasone following the topical application of Daivobet® gel and Daivobet® ointment to patients with psoriasis.

Daivobet® gel was applied to psoriasis lesions on the scalp and Daivobet® ointment was applied to psoriasis lesions on the body, once daily for the first 4 weeks of the study in 35 patients. Patients whose scalp psoriasis cleared at 4 weeks were allowed to leave the study at that time. The patients who continued in the study up to week 8 (12 of the 35 patients included) used Daivobet® gel once daily and Daivobet® ointment as required during the last 4-week period.

It should be noted that patients in the study applied Daivobet® gel to psoriasis lesions on the scalp and Daivobet® ointment to psoriasis lesions on the body. Therefore it is not possible to evaluate the single effect of Daivobet® gel applied to the scalp. Instead, the study provides information on the maximum combined exposure to the two products (up to 110 g/week, which is slightly higher than the recommended maximum dosage for Daivobet® ointment of 100 g/week) which is likely to occur in clinical practice. The results therefore are expected to represent the maximum clinically relevant exposure. Please note that the actual weekly use of gel plus ointment ranged from 29.7 to 105.8 g with a mean amount of 62.5 g. The mean weekly use of the gel was 23.7 g. The actual severity of scalp psoriasis was moderate in 42.9%, severe in 48.6% and very severe in 8.6%, whereas severity of body psoriasis was moderate in 40.0% and severe in 60.0% of the 35 patients.

Effects on calcium metabolism:

Effects on calcium metabolism were evaluated in terms of serum calcium measured and 24-hour urinary calcium excretion, measured at baseline, week 4 and week 8. Serum calcium results at baseline, week 4 and week 8 are summarized in Table 2.

Table 2: Summary of serum calcium results from study MBL 0404 FR (combined treatment with Daivobet® gel and Daivobet® ointment): safety analysis set.

| Visit | Serum calcium (mmol/l) | Change in serum calcium (mmol/l) |
|---------------------------|------------------------|----------------------------------|
| Visit 3 (baseline) | | |
| Mean | 2.45 | NA |
| SD | 0.09 | NA |
| Median | 2.45 | NA |
| Minimum | 2.28 | NA |
| Maximum | 2.65 | NA |
| Number | 35 | NA |
| Visit 7 (week 4) | | |
| Mean | 2.40 | -0.05 |

| | | |
|--------------------------|------|-------|
| SD | 0.07 | 0.07 |
| Median | 2.40 | -0.05 |
| Minimum | 2.28 | -0.20 |
| Maximum | 2.55 | 0.12 |
| Number | 33 | 33 |
| Lower 95% CL | | -0.08 |
| Upper 95% CL | | -0.02 |
| Visit 11 (week 8) | | |
| Mean | 2.42 | -0.03 |
| SD | 0.09 | 0.08 |
| Median | 2.41 | -0.04 |
| Minimum | 2.28 | -0.13 |
| Maximum | 2.60 | 0.15 |
| Number | 12 | 12 |
| Lower 95% CL | | -0.08 |
| Upper 95% CL | | 0.02 |

Mean serum calcium was similar at all visits. All serum calcium values were within the reference range (2.25 to 2.67 mmol/L) and hence there were no patients with abnormal serum calcium at any visit. The mean change in serum calcium from baseline to week 4 was -0.05 mmol/L (95% CI -0.08 to -0.02) and to week 8 was -0.03 mmol/L (95% CI -0.08 to 0.02).

Results of the 24-hour urinary calcium excretion are summarized in Table 3. The mean 24-hour urinary calcium excretion was similar at baseline and weeks 4 and 8. The reference range was 2.50 to 6.25 mmol/24h for females and, 2.50 to 7.50 mmol/24 h for males. The mean change in 24-hour urinary calcium from baseline to week 4 was -0.89 mmol/24h (95% CI -1.44 to -0.35) and to week 8 was 0.33 mmol/24h (95% CI -0.92 to 1.58).

Table 3: Summary of 24-hour urinary calcium from study MBL 0404 FR (combined treatment with Daivobet[®] gel and Daivobet[®] ointment): safety analysis set.

| Visit | Urinary calcium (mmol/24h) | Change in urinary calcium (mmol/24h) |
|---------------------------|----------------------------|--------------------------------------|
| Visit 3 (baseline) | | |
| Mean | 6.07 | NA |
| SD | 3.04 | NA |
| Median | 5.40 | NA |
| Minimum | 1.77 | NA |
| Maximum | 13.74 | NA |
| Number | 35 | NA |
| Visit 7 (week 4) | | |
| Mean | 5.33 | -0.89 |

| | | |
|--------------------------|-------|-------|
| SD | 3.08 | 1.50 |
| Median | 4.83 | -0.88 |
| Minimum | 1.08 | -4.01 |
| Maximum | 16.80 | 3.06 |
| Number | 32 | 32 |
| Lower 95% CL | | -1.44 |
| Upper 95% CL | | -0.35 |
| Visit 11 (week 8) | | |
| Mean | 6.91 | 0.33 |
| SD | 2.92 | 1.96 |
| Median | 6.96 | 0.69 |
| Minimum | 2.13 | -3.33 |
| Maximum | 10.37 | 3.97 |
| Number | 12 | 12 |
| Lower 95% CL | | -0.92 |
| Upper 95% CL | | 1.58 |

There were two patients with a change in 24-hour urinary calcium excretion as follows:

Patient MBL0404_0037_DE117 had a high 24-hour urine calcium excretion of 13.74 mmol (reference range 2.50 to 6.25 mmol/24h) at baseline but this increased further to 16.80 mmol at week 4. In contrast, serum calcium values were within the reference range (2.25 to 2.67 mmol/L) throughout the study. There was an increase from 2.45 mmol/L at baseline to 2.62 mmol/L at week 2, but at week 4 the value was similar to the baseline level (2.38 mmol/L). This patient used an average weekly amount of 48.0 g gel and 57.8 g ointment (average total weekly amount of medication 105.8 g) between baseline and week 4. The patient left the study at week 4 as the scalp psoriasis had cleared.

Patient MBL0404_0044_DE117 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, but at week 8 it increased to 10.37 mmol. Serum calcium values were within the reference range (2.25 to 2.67 mmol/L) throughout the study and there was no trend of increasing values (2.45 mmol/L at baseline, 2.33 mmol/L at weeks 4 and 8). This patient used an average weekly amount of 10.9 g gel and 55.6 g ointment (average total weekly amount of medication 66.5 g) between baseline and week 4, and an average weekly amount of 22.2 g gel and 48.2 g ointment (average total weekly amount of medication 70.4 g) between week 5 and week 8.

Reviewer's Comments: In summary, all serum calcium values were within the reference range at all visits. The mean 24-hour urinary calcium excretion was similar at baseline and weeks 4 and 8. However, an evaluation of the individual 24-hour urinary excretion data indicated that two patients were identified with an increase in 24-hour urinary calcium excretion indicating systemic exposure to calcipotriol. This indicates that there is the possibility of patients developing hypercalcemia with the application of an amount of medication that is within the recommended dosing regimen although less than the recommended maximum total weekly amount of 100 g. Although the applicant indicated that they did not consider the increase in urinary excretion in 2 patients to be

clinically relevant, this reviewer believes that the information should still be incorporated in the label (see labeling recommendations in section 3.1)

In addition to the serum and urinary calcium data obtained in study MBL 0404, albumin corrected calcium was also measured in studies MBL 0405 INT, MBL 0406 INT and MBL 0502 US and this data was pooled for these studies by the applicant. The albumin-corrected serum calcium values that were obtained from these studies indicated that there were 5 of 1085 (0.5 %) patients that shifted from a normal value at baseline to a value above the reference limit when Daivobet® gel was applied once daily for up to 4 weeks for treating scalp psoriasis. The patients with shifts from normal at baseline to high at Week 4 in the Daivobet® gel group are shown in Table 4 below.

Table 4: 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 | 2.6 | 2.25 | 2.64 |
| | | | Week 1 | 2.53 | 2.25 | 2.64 |
| | | | Week 4 | 2.75 H ^a | 2.25 | 2.64 |
| | | | Week 4 | ^b R 2.6 | 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 | 2.5 | 2.12 | 2.56 |
| | | | Week 1 | 2.52 | 2.12 | 2.56 |
| | | | Week 4 | 2.58 H | 2.12 | 2.56 |

^aH represents a shift from normal at baseline to high at week 4; ^bR represents a repeat or follow-up sample

Reviewer’s Comments: The increase in albumin corrected calcium observed in the individual data in these three Phase 3 studies support the possibility of patients developing hypercalcemia with the application of an amount of medication that is less than the recommended maximum total weekly amount of 100 g. Although the applicant indicated that they did not consider the increase in albumin corrected calcium to be clinically relevant because the changes were small and similar in all treatment groups,

b(4)

Effects on the HPA axis

The HPA axis testing in study MBL 0404 FR was conducted by administration of a standard dose of _____ at baseline, week 4 and week 8. The ACTH challenge test consists of blood sampling at 8 a.m. (± 30 minutes) (T=0) for assessment of baseline serum cortisol concentration (reference ranges between 5.0 to 22.4 mcg/dL). An intravenous bolus injection of 250 mcg _____ is given and blood samples were taken at 30 and 60 minutes for assessment of the stimulation serum cortisol concentration. The primary response criterion of HPA axis suppression in the study was the serum cortisol level 30 minutes after ACTH stimulation, which should be > 18 mcg/dL to be considered normal. The primary criterion was chosen based on advice from the FDA. Secondary criteria were the serum cortisol level 60 minutes after ACTH stimulation and the change in serum cortisol from baseline (time zero) to 30 and 60 minutes after ACTH stimulation, respectively.

b(4)

The results of the HPA axis testing were evaluated for the per protocol analysis set (n=32). Three patients who had a serum cortisol level ≤18 mcg/dL before treatment were excluded from the per protocol analysis set. At week 4, five (15.6%) patients (Patients MBL0404_0001_FR187, MBL0404_0025_DK177, MBL0404_0035_DE117, MBL0404_0056_DE117 and MBL0404_0058_DE117) had a serum cortisol ≤18 mcg/dL 30 minutes after ACTH stimulation. Of the 11 patients who continued to week 8, two (18.2%) patients (Patients MBL0404_0001_FR187 and MBL0404_0003_FR187) had serum cortisol ≤18 mcg/dL.

Individual data for the patients with serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test are presented for the per protocol analysis set in Table 6. The applicant stated that although these patients did not meet the first criterion, they did meet the second criteria. Basically, all patients with serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test had serum cortisol >18 mcg/dL at 60 minutes at either week 4 or week 8. Furthermore, their baseline (time zero) serum cortisol values were above the lower limit of the reference range (5 mcg/dL) at both weeks 4 and 8.

Table 5: Individual data for patients with cortisol levels ≤18 mcg/dL 30 minutes after the ACTH challenge test from study MBL 0404 FR (combined treatment with Daivobet® gel and Daivobet® ointment): per protocol analysis set.

| Patient | Visit | Before (Time zero) | 30 min | | 60 min | |
|---------------------|----------|-----------------------|--------|---------|--------|---------|
| | | | Obs1 | Change2 | Obs1 | Change2 |
| MBL0404_0001_FR187 | Baseline | 15.32 | 22.09 | 6.77* | 22.02 | 6.70* |
| | Week 4 | 11.41 | 17.71* | 6.30* | 22.20 | 10.79 |
| | Week 8 | 10.54 | 16.77* | 6.23* | 22.42 | 11.88 |
| MBL0404_0003_FR187 | Baseline | 10.68 | 18.91 | 8.22 | 22.64 | 11.95 |
| | Week 4 | 11.34 | 18.65 | 7.32 | 22.38 | 11.05 |
| | Week 8 | 11.55 | 17.57* | 6.01* | 18.25 | 6.70* |
| MBL0404_0025_DK1773 | Baseline | 9.53 | 18.83 | 9.31 | 19.56 | 10.03 |
| | Week 4 | 14.31 | 17.71* | 3.40* | 20.32 | 6.01* |

| | | | | | | |
|--------------------|-----------|-------|--------|-------|-------|-------|
| | Follow-up | 3.19 | 16.30* | 13.11 | 21.04 | 17.86 |
| MBL0404_0035_DE117 | Baseline | 8.55 | 19.20 | 10.65 | 22.02 | 13.47 |
| | Week 4 | 13.76 | 17.31* | 3.55* | 21.08 | 7.32 |
| | Follow-up | 10.65 | 24.37 | 13.73 | 25.24 | 14.60 |
| MBL0404_0056_DE117 | Baseline | 10.32 | 24.01 | 13.69 | 27.53 | 17.20 |
| | Week 4 | 8.40 | 17.09* | 8.69 | 20.64 | 12.24 |
| | Follow-up | 10.97 | 18.07 | 7.10 | 20.39 | 9.42 |
| MBL0404_0058_DE117 | Baseline | 9.45 | 18.83 | 9.38 | 21.73 | 12.28 |
| | Week 4 | 8.69 | 17.20* | 8.51 | 20.17 | 11.48 |
| | Follow-up | 13.58 | 20.50 | 6.92* | 24.88 | 11.30 |

1) Obs = observed value.

2) Changes are from before the ACTH injection (time 0) to 30 or 60 mins as appropriate.

3) Follow up ACTH challenge test occurred 83 days after the Week 4 test, not at 28 days as stated in the protocol.

* denotes a value below the lower reference limit (≤ 18 mcg/dL for observed values and ≤ 7 mcg/dL for change).

The applicant also stated that no correlation between amount of drug used and 30-minute serum cortisol levels after 4 weeks treatment was observed. In summary, 5 of 32 (15.6%) patients in the per protocol analysis set had a serum cortisol ≤ 18 mcg/dL at 30 minutes at week 4. Two of the 11 (18.2%) patients who continued to week 8 had a serum cortisol ≤ 18 mcg/dL at 30 minutes. All patients had serum cortisol > 18 mcg/dL at 60 minutes at weeks 4 or 8 (where assessed). Furthermore, the baseline (time zero) serum cortisol values of all patients who recorded a serum cortisol ≤ 18 mcg/dL at 30 minutes were above the lower limit of the reference range (5 mcg/dL) of the endogenous cortisol levels at both weeks 4 and 8 suggesting that any possible HPA axis suppression detected by the ACTH challenge test did not lead to low endogenous serum cortisol levels.

b(4)

Exploratory Pharmacokinetic Analysis:

In Study MBL 0404 FR, the pharmacokinetic analysis was conducted at week 4 and week 8. Blood samples were collected at the following times 0 (before initiation of the application of the gel and ointment) and then at 1, 2, 3, 5 and 7 hours post-dosing. Analyses of serum samples were conducted for calcipotriol, its major metabolite (MC1080), betamethasone dipropionate, and its major metabolite (betamethasone 17-propionate or B17P). Calcipotriol and betamethasone dipropionate were below the lower limit of quantification (LOQ: 50 pg/mL and 30 pg/mL, respectively) in all

serum samples. MC1080 was quantifiable in 10 of 34 (29.4%) patients at week 4 and in five of 12 (41.7%) patients at week 8. B17P was 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 (LOQ 20 pg/mL) ranged from 20-75 pg/mL and for betamethasone 17-propionate (LOQ 30 pg/mL) the serum concentrations ranged from 30-170 pg/mL. No pharmacokinetic parameters could be calculated due to the very high degree of variability within patients and also several patients had values below or close to the LOQ, such that full PK profiles could not be obtained.

Reviewer's Comments: The data obtained for B17P should be interpreted with caution and may not be reliable due to the highly variable long term stability data obtained for B17P.

Q. Were the active moieties in plasma appropriately identified and measured?

Yes, they were adequately identified and measured for calcipotriol, MC1080 (its metabolite), and betamethasone. However, the analytical method was not adequately validated for betamethasone 17-propionate (the metabolite of betamethasone) (see Section 2.6 for analytical methods and validation data).

2.3. Intrinsic Factors:

Pediatrics:

In this submission, the applicant included a partial waiver for pediatric studies in patients aged from 0 to 11 years old. A study comparing the effect on the HPA axis and calcium metabolism of once daily use of Daivobet gel in adolescent patients aged 12 to 17 years old is planned to be conducted and submitted after NDA approval. The protocol for this study was included in the Request for Deferral of Pediatric Studies section of the submission. However, the applicant stated that a protocol will be submitted _____

b(4)

2.4. Extrinsic Factors

Drug-Drug Interactions:

The applicant did not conduct any drug-drug interaction studies with co-administered drugs since the systemic exposure of calcipotriol and betamethasone dipropionate was found to be minimal.

2.5. General Biopharmaceutics

Q. What is the in vivo relationship between the to-be-marketed formulation (TBMF) and the pivotal clinical trial formulation(s)?

The pivotal clinical trial formulation was the same as the TBMF. Inserted below is a table showing the quantitative composition of the TBMF of Taclonex Scalp[®] gel.

Table 1 Composition of the Drug Product:

| Name of Components | Quantity per g | Function |
|--|------------------------|----------------|
| Drug Substance(s) | | |
| Calcipotriol (as Hydrate) | 50 mcg ¹⁾ | Drug Substance |
| Betamethasone Dipropionate | 0.643 mg ²⁾ | Drug substance |
| Excipients | | |
| Paraffin, Liquid ³⁾ | | |
| PPG-15 Stearyl Ether ⁴⁾ | | |
| Castor Oil, Hydrogenated ⁵⁾ | | |

b(4)

The batch size — of the Taclonex Scalp[®] gel used in the clinical pharmacology studies and the Phase III clinical studies was the same as the batch size of the to-be-marketed formulation.

b(4)

Q. What is the corticosteroid potency of Taclonex Scalp[®] gel?

The data obtained from study MBL 0403 FR, a vasoconstriction study, suggested that Taclonex Scalp[®] gel may be a less potent topical corticosteroid than Diprosone[®] ointment based on the comparison of their vasoconstrictive action. The objective of study MBL 0403 FR was to determine the corticosteroid potency of betamethasone dipropionate in Taclonex Scalp[®] gel. The comparator chosen was Diprosone[®] ointment, a formulation of betamethasone 0.5 mg/g (as dipropionate) marketed in the USA. The US approved product information for Diprosone[®] classifies the ointment in the high range of potency. This study MBL 0403 FR compared the vasoconstrictive effect of a single application of Taclonex Scalp[®] gel with a single application of betamethasone dipropionate Diprosone[®] ointment in healthy volunteers. The study was designed as a bioequivalence study conducted according to the vasoconstrictor assay described in the FDA guideline on *in vivo* bioequivalence of topical dermatologic corticosteroids.

The parameter used for the bioequivalence evaluation was the chromameter reading (a*). According to the results obtained with a* data and using the Locke method, the 90 % confidence interval for the skin blanching response ratio (Taclonex Scalp[®] gel to Diprosone[®] ointment) was (0.64; 0.95) which is outside the interval of 0.80 to 1.25 defined by the applicable FDA guideline. Therefore, Taclonex Scalp[®] gel was not bioequivalent to Diprosone[®] ointment. Since the data indicated that Daivobet[®] gel induced less skin blanching than Diprosone[®] ointment this suggests that Taclonex Scalp[®] gel may be considered a less potent corticosteroid than Diprosone[®] ointment when evaluated by this model.

Reviewer's Comments: Since this BE study was not designed to bracket (i.e. by inclusion of other corticosteroids with different potencies) the corticosteroid potency of betamethasone in Taclonex gel, this could not be definitively classified at this time.

his is acceptable at this time since the data from the BE study indicates that Taclonex Scalp[®] gel may be considered as a less potent corticosteroid than the highly potent Diprosone[®] Ointment that contains betamethasone alone, therefore safety may not be a concern.

b(4)

2.6. Analytical

Q. Were the analytical methods used adequately validated?

Yes, they were for calcipotriol and its' metabolite MC1080 and, betamethasone dipropionate. The method was not adequately validated for the metabolite of betamethasone dipropionate, betamethasone 17 dipropionate (B17P) due to inconclusive data following long term stability.

Table: Analytical Methods and Validation Data

| Method | LC/MS/MS | LC/MS/MS |
|----------------------|--|--|
| Compound | <i>Calcipotriol</i> | <i>Betamethasone Dipropionate</i> |
| Internal Standard | | |
| Matrix | Human Serum | Human Serum |
| Accuracy (% Bias) | | |
| <i>Within-Day</i> | 93-101 % | 99-117 % |
| <i>Between-Day</i> | 95 to 100 % | 97 to 111% |
| Precision (% CV) | | |
| <i>Within-Day</i> | 7 to 22 % | 8-9 % |
| <i>Between-Day</i> | 9 to 17 % | 7 to 13 % |
| Standard curve range | 50 to 250 pg/mL ($r \geq 0.99$) | 30 to 500 pg/mL ($r \geq 0.99$) |
| Sensitivity (LOQ) | 50 pg/mL (CV % = 12 %) | 30 pg/mL (CV % = 9 %) |
| Selectivity | No interfering peaks were observed i.e. the response of the blank serum samples were less than 5 times the average (of 3 runs) of the response of the standard at the LOQ. | |
| Recovery | 93 % to 113 % (Average = 102 %) | 95 5 to 112 % (Average = 104 %) |
| Stability | The serum samples are stable after 3 freeze-thaw cycles @ -80°C and also following storage at ~ -80°C for up to three months. | The serum samples are stable after 3 freeze-thaw cycles @ -80°C and also following storage at ~ -80°C for up to twenty three days. |
| Conclusions | Method validation is acceptable | Method validation is acceptable |

| Method | LC/MS/MS | LC/MS/MS |
|----------------------|------------------------------------|--------------------------------------|
| Compound | <i>MC1080</i> | <i>Betamethasone 17-Dipropionate</i> |
| Internal Standard | | |
| Matrix | Human Serum | Human Serum |
| Accuracy (% Bias) | | |
| <i>Within-Day</i> | 88 to 110 % | 99 to 112 % |
| <i>Between-Day</i> | 95 to 104 % | 99 |
| Precision (% CV) | | |
| <i>Within-Day</i> | 5-19 % | 6-9 % |
| <i>Between-Day</i> | 7 to 14 % | 7 to 13 % |
| Standard curve range | 20 to 500 pg/mL ($r \geq 0.997$) | 30 to 500 pg/mL ($r \geq 0.99$) |
| Sensitivity (LOQ) | 20 pg/mL (CV % = 9 %) | 30 pg/mL (CV % = 9%) |

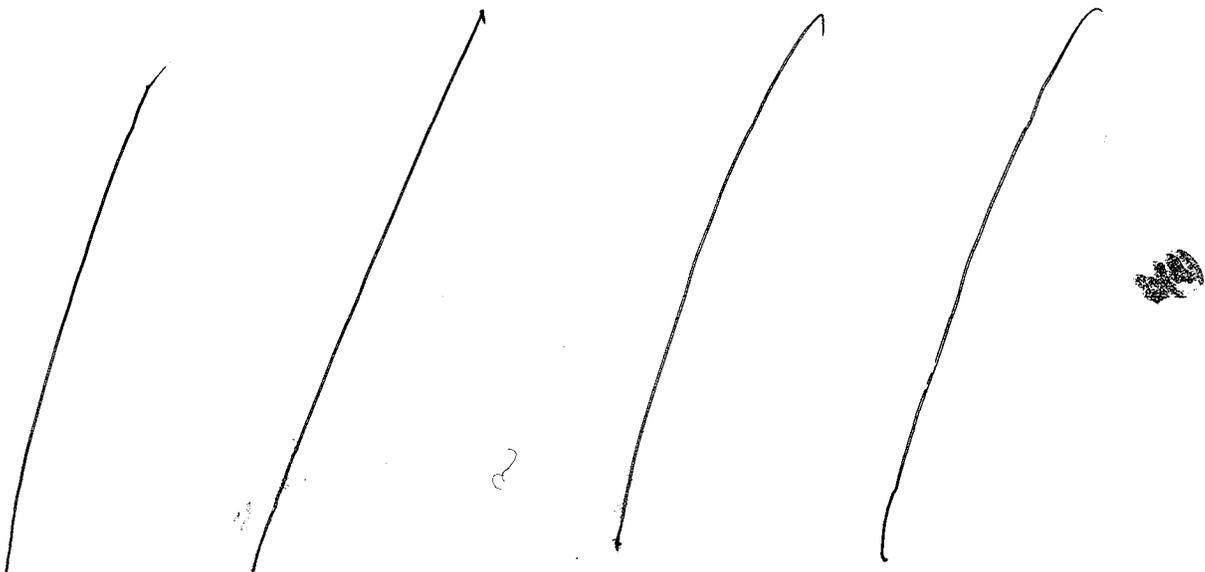
| | | |
|--------------------|--|---|
| Selectivity | No interfering peaks were observed i.e. the response of the blank serum samples were less than 5 times the average (of 3 runs) of the response of the standard LLOQ. | |
| Recovery | 86 to 101 % (Average = 94 %) | 73 to 80 % (Average = 77 %) |
| Stability | The serum samples are stable after 3 freeze-thaw cycles @ -80°C and also following storage at ~ -80°C for up to three months. | The serum samples are stable after 3 freeze-thaw cycles @ -80°C. Stability following storage at ~ -80°C for up to 23 days was inconclusive due to high variability in differences (ranging from -24 % to 208 %) observed between the concentration values obtained before (Day 0) storage and after storage of B17P for 5, 14 and 23 days i.e the long term stability data to cover the plasma sample storage period. |
| Conclusion | Method validation is acceptable | Method validation is not acceptable. |

3. **Labeling Recommendation** (*Please see labeling changes in product package insert in Section 4.2 below*). *This reviewer's changes are shown as deletions which are "strikethroughs" and additions are "underlined"*.

4. **Appendix**

4.1. **Consult Review:** None

4.2. **Proposed Package Insert**



b(4)

15 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Manufactured by:
LEO Pharmaceutical Products Ltd. A/S
Industriparken 55
DK-2750 Ballerup
Denmark

4.3. Individual Study Reviews

A. Human Pharmacodynamic Studies:

1. *Effects on the HPA Axis*

The HPA axis test was performed using synthetic adrenocorticotrophic hormone (ACTH) _____ in which the active compound is identical to the US product Cortrosyn[®] (This brand of ACTH was previously used in NDA 21-852 for Taclonex[®] ointment and found acceptable).

b(4)

Study #: MBL 0404 FR

Study Title: Effect of DAIVOBET/DOVOBET Gel on the HPA Axis and Calcium Metabolism in Patients with Extensive Scalp Psoriasis

b(4)

Investigators: Multicenter study conducted at 3 centers (Denmark: 1, France:1, and Germany:1),
International Co-ordinating Investigator: _____

Studied period:

First patient enrolled (inclusion): September 21st, 2005
Last patient discharged (completion): June 19th, 2006

Clinical Phase of Development: 1

Objectives: To evaluate the effect of once daily use of DAIVOBET/DOVOBET gel and ointment on the hypothalamic-pituitary-adrenal (HPA) axis and on calcium metabolism in patients with extensive scalp and body psoriasis

Study Design: This was a multi-center, prospective, non-controlled, 8-week study with one topical application daily, in patients with extensive scalp and body psoriasis. Sufficient patients were to be enrolled to ensure that 30 patients completed the study. Completers were patients who completed either 4 weeks (if the scalp psoriasis had cleared) or 8 weeks treatment and were evaluable for the primary endpoint (HPA axis assessment). Prior to initiation of study treatment and following 4 weeks and 8 weeks treatment adrenal function was assessed with a rapid standard dose (250 mcg) ACTH _____ challenge test. Calcium metabolism was evaluated by measuring serum calcium once weekly and 24 hour urinary calcium excretion on three occasions (prior to initiation of study treatment and following 4 and 8 weeks treatment). The week 8 assessments were performed in those patients who did not achieve clearance of their scalp psoriasis at week 4. The duration of

b(4)

the study for each patient was a maximum of 14 weeks, consisting of a two week initial phase followed by a treatment phase of up to 8 weeks and a possible 4-week follow-up phase. A completion visit was performed during the last day of assessment after 4 weeks (if the scalp psoriasis had cleared) or 8 weeks treatment. Patients were to attend the centre for at least 7 or 11 visits (depending on clearance of scalp psoriasis) consisting of 5 or 8 out-patient visits and 2 or 3 in-patient visits. Additional out-patient visits were to be performed at the investigator's discretion and/or depending on the safety and tolerability results.

All the planned visits were to be performed within ± 2 days of the scheduled visit days under the following conditions:

- The complete treatment duration was:
 - 28 days for patients whose scalp psoriatic lesions cleared during this period
 - 56 days for patients whose scalp psoriatic lesions did not clear after 28 days
- The first ACTH challenge test (Visit 2) was performed between Day -10 and Day -5
 - The in-patient visits (7 and 11) were carried out Days 27 to 29 and Days 55 to 57, respectively

Out-patient visits took place as follows:

- 1 (day -14); initiation visit
- 2 (between Day -10 and Day -5); ACTH challenge test
- 4, 5, 6, 8, 9 and 10 (Days 8 ± 2 , 15 ± 2 , 22 ± 2 , 36 ± 2 , 43 ± 2 , 50 ± 2); during treatment
- FU1 (+14 days); safety follow-up visit (if necessary)
- FU2 (+28 days); ACTH challenge follow-up (if necessary)

In-patient visits took place as follows:

- 3 (Days -2 to 1), 7 (Days 27 to 29) and 11 (Days 55 to 57); individual patient calcium diet; 24 hour urine collection on Days -1 to 1, 28 to 29 and 56 to 57 and ACTH challenge test on Days 29 and 57.

Patient Population: A sufficient number of patients were to be enrolled so that at least 30 patients (aged 18 to 60 years) completed the study. Inclusion criteria were as follows:

- Patients with psoriasis on scalp and trunk/limbs with a total extent of 15-30% of BSA, with extent on the scalp of $\geq 30\%$ of the scalp
- Psoriasis vulgaris (scalp, trunk and limbs) amenable to topical treatment with a maximum of 110 g of study medication (total amount of gel and ointment) per week
- Disease severity on the scalp as well as on trunk/limbs graded as moderate, severe or very severe according to the investigator's global assessment of disease severity
- Patients with normal HPA axis function defined by:
 - baseline serum cortisol concentration above 5 mcg/dL
 - serum cortisol above 18 mcg/dL 30 minutes after ACTH stimulation **(4)**

Test product: Daivobet/Dovobet gel- calcipotriol (as hydrate) 50 mcg/g and betamethasone dipropionate 0.5 mg/g (as dipropionate) manufactured by LEO Pharma.

Lot numbers / Expiry dates/Relevant Centre: 042196101 / 08/2006 (DE117 and DK177), 04224101/ 08/2006 (FR187)

Test product: Daivobet/Dovobet ointment- calcipotriol (as hydrate) 50 mcg/g and betamethasone dipropionate 0.5 mg/g (as dipropionate) manufactured by LEO Pharma.

Lot numbers / Expiry dates/Relevant Centre: 0520761 / 04/2007 (DE117), Z2038/ 11/2006 (FR187) and Z5544/03/2007 (DK177)

Reviewer's Comments: Batch numbers are the same as those of the product used in the Phase 3 trials.

Administration of Investigational Product: Topical, non occlusive, once daily application to affected lesions on the scalp (gel) and body (ointment). Weekly maximum dose was 110 g in total per week (1 bottle of 50 g gel and 1 tube of 60 g ointment).

Time of day for dosing: **8 p.m.**

Relation of time of dosing to dietary intake: No specific requirements.

Patients who experienced complete recovery of their psoriatic lesions during the first 4 weeks of treatment were asked to complete the entire 4-week treatment period and were instructed to apply gel and ointment daily to the sites of the initial lesions. Patients whose scalp psoriasis lesions did not clear during the first 4-week treatment period were to be treated for a further 4- week period. If the scalp psoriasis cleared during this second treatment period, the patients were instructed to apply gel to the sites of the initial lesions. Treatment with DAIVOBET/DOVOBET ointment during the second 4-week period was applied as required.

Reviewer's Comments: Since the ointment was applied as required (instead of daily) during weeks 5-8, treatment during this period may not be truly representative of maximal use conditions.

Adrenal Function, Calcium Metabolism and Pharmacokinetic Assessment:

Adrenal Function:

Adrenal function was assessed from serum cortisol using a standard-dose ACTH challenge test at visits 2 (Study Day -10 to -5), 7 (Day 29) and 11 (Day 57). The ACTH challenge test consisted of blood sampling at 8 a.m. (\pm 30 minutes) (T=0) for assessment of baseline serum cortisol concentration (reference ranges between 5.0 to 22.4 mcg/dL). An intravenous bolus injection of 250 mcg _____ was given and blood samples were taken at 30 and 60 minutes for assessment of the _____ stimulated serum cortisol concentration. The time of specimen collection was recorded on the CRF. Patients were to be tested at the same time throughout the study (including 30 minutes range) and any deviation was to be reported and explained in the CRF. If laboratory results suggested suppression according to the definitions in inclusion criterion 5 [patients with normal HPA axis function defined by (a) baseline serum cortisol concentration above 5 mcg/dL and (b) serum cortisol above 18 mcg/dL, 30 minutes after ACTH _____ stimulation, the following procedure was adopted:

- at Visit 2; the patients were to be withdrawn from the study and asked to see their general practitioner for further examination
- at Visit 7; a follow-up ACTH challenge test was to be performed 4 weeks later (i.e. at FU2)
- at Visit 11; a follow-up ACTH challenge test was to be performed 4 weeks later (i.e. at FU2)

Calcium Metabolism:

Serum calcium was assessed at all visits except Visit 2. The 24 hour urine calcium excretion was assessed during the in-patient visits at Visit 3 (Day -1), Visit 7 (Day 28) and Visit 11 (Day 56). During these in-patient visits the patients received an individualized calcium diet based on their average calcium intake as assessed in the interview with a dietician at Visit 2.

Primary Response Criterion

The primary endpoint was the adrenal response to ACTH stimulation test defined as the serum cortisol concentration obtained after 30 minutes at baseline, week 4 and week 8. Values above 18 mcg/dL were considered to be a normal response.

Secondary Response Criteria

The secondary endpoints were as follows:

- Adrenal response to ACTH stimulation test defined as the serum cortisol concentration obtained after 60 minutes at baseline, week 4 and week 8
- Adrenal response to ACTH stimulation test defined as rise in serum cortisol from time zero to 30 and 60 minutes after injection at baseline, week 4 and week 8
- Change in 24 hour urinary calcium excretion from baseline to week 4 and week 8
- Change in serum calcium from baseline to week 4 and week 8

Reviewer's Comments:

Please note that the Agency criteria of a serum cortisol concentration, obtained at 30 minutes after injection, > 18 mcg/dL was used to indicate a normal HPA axis function in this review.

b(4)

/ / / / /

Pharmacokinetic Assessment:

One pre-treatment sample was obtained per subject on Day 0 prior to dosing (Visit 3). On Day 27 (Visit 7) samples were obtained pre-dosing (0) and 1, 2, 3, 5, and 7 hours post dosing. The patients with cleared scalp psoriatic lesions on Day 29 left the study. For the remaining patients the dosing was continued and on Day 55 (Visit 11) samples were obtained pre-dosing (0) and 1, 2, 3, 5, and 7 hours post dosing. The time of initiation and completion of the application was noted and venous puncture was to be made through untreated areas of the skin.

The serum samples were sent to LEO Pharma on several occasions. All samples were received in frozen conditions in the period from 2005-10-07 to 2006-06-28 (including the 2nd aliquot of the samples). Immediately after receipt, the samples were placed in a -80°C freezer until analysis. A validated bioanalytical assay for quantification of calcipotriol, betamethasone dipropionate, MC1080 and betamethasone 17-propionate was used and, if scientifically valid, the following pharmacokinetic parameters were to be determined for each assayed compound: AUC_{0→t}, AUC_{0→∞}, C_{max}, t_{max} and t_{1/2}.

Statistical Methods:

Primary endpoint

**APPEARS THIS WAY
ON ORIGINAL**

The adrenal response to the ACTH stimulation test after 30 minutes recorded at Visit 2 (baseline), Visit 7 (week 4) and Visit 11 (week 8) was listed for each patient and values ≤ 18 mcg/dL were flagged. The frequency of patients with values ≤ 18 mcg/dL was calculated.

Secondary endpoint

The adrenal response to the ACTH stimulation test after 60 minutes recorded at baseline, week 4 and week 8 was listed for each patient and values of 18 mcg/dL and lower were flagged. The frequency of patients with values ≤ 18 mcg/dL was calculated.

The rise from time zero to 30 and 60 minutes was calculated for the evaluations performed at Visit 2 (baseline), Visit 7 (week 4) and Visit 11 (week 8), and listed individually. Descriptive statistics were presented by visit for the calculated values and for the change from baseline. Additionally, the frequency of patients with change from baseline values ≤ 7 mcg/dL and >7 mcg/dL was presented by visit.

Descriptive statistics for each visit were presented for 24 hour urinary calcium excretion. The mean change in 24 hour urinary calcium excretion from Visit 3 (baseline) to Visit 7 (week 4) and Visit 11 (week 8) was estimated and 95% confidence intervals (CI) were calculated.

Descriptive statistics for each visit were presented for serum calcium measurements. The mean change from Visit 3 (baseline) to Visit 7 (week 4) and Visit 11 (week 8) was estimated together with its 95% CI.

The estimated pharmacokinetic parameters AUC_{0-t}, AUC_{0-∞}, C_{max}, t_{max} and t_{1/2} were to be listed and summary statistics (mean, median, SD, minimum and maximum) given for each compound if scientifically valid.

Results:

Disposition of Study Subjects:

A total of 58 patients were enrolled (defined as signed informed consent and a CRF book started) at three centers in three countries (Denmark: 1, France: 1, Germany: 1) 20 patients withdrew after Visit 1 and a further two patients withdrew after Visit 2 and did not attend subsequent visits. At Visit 3 one patient did not meet the inclusion criteria for the ACTH challenge test and was withdrawn before being assigned to treatment. Therefore as shown in the Table below, a total of 35 patients were found to be eligible for the study and were assigned treatment.

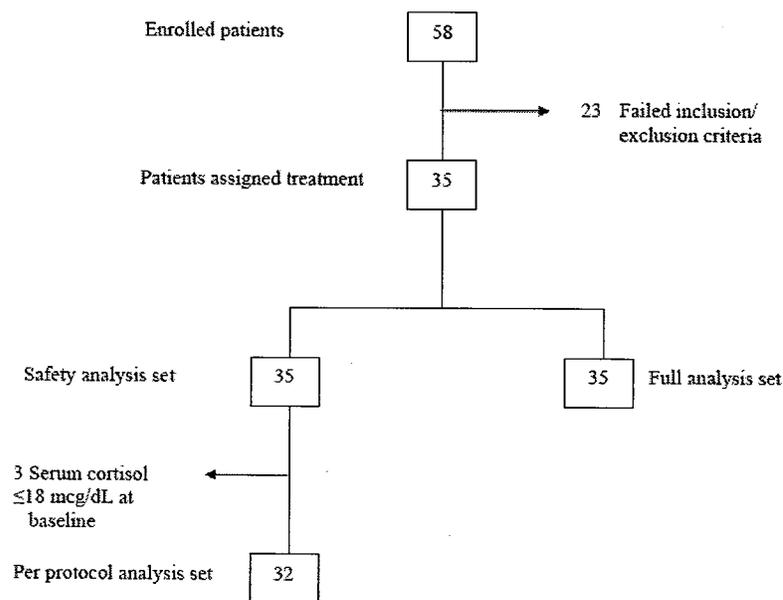
Enrolled patients and patients assigned treatment by center

| Centre | Total number of patients enrolled | Total number of patients assigned treatment |
|--------|-----------------------------------|---|
| DE117 | 31 | 13 |
| DK177 | 21 | 17 |
| FR187 | 6 | 5 |

| | | |
|-------|----|----|
| Total | 58 | 35 |
|-------|----|----|

Of the 35 patients who were assigned treatment one patient (CRF=0029) withdrew from the study at Visit 5 (week 6) due to an exclusion criterion (serum cortisol not >18 mcg/dL 30 minutes after ACTH stimulation at Visit 3) and for one patient (CRF=0021) the investigator gave the reason for leaving the study at Visit 11 (week 8) as “other” stating that the patient did not complete the study according to the protocol as many assessments were missed.

Schematic presentation of analysis sets:



Data Sets Analyzed:

As shown above, the per protocol analysis set was defined as all included patients who received study treatment, who satisfied the entry criteria and completed the entire study without serious protocol violations. As the primary objective of the study is safety, the per protocol analysis set was based on the safety analysis set. The following were identified as serious protocol violations and resulted in the exclusion of patients from the safety analysis set to form the per protocol analysis set:

- The patient did not provide any data related to the HPA axis tests following the start of treatment
- The patient did not have a baseline (Visit 2) serum cortisol concentration >18 mcg/dL 30 minutes after ACTH stimulation (Visit 3 inclusion criterion 1.5b see section 11.4.1)
- All patients provided data related to HPA axis function testing following start of treatment. Three patients (CRF=0023, 0024 and 0029) had serum cortisol concentrations ≤18 mcg/dL 30 minutes after pre-treatment ACTH stimulation at Visit 2 and were excluded from the per protocol analysis set. Therefore, the per protocol analysis set consists of 32 patients.

Reviewer's Comments: The applicant also had a full analysis set and a safety analysis set which were identical i.e. they both consisted of all 35 subjects.

Demographic and Other Baseline Characteristics:

Safety Analysis Data Set

The mean age of patients in the safety analysis set (N=35) was 41.3 (range 21 to 60) years and 26 patients (74.3 %) were male and 9 patients (25.7 %) were female. Two patients did not provide data on race and all patients who did were Caucasian. The mean weight of patients was 82.4 kg (range 55.5 to 119.0 kg), mean height was 174.3 cm (range 160 to 196 cm) and the mean BMI was 27.0 kg/m² (range 19.3 to 33.8 kg/m²). The mean duration of scalp psoriasis was 17.3 years (range 0 to 37 years).

Per Protocol Analysis Set:

The mean age of patients in the per protocol analysis set (N = 32) was 40.3 (range 21 to 60) years and 24 patients (75.0 %) were male and 9 patients (25 %) were female. Two patients did not provide data on race and all patients who did were Caucasian. The mean weight of patients was 81.5 kg (range 55.5 to 119.0 kg), mean height was 174.6 cm (range 160 to 196 cm) and the mean BMI was 26.6 kg/m² (range 19.3 to 33.6 kg/m²). The mean duration of scalp psoriasis in the safety analysis set was 18.4 years (range 2 to 37 years).

Baseline Disease Severity on the Scalp and Body for Safety Analysis Set and Per Protocol Set:

Investigator's global assessment of disease severity on the scalp: safety and per protocol analysis sets¹

| Investigator's global assessment | All enrolled patients (n=58) | | Safety (n=35) | | Per Protocol (n=32) | |
|-------------------------------------|------------------------------------|--------------|-----------------------|--------------|------------------------|--------------|
| | Number of patients | % | Number of patients | % | Number of patients | % |
| Clear | 1 | 1.7 | 0 | 0.0 | 0 | 0.0 |
| Minimal | 4 | 6.9 | 0 | 0.0 | 0 | 0.0 |
| Mild | 5 | 8.6 | 0 | 0.0 | 0 | 0.0 |
| Moderate | 19 | 32.8 | 15 | 42.9 | 13 | 40.6 |
| Severe | 25 | 43.1 | 17 | 48.6 | 17 | 53.1 |
| Very Severe | 4 | 6.9 | 3 | 8.6 | 2 | 6.3 |
| Total | 58 | 100.0 | 35 | 100.0 | 32 | 100.0 |

1) Visit 1 assessment was used for the 23 patients who failed screening, otherwise the visit 3 assessment was used for patients assigned treatment.

Investigator's global assessment of disease severity on the body (trunk/limbs): safety and per protocol analysis sets¹

| Investigator's global assessment | All enrolled patients (n=58) | | Safety (n=35) | | Per Protocol (n=32) | |
|-------------------------------------|------------------------------------|-------|--------------------------|-------|------------------------|-------|
| | Number of patients | % | Number of patients | % | Number of patients | % |
| Clear | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Minimal | 3 | 5.2 | 0 | 0.0 | 0 | 0.0 |
| Mild | 10 | 17.2 | 0 | 0.0 | 0 | 0.0 |
| Moderate | 20 | 34.5 | 14 | 40.0 | 12 | 37.5 |
| Severe | 24 | 41.4 | 21 | 60.0 | 20 | 62.5 |
| Very Severe | 1 | 1.7 | 0 | 0.0 | 0 | 0.0 |
| Total | 58 | 100.0 | 35 | 100.0 | 32 | 100.0 |

1) Visit 1 assessment was used for the 23 patients who failed screening, otherwise the visit 3 assessment was used for patients' assigned treatment.

Reviewer's Comments: To ensure that each patient would require extensive doses of gel and ointment, the total extent of psoriasis on scalp and trunk/limbs had to be 15-30% of body surface area and >30% of the scalp. Disease severity on scalp and body (trunk/limbs) was to be at least moderate according to the Investigator's Global Assessment of disease severity.

At baseline, the majority of patients in the safety analysis set had either moderate or severe disease on the scalp (91.4%) and all patients had either moderate or severe disease on the body. Some patients in the safety analysis set had very severe disease on the scalp but no patients had very severe disease on the body.

The mean total amount used during the study on the scalp alone was 125.3g (range 18.0 to 308.1g) and on the body and scalp together was 331.0g (range 106.1 to 711.3). On the body and the scalp together the mean amount of medication used per week was 62.5g (range 29.7g to 105.8g). On the scalp the mean amount used per week was 23.7g (range 4.7g to 49.7g) and the mean amount used on the body per week was 40.2g (range 17.7g to 61.0g).

Average weekly amount of Daivobet® gel and Daivobet® ointment used on the scalp and body (trunk/limbs) in study MBL 0404 FR (combined treatment with Daivobet® gel and Daivobet® ointment): safety analysis set.

| Average amount of gel and ointment per week1 (grams) | Daivobet® gel plus Daivobet® ointment (n=35) |
|--|--|
| Mean | 62.5 |
| SD | 20.6 |
| Median | 63.5 |
| Minimum | 29.7 |

| | |
|---------------------|-------|
| Maximum | 105.8 |
| Number ² | 29 |

1) Calculated by subtracting the weight of the used bottles and tubes from the mean normal weight of full bottles and tubes, dividing by the number of days exposed to treatment and multiplying by 7. Negative weights have been set to zero.

2) Only patients who returned all dispensed bottles and tubes provide data.

Effect on Adrenal Function

Primary Response Criterion:

Patients with serum cortisol ≤ 18 mcg/dL 30 minutes after the ACTH challenge test at weeks 4 and 8: per protocol analysis set

| Visit Serum cortisol after 30 minutes | DAIVOBET gel plus DAIVOBET ointment (n=32) | |
|---|---|-------|
| | Number of Patients | % |
| Visit 7 (week 4) | | |
| >18 mcg/dL | 27 | 84.4 |
| ≤ 18 mcg/dL | 5 | 15.6 |
| Total | 32 | 100.0 |
| Visit 11 (week 8) | | |
| >18 mcg/dL | 9 | 81.8 |
| ≤ 18 mcg/dL | 2 | 18.2 |
| Total | 11 | 100.0 |

At week 4 (Visit 7), five (15.6%) patients (CRF= 0001, 0025, 0035, 0056 and 0058) had a serum cortisol ≤ 18 mcg/dL. Of the 11 patients who continued to week 8 (Visit 11), two (18.2%) patients (CRF=0001 and 0003) had serum cortisol ≤ 18 mcg/dL.

None of the patients with serum cortisol ≤ 18 mcg/dL 30 minutes after the ACTH stimulation test had serum cortisol ≤ 18 mcg/dL at 60 minutes at either week 4 or week 8. Furthermore their pre-test (time zero) serum cortisol values were above the lower limit of the reference range (5 mcg/dL) at both weeks 4 and 8.

| Patient | Visit | Before | 30 minutes | | 60 minutes | |
|---------|----------|--------|------------|---------|------------|---------|
| | | | Obs1 | Change2 | Obs1 | Change2 |
| 0001 | Baseline | 15.32 | 22.09 | 6.77* | 22.02 | 6.70* |
| | Week 4 | 11.41 | 17.71* | 6.30* | 22.20 | 10.79 |
| | Week 8 | 10.54 | 16.77* | 6.23* | 22.42 | 11.88 |
| 0003 | Baseline | 10.68 | 18.91 | 8.22 | 22.64 | 11.95 |
| | Week 4 | 11.34 | 18.65 | 7.32 | 22.38 | 11.05 |
| | Week 8 | 11.55 | 17.57* | 6.01* | 18.25 | 6.70* |

| | | | | | | |
|-------|-----------|-------|--------|-------|-------|-------|
| 00253 | Baseline | 9.53 | 18.83 | 9.31 | 19.56 | 10.03 |
| | Week 4 | 14.31 | 17.71* | 3.40* | 20.32 | 6.01* |
| | Follow-up | 3.19 | 16.30* | 13.11 | 21.04 | 17.86 |
| 0035 | Baseline | 8.55 | 19.20 | 10.65 | 22.02 | 13.47 |
| | Week 4 | 13.76 | 17.31* | 3.55* | 21.08 | 7.32 |
| | Follow-up | 10.65 | 24.37 | 13.73 | 25.24 | 14.60 |
| 0056 | Baseline | 10.32 | 24.01 | 13.69 | 27.53 | 17.20 |
| | Week 4 | 8.40 | 17.09* | 8.69 | 20.64 | 12.24 |
| | Follow-up | 10.97 | 18.07 | 7.10 | 20.39 | 9.42 |
| 0058 | Baseline | 9.45 | 18.83 | 9.38 | 21.73 | 12.28 |
| | Week 4 | 8.69 | 17.20* | 8.51 | 20.17 | 11.48 |
| | Follow-up | 13.58 | 20.50 | 6.92* | 24.88 | 11.30 |

1) Obs = observed value.
2) Changes are from before the ACTH injection (time 0) to 30 or 60 minutes as appropriate.
3) Follow up ACTH challenge test occurred 83 days after the Week 4 test, not at 28 days as stated in the protocol.
* Serum cortisol value ≤ 18 mcg/dL or a change of ≤ 7 mcg/dL in serum cortisol value from baseline.

Secondary Response Criterion:

Adrenal response to ACTH stimulation test after 60 minutes: At weeks 4 and 8 (Visits 7 and 11) all patients had a serum cortisol level >18 mcg/dL after 60 minutes.

Serum cortisol concentration after 60 minutes by visit

| Visit Serum cortisol (mcg/dL) | DAIVOBET gel plus DAIVOBET ointment (n=32) |
|-------------------------------------|--|
| Visit 2 (baseline) | |
| Mean | 26.4 |
| SD | 5.9 |
| Median | 25.4 |
| Minimum | 19.6 |
| Maximum | 54.0 |
| Number | 32 |
| Visit 7 (week 4) | |
| Mean | 25.4 |
| SD | 5.2 |
| Median | 24.1 |
| Minimum | 20.2 |
| Maximum | 46.0 |
| Number | 32 |
| Visit 11 (week 8) | |

| | |
|---------|------|
| Mean | 25.3 |
| SD | 4.2 |
| Median | 26.3 |
| Minimum | 18.3 |
| Maximum | 31.0 |
| Number | 11 |

Rise in serum cortisol from time zero to 30 and 60 minutes after injection: At each visit the number of patients with an increase in serum cortisol from time zero to 60 minutes of ≤ 7 mcg/dL was lower than from time zero to 30 minutes. The mean changes were also greater at 60 minutes than at 30 minutes at every visit.

Patients with an increase in serum cortisol from time zero to 30 minutes of ≤ 7 mcg/dL by visit: per protocol analysis set

| Visit Change from baseline to 30 minutes | DAIVOBET gel plus DAIVOBET ointment (n=32) | |
|--|--|-------|
| | Number of Patients | % |
| Visit 2 (baseline) | | |
| >7 mcg/dL | 24 | 75.0 |
| ≤ 7 mcg/dL | 8 | 25.0 |
| Total | 32 | 100.0 |
| Visit 7 (week 4) | | |
| >7 mcg/dL | 17 | 53.1 |
| ≤ 7 mcg/dL | 15 | 46.9 |
| Total | 32 | 100.0 |
| Visit 11 (week 8) | | |
| >7 mcg/dL | 8 | 72.7 |
| ≤ 7 mcg/dL | 3 | 27.3 |
| Total | 11 | 100.0 |

Change in serum cortisol from time zero to 30 minutes by visit: per protocol analysis set

| Visit Change in serum cortisol (mcg/dL) | DAIVOBET gel plus DAIVOBET ointment (n=32) |
|---|--|
| Visit 2 (baseline) | |

| | |
|-------------------|------|
| Mean | 10.8 |
| SD | 4.6 |
| Median | 10.1 |
| Minimum | 4.8 |
| Maximum | 26.9 |
| Number | 32 |
| Visit 7 (week 4) | |
| Mean | 8.1 |
| SD | 4.0 |
| Median | 7.5 |
| Minimum | 0.1 |
| Maximum | 19.4 |
| Number | 32 |
| Visit 11 (week 8) | |
| Mean | 11.6 |
| SD | 4.8 |
| Median | 10.2 |
| Minimum | 6.0 |
| Maximum | 18.5 |
| Number | 11 |

Patients with an increase in serum cortisol from time zero to 60 minutes of ≤ 7 mcg/dL by visit: per protocol analysis set

| Visit Change from baseline to 60 minutes | DAIVOBET gel plus DAIVOBET ointment (n=32) | |
|--|---|-------|
| | Number of Patients | % |
| Visit 2 (baseline) | | |
| >7 mcg/dL | 29 | 90.6 |
| ≤ 7 mcg/dL | 3 | 9.4 |
| Total | 32 | 100.0 |
| Visit 7 (week 4) | | |
| >7 mcg/dL | 26 | 81.3 |
| ≤ 7 mcg/dL | 6 | 18.8 |
| Total | 32 | 100.0 |
| Visit 11 (week 8) | | |
| >7 mcg/dL | 10 | 90.9 |
| ≤ 7 mcg/dL | 1 | 9.1 |
| Total | 11 | 100.0 |

Change in serum cortisol from time zero to 60 minutes by visit: per protocol analysis set

| Visit Change in serum cortisol (mcg/dL) | DAIVOBET gel plus DAIVOBET ointment (n=32) |
|--|---|
| Visit 2 (baseline) | |
| Mean | 13.6 |
| SD | 5.4 |
| Median | 12.4 |
| Minimum | 6.0 |
| Maximum | 30.8 |
| Number | 32 |
| Visit 7 (week 4) | |
| Mean | 10.9 |
| SD | 4.7 |
| Median | 10.6 |
| Minimum | 2.9 |
| Maximum | 24.9 |
| Number | 32 |
| Visit 11 (week 8) | |
| Mean | 14.6 |
| SD | 5.5 |
| Median | 13.6 |
| Minimum | 6.7 |
| Maximum | 24.0 |
| Number | 11 |

The applicant stated that in order to obtain unbiased expert opinion on the clinical significance of these findings, two independent expert endocrinologists (Prof. _____ and (Prof. _____) were asked to review the data from the study. Their statements are provided in this submission (currently being reviewed by the medical reviewer). In summary, both experts considered it unlikely that the changes in response to ACTH stimulation represented clinically relevant suppression due to the observed changes being small (close to 18 mcg/dL) and that both pre-stimulation and 60-minutes values were adequate. It was also noted that the differences in the pre-treatment results were small. When patients with suboptimal responsiveness were compared with other patients in the study, the suboptimal responsiveness could already be observed before treatment. This would indicate that the possible weak effect on the HPA axis was present prior to the study, probably due to previous corticosteroid treatment. The applicant stated that this hypothesis could be further supported by the lack of dose response to study treatment found in the study.

b(4)

Effect on Calcium Metabolism:

Change in serum calcium from baseline to weeks 4 and 8: Mean serum calcium was similar at all visits. All serum calcium values were within the reference range (2.25 to 2.67 mmol/L) and hence there were no patients with abnormal serum calcium at any visit.

Change in 24 hour urinary excretion from baseline to weeks 4 and 8: The mean 24 hour urinary calcium excretion was similar at baseline (Visit 3) and weeks 4 and 8 (Visits 7 and 11). The reference range was 2.50 to 6.25 mmol/24h for females and it was 2.50 to 7.50 mmol/24 h for males. The mean change in 24 hour urinary calcium from baseline to week 4 was -0.89 mmol/24h (95% CI -1.44 to -0.35) and to week 8 was 0.33 mmol/24h (95% CI -0.92 to 1.58).

There were two patients with a possibly clinically relevant change in 24 hour urinary calcium excretion:

- Case Report Form (CRF)=0037 (female) had a high 24 hour urine calcium excretion of 13.74 mmol (reference range 2.50 to 6.25 mmol/24h) at baseline but this increased further to 16.80 mmol at week 4. Serum calcium values were within the reference range (2.25 to 2.67 mmol/L) throughout study. There was an increase from 2.45 mmol/L at baseline to 2.62 mmol/L at week 2, but at week 4 the value was similar to the baseline level (2.38 mmol/L). This patient used an average weekly amount of 48.0 g gel and 57.8 g ointment (average total weekly amount of medication 105.8 g) between baseline and week 4. The patient left the study at week 4 as scalp psoriasis had cleared.
- CRF=0044 (male) 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, but at week 8 it increased to 10.37 mmol. Serum calcium values were within the reference range (2.25 to 2.67 mmol/L) throughout study and there was no trend of increasing values (2.45 mmol/L at baseline, 2.33 mmol/L at weeks 4 and 8). This patient used an average weekly amount of 10.4 g gel 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 gel and 50.0 g ointment (average total weekly amount of medication 72.9 g) between week 5 and week 8.

Applicant's adrenal function and calcium metabolism conclusions:

Prior to treatment, 3 of 35 (8.6%) patients had serum cortisol ≤ 18 mcg/dL at 30 minutes. These patients were excluded from the per protocol analysis set. For the primary response criterion, 5 of 32 (15.6%) patients in the per protocol analysis set had serum cortisol ≤ 18 mcg/dL at 30 minutes at week 4. All five of these patients had serum cortisol >17 mcg/dL at 30 minutes. Two of the 11 (18.2%) patients who continued to week 8 had serum cortisol ≤ 18 mcg/dL at 30 minutes. All patients had serum cortisol >18 mcg/dL at 60 minutes at weeks 4 and 8. Furthermore the pre-test (time zero) serum cortisol values of all patients who recorded a serum cortisol ≤ 18 mcg/dL at 30 minutes were above the lower limit of the reference range (5 mcg/dL) at both weeks 4 and 8 indicating that any possible HPA axis suppression detected by the ACTH challenge test did not lead to low endogenous serum cortisol levels.

All serum calcium values were within the reference range at all visits. The mean 24 hour urinary calcium excretion was similar at baseline (Visit 3) and weeks 4 and 8. Two patients were identified

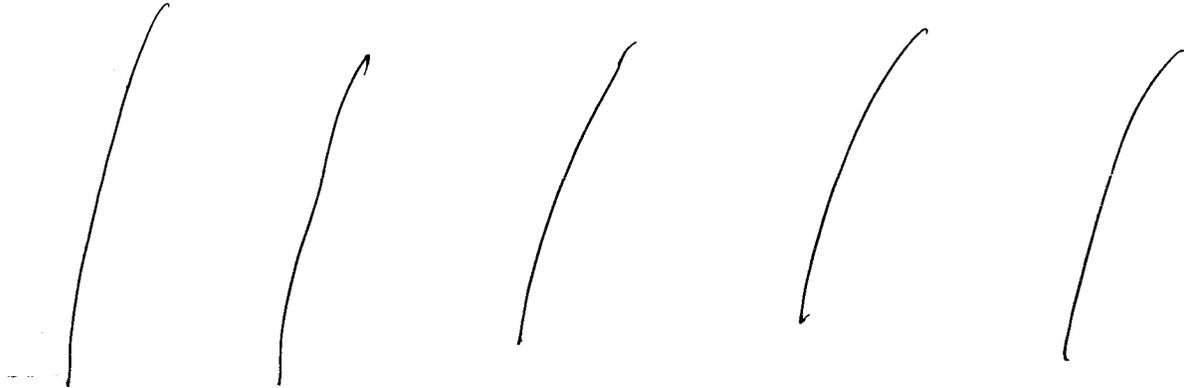
with a possibly clinically relevant increase in 24 hour urinary calcium excretion. Regarding the effect on calcium metabolism overall there were no changes of clinical concern.

Reviewer's Comments: Individual data indicated that there was the potential for 2 patients to develop hypercalcemia.

Pharmacokinetic Evaluation:

Analytical Method:

b(4)



Analytical Method Validation:

Calcipotriol:

Lower limit of quantification: 50 pg/mL

Upper limit of quantification: 250 pg/mL

Calcipotriol Precision and Accuracy

| Conc. levels calcipotriol (pg/mL) | Repeatability ¹ , r (%) | Reproducibility ² , R (%) | Intra-batch accuracy (index) | Inter-batch accuracy (index) |
|---|---------------------------------------|---|------------------------------------|------------------------------------|
| 50 | 12 | 17 | 101 | 97 |
| 70 | 22 | 17 | 91 | 95 |
| 150 | 11 | 11 | 93 | 100 |
| 250 | 7 | 9 | 99 | 97 |

¹Repeatability = within-run precision; ²Reproducibility = between-run precision

Calcipotriol Recovery

| Conc. levels, calcipotriol (pg/mL) | Recovery, calcipotriol (%) |
|--|----------------------------------|
| 50 | 113 |
| 150 | 93 |
| 250 | 101 |

Recovery for the internal standard ————— 93%.

b(4)

MC1080:

Lower limit of quantification: 20 pg/mL

Upper limit of quantification: 500 pg/mL

MC1080 Precision and Accuracy

| Conc. levels MC1080 (pg/mL) | Repeatability, r ¹ (%) | Reproducibility ² , R (%) | Intra-batch accuracy (index) | Inter-batch accuracy (index) |
|-----------------------------------|--------------------------------------|---|------------------------------------|------------------------------------|
| 20 | 9 | 14 | 102 | 97 |
| 30 | 19 | 13 | 88 | 95 |
| 150 | 7 | 6 | 99 | 101 |
| 500 | 5 | 7 | 110 | 104 |

¹Repeatability = within-run precision; ²Reproducibility = between-run precision

MC1080 Recovery

| Conc. levels, MC1080 (pg/mL) | Recovery, MC1080 (%) |
|------------------------------------|----------------------------|
| 20 | 94 |
| 150 | 86 |
| 500 | 101 |

Betamethasone dipropionate:

Lower limit of quantification: 30 pg/mL

Upper limit of quantification: 500 pg/mL

Betamethasone dipropionate Precision and Accuracy

| Conc. levels betamethasone dipropionate (pg/mL) | Repeatability, r (%) | Reproducibility, R (%) | Intra-batch accuracy (index) | Inter-batch accuracy (index) |
|--|-------------------------|---------------------------|------------------------------------|------------------------------------|
| 30 | 9 | 13 | 114 | 106 |
| 50 | 9 | 13 | 117 | 111 |
| 150 | 8 | 7 | 110 | 104 |
| 500 | 8 | 8 | 99 | 97 |

¹Repeatability = within-run precision; ²Reproducibility = between-run precision

Betamethasone dipropionate:Recovery

| Conc. levels betamethasone | Recovery, betamethasone dipropionate |
|-------------------------------|---|
|-------------------------------|---|

| dipropionate (pg/mL) | (%) |
|-------------------------|-----|
| 30 | 95 |
| 150 | 112 |
| 500 | 104 |

b(4)

Recovery for the internal standard: 88%.

Betamethasone 17-propionate:

Lower limit of quantification: 30 pg/mL

Upper limit of quantification: 500 pg/mL

Betamethasone 17-propionate Precision and Accuracy

| Conc. levels betamethasone 17-propionate (pg/mL) | Repeatability ¹ , r (%) | Reproducibility ² , R (%) | Intra-batch accuracy (index) | Inter-batch accuracy (index) |
|---|---------------------------------------|---|------------------------------------|------------------------------------|
| 30 | 9 | 13 | 99 | 99 |
| 40 | 6 | 11 | 103 | 100 |
| 150 | 6 | 7 | 106 | 103 |
| 500 | 6 | 11 | 112 | 100 |

¹Repeatability = within-run precision; ²Reproducibility = between-run precision

Betamethasone 17-propionate Recovery

| Conc. levels, betamethasone 17- propionate (pg/mL) | Recovery, betamethasone 17- propionate (%) |
|---|---|
| 30 | 80 |
| 150 | 73 |
| 500 | 79 |

Stability

Applicant's stability data after three thaw/freez cycles:

Run 3 Calcipotriol

| Thaw Cycles | Level (90 pg/mL) | | Level (250 pg/mL) | |
|--------------|------------------|----|-------------------|-----|
| 1 | 58 | 64 | 245 | 186 |
| | 65 | 45 | 234 | 237 |
| 3 | 63 | 59 | 240 | 229 |
| | 66 | 55 | 255 | 242 |
| Difference % | 5 | | 7 | |

Run 3 MC1080

| Thaw Cycles | Level (60 pg/mL) | | Level (500 pg/mL) | |
|--------------|------------------|----|-------------------|-----|
| 1 | 90 | 83 | 687 | 625 |
| | 85 | 75 | 604 | 600 |
| 3 | 93 | 80 | 645 | 613 |
| | 87 | 70 | 617 | 599 |
| Difference % | -1 | | -2 | |

Run 20050929 BDP

| Thaw Cycles | Level (50 pg/mL) | | Level (500 pg/mL) | |
|--------------|------------------|----|-------------------|-----|
| 1 | 79 | 75 | 549 | 445 |
| | 69 | 64 | 534 | 484 |
| 3 | 55 | 61 | 213** | 492 |
| | 67 | 76 | 518 | 463 |
| Difference % | -10 | | -2 | |

Run 20050929 B17P

| Thaw Cycles | Level (50 pg/mL) | | Level (500 pg/mL) | |
|--------------|------------------|----|-------------------|-----|
| 1 | 57 | 52 | 563 | 576 |
| | 58 | 45 | 531 | 504 |
| 3 | 50 | 45 | n.r.* | 515 |
| | 59 | 48 | 443 | 610 |
| Difference % | -5 | | -4 | |

* No result

** Outlier according to Dixon

Applicant's Freeze-thaw Stability Conclusions: Based on the tables above it can be concluded that samples can be thawed and frozen at -80°C up to three cycles. The acceptance criterion is met.

Extended Storage Stability:

The examination of the effect of storing serum samples spiked with calcipotriol, MC1080, betamethasone dipropionate and betamethasone 17-propionate at room temperature and at -80°C was examined. Data for up to 3 months storage for calcipotriol and MC1080 were provided (see tables below) and Data for up to 23 days storage for betamethasone dipropionate and betamethasone 17-propionate were provided (see tables below). The tables below show the measured serum concentrations of the different analytes following storage at the following times: room temperature, 1 month, 2 months and 3 months. Please note that the storage times for B17 P was different i.e. 5 days, 14 days and 23 days. The numbers in the table are the concentrations measured for 4 replicate standard samples following storage at the different times described above.

Calcipotriol

| Concentration | 0 day | Roomtemp. | 1 months | 2 months | 3 months |
|---------------|-------|-----------|----------|----------|----------|
|---------------|-------|-----------|----------|----------|----------|

| | Run 20051013 | 24h Run 20051013 | Run 20051116 | Run 20051208 | Run 20060111 |
|--------------|-----------------|------------------------|-----------------|-----------------|-----------------|
| 90 pg/mL | 69 | 83 | 83 | 76 | 65 |
| | 81 | 86 | 72 | 89 | 69 |
| | 70 | 66 | 79 | 88 | 84 |
| | 78 | 72 | 62 | 89 | 85 |
| Average | 75 | 77 | 74 | 86 | 76 |
| % Difference | | 3 | -1 | 15 | 2 |
| 250 pg/mL | 226 | 231 | 145 | 216 | 203 |
| | 212 | 218 | 192 | 327 | 216 |
| | 280 | 286 | 149 | 236 | 205 |
| | 252 | 267 | 158 | 255 | 205 |
| Average | 243 | 251 | 161 | 259 | 207 |
| % Difference | | 3 | -34 | 7 | -15 |

MC1080

| Concentration | 0 day Run 20051013 | Roomtemp. 2h Run 20051013 | 1 months Run 20051116 | 2 months Run 20051208 | 3 months Run 20060111 |
|---------------|--------------------------|---------------------------------|-----------------------------|-----------------------------|-----------------------------|
| 60 pg/mL | 53 | 67 | 56 | 47 | 68 |
| | 60 | 69 | 62 | 67 | 62 |
| | 45 | 61 | 50 | 46 | 64 |
| | 64 | 66 | 66 | 57 | 62 |
| Average | 56 | 66 | 59 | 54 | 64 |
| % Difference | | 18 | 5 | -2 | 15 |
| 500 pg/mL | 466 | 593 | 413 | 510 | 456 |
| | 466 | 652 | 420 | 584 | 627 |
| | 548 | 635 | 364 | 449 | 499 |
| | 487 | 685 | 389 | 415 | 455 |
| Average | 492 | 641 | 397 | 490 | 509 |
| % Difference | | 30 | -19 | 0 | 4 |

Betamethasone dipropionate

| Concentration | Day 0 Run 20060111 | Day 5 Run 20060116 | Day 14 Run 20060125 | Day 23 Run 20060203 |
|---------------|--------------------------|--------------------------|---------------------------|---------------------------|
| 60 pg/mL | 55 | 68 | 50 | 53 |
| | 60 | 54 | 60 | 58 |
| | 101* | 56 | 62 | 55 |
| | 59 | 57 | 59 | 55 |
| Average | 58 | 59 | 58 | 55 |
| % Difference | | 1 | 0 | -5 |

| | | | | |
|--------------|-----|-----|-----|-----|
| 500 pg/mL | 433 | 404 | 444 | 392 |
| | 388 | 399 | 466 | 452 |
| | 437 | 403 | 482 | 432 |
| | 404 | 396 | 442 | 427 |
| Average | 416 | 401 | 459 | 426 |
| % Difference | | -4 | 10 | 2 |

* Outlier according to Dixon's Q

Betamethasone 17-propionate

| Concentration | Day 0 | Day 5 | Day 14 | Day 23 ** |
|---------------|-----------------|-----------------|-----------------|-----------------|
| | Run 20060111 | Run 20060116 | Run 20060125 | Run 20060203 |
| 60 pg/mL | 31 | 34 | 98 | 35 |
| | 22 | 54 | 86 | 41 |
| | 26 | 47 | 72 | 39 |
| | 41 | 79 | 113 | 33 |
| Average | 30 | 54 | 92 | 37 |
| % Difference | | 78 | 208 | 23 |
| 500 pg/mL | 338 | 344 | 570 | 186 |
| | 265 | 378 | 729 | 216 |
| | 241 | 567 | 555 | 242 |
| | 336 | 637 | 643 | 256 |
| Average | 295 | 482 | 624 | 225 |
| % Difference | | 63 | 112 | -24 |

** 20060203_ess_dag23 B17P not accepted

Applicant's summary of long term stability data:

Calcipotriol in serum samples is stable up to three months at app. -80°C. MC1080 in serum samples is stable up to three months at app. -80°C. Betamethasone dipropionate in serum samples is stable up to at least 23 days at app. -80°C. The results for betamethasone 17-propionate are highly variable. Thus, no conclusions regarding the stability of betamethasone 17-propionate in serum can be drawn. However, the concentration of betamethasone 17-propionate generally tend to increase during the different storage periods investigated. Therefore, with the current method betamethasone 17-propionate concentrations might be overestimated.

Reviewer's Comments: Applicant stated that all samples were analyzed within 23 days except for samples re-analyzed for B17P which were analyzed within 6 months from the date they were obtained. However, this reviewer believes that the serum concentrations obtained for B17P should be interpreted with caution and may not be reliable due to the wide differences (ranging from -24 % to 208 %) observed between the concentration values obtained before (Day 0) storage and after storage of B17P in serum for up to 23 days i.e. the long term stability data to cover the serum sample storage period

Pharmacokinetics Results:

Calcipotriol and betamethasone dipropionate (BDP) were below the lower limit of quantification in all samples evaluated following multiple dermal dosing with Daivobet ointment and gel once daily for 4 and 8 weeks.

However, MC1080, a main metabolite of calcipotriol, was quantifiable in 10 of 34 (29.4%) patients at week 4 (Visit 7) and in 5 of 12 (41.7%) patients at week 8 (Visit 11). The maximum concentration of MC1080 was 75 pg/mL in males (measured in patient # U005, 3 hours post administration on Day 55) and 50 pg/mL in females (measured in patient # U024 at pre-dosing on Day 55).

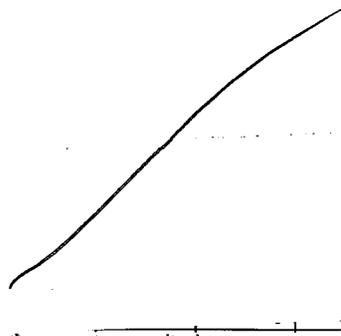
Individual serum concentrations of MC1080 after multiple dermal dosing with DOVOBET/DAIVOBET Ointment and DOVOBET/DAIVOBET gel once daily for 27 days.

| Visit 7, Day 27 | | Approximate use of drug product (g), week 1 - week 4 | | | concentration of MC1080 (pg/mL) time (hours) | | | | | | |
|-----------------|-----|--|-------|-------|---|---|---|---|---|---|---|
| Sample ID | Sex | Ointment | Gel | total | pretreat | 0 | 1 | 2 | 3 | 5 | 7 |
| U001 | M | 218.0 | 57.6 | 275.6 | | | | | | | |
| U002 | M | 226.4 | 71.9 | 298.3 | | | | | | | |
| U003 | M | 167.6 | 111.0 | 278.6 | | | | | | | |
| U004 | M | 151.2 | 37.6 | 188.8 | | | | | | | |
| U005 | M | 221.6 | n.d. | n.a. | | | | | | | |
| U017 | M | n.d. | n.d. | n.d. | | | | | | | |
| U023 | M | 118.6 | 52.0 | 170.6 | | | | | | | |
| U025 | M | 157.1 | 30.8 | 187.9 | | | | | | | |
| U026 | M | 166.3 | 143.5 | 309.8 | | | | | | | |
| U027 | M | 146.1 | 18.0 | 164.1 | | | | | | | |
| U031 | M | 197.7 | 159.3 | 357.0 | | | | | | | |
| U033 | M | 131.0 | 69.3 | 200.3 | | | | | | | |
| U035 | M | 235.2 | 161.1 | 396.3 | | | | | | | |
| U041 | M | 173.9 | 122.8 | 296.7 | | | | | | | |
| U044 | M | 206.6 | 40.3 | 246.9 | | | | | | | |
| U045 | M | n.d. | 158.6 | n.a. | | | | | | | |
| U051 | M | 201.9 | 118.1 | 320.0 | | | | | | | |
| U056 | M | 178.6 | 49.8 | 228.4 | | | | | | | |
| U058 | M | 144.9 | 83.8 | 228.7 | | | | | | | |
| U059 | M | 194.7 | 116.1 | 310.8 | | | | | | | |
| U091 | M | 101.0 | 97.0 | 198.0 | | | | | | | |
| U092 | M | 87.1 | 39.7 | 126.8 | | | | | | | |
| U093 | M | 80.7 | 54.0 | 134.7 | | | | | | | |
| U095 | M | n.d. | n.d. | n.d. | | | | | | | |
| U096 | M | 117.2 | 191.7 | 308.9 | | | | | | | |
| U020 | F | 93.0 | 47.3 | 140.3 | | | | | | | |
| U021 | F | n.d. | n.d. | n.d. | | | | | | | |
| U024 | F | n.d. | 126.8 | n.a. | | | | | | | |
| U028 | F | 102.5 | 58.9 | 161.4 | | | | | | | |
| U030 | F | 128.9 | 46.1 | 175.0 | | | | | | | |
| U036 | F | 214.7 | 175.9 | 390.6 | | | | | | | |
| U037 | F | 223.1 | 185.0 | 408.1 | | | | | | | |
| U053 | F | 181.8 | 159.8 | 341.6 | | | | | | | |
| U094 | F | 107.4 | 178.4 | 285.8 | | | | | | | |

n.d. = no data; n.a. = not applicable

Individual serum concentrations of MC1080 after multiple dermal dosing with DOVOBET/DAIVOBET® Ointment and DOVOBET/DAIVOBET gel once daily for 55 days.

| Visit 11, Day 55 | | Approximate use of drug product (g), week 5 - week 8 | | | concentration of MCI080 (pg/mL) | | | | | | |
|------------------|-----|--|-------|-------|---------------------------------|---|---|---|---|---|--|
| Sample ID | Sex | Ointment | Gel | total | time (hours) | | | | | | |
| | | | | | 0 | 1 | 2 | 3 | 5 | 7 | |
| U001 | M | 218.0 | 30.2 | 248.2 | | | | | | | |
| U002 | M | 211.8 | 72.9 | 284.7 | | | | | | | |
| U003 | M | 150.9 | 82.3 | 233.2 | | | | | | | |
| U005 | M | 237.2 | n.d. | n.a. | | | | | | | |
| U031 | M | 98.7 | 48.1 | 146.8 | | | | | | | |
| U044 | M | 199.8 | 91.9 | 291.7 | | | | | | | |
| U059 | M | 231.1 | 100.5 | 331.6 | | | | | | | |
| U021 | F | n.d. | n.d. | n.d. | | | | | | | |
| U024 | F | n.d. | 108.2 | n.a. | | | | | | | |
| U036 | F | 206.5 | 114.2 | 320.7 | | | | | | | |
| U053 | F | 191.7 | 101.9 | 293.6 | | | | | | | |
| U094 | F | 83.8 | 129.7 | 213.5 | | | | | | | |



b(4)

*non-valid result. The internal standard exceeded the limit given as the acceptance criterion.
n.d. = no data; n.a. = not applicable

B17P, a main metabolite of BDP was also quantifiable in 19 out of 34 (55.9%) patients at week 4 (Visit 7) and 7 of 12 (58.3%) patients at week 8 (Visit 11). Despite the fact that the concentration was below the LLOQ (30 pg/mL) in most of the samples, B17P could be visually identified in the chromatograms of all samples from Day 27 and Day 55. The maximum concentration of B17P was 106 pg/mL in males (measured in subject # U005, 2 hours post administration on Day 55) and 170 pg/mL in females (measured in subject # U024, 3 hours post administration on Day 27).

Individual serum concentrations of betamethasone 17-propionate in humans after multiple dermal dosing with DOVOBET/DAIVOBET Ointment and DOVOBET/DAIVOBET gel once daily for 27 days.

APPEARS THIS WAY
ON ORIGINAL

| Visit 7, Day 27 | | Approximate use of drug product (g), week 1 - week 4 | | | concentration of betamethasone 17-propionate (pg/mL) | | | | | | | |
|-----------------|-----|--|-------|-------|--|---|---|---|---|---|---|--|
| Sample ID | Sex | Ointment | Gel | total | time (hours) | | | | | | | |
| | | | | | pretreat | 0 | 1 | 2 | 3 | 5 | 7 | |
| U001 | M | 218.0 | 57.6 | 275.6 | | | | | | | | |
| U002 | M | 226.4 | 71.9 | 298.3 | | | | | | | | |
| U003 | M | 167.6 | 111.0 | 278.6 | | | | | | | | |
| U004* | M | 151.2 | 37.6 | 188.8 | | | | | | | | |
| U005 | M | 221.6 | n.d. | n.a. | | | | | | | | |
| U017 | M | n.d. | n.d. | n.d. | | | | | | | | |
| U023 | M | 118.6 | 52.0 | 170.6 | | | | | | | | |
| U025* | M | 157.1 | 30.8 | 187.9 | | | | | | | | |
| U026* | M | 166.3 | 143.5 | 309.8 | | | | | | | | |
| U027 | M | 146.1 | 18.0 | 164.1 | | | | | | | | |
| U031 | M | 197.7 | 159.3 | 357.0 | | | | | | | | |
| U033 | M | 131.0 | 69.3 | 200.3 | | | | | | | | |
| U035 | M | 235.2 | 161.1 | 396.3 | | | | | | | | |
| U041 | M | 173.9 | 122.8 | 296.7 | | | | | | | | |
| U044 | M | 206.6 | 40.3 | 246.9 | | | | | | | | |
| U045 | M | n.d. | 158.6 | n.a. | | | | | | | | |
| U051* | M | 201.9 | 118.1 | 320.0 | | | | | | | | |
| U056 | M | 178.6 | 49.8 | 228.4 | | | | | | | | |
| U058 | M | 144.9 | 83.8 | 228.7 | | | | | | | | |
| U059 | M | 194.7 | 116.1 | 310.8 | | | | | | | | |
| U091 | M | 101.0 | 97.0 | 198.0 | | | | | | | | |
| U092 | M | 87.1 | 39.7 | 126.8 | | | | | | | | |
| U093 | M | 80.7 | 54.0 | 134.7 | | | | | | | | |
| U095 | M | n.d. | n.d. | n.d. | | | | | | | | |
| U096 | M | 117.2 | 191.7 | 308.9 | | | | | | | | |
| U020 | F | 93.0 | 47.3 | 140.3 | | | | | | | | |
| U021 | F | n.d. | n.d. | n.d. | | | | | | | | |
| U024 | F | n.d. | 126.8 | n.a. | | | | | | | | |
| U028 | F | 102.5 | 58.9 | 161.4 | | | | | | | | |
| U030 | F | 128.9 | 46.1 | 175.0 | | | | | | | | |
| U036 | F | 214.7 | 175.9 | 390.6 | | | | | | | | |
| U037 | F | 223.1 | 185.0 | 408.1 | | | | | | | | |
| U053 | F | 181.8 | 159.8 | 341.6 | | | | | | | | |
| U094 | F | 107.4 | 178.4 | 285.8 | | | | | | | | |

b(4)

* The samples were analysed and re-analysed in two analytical runs in which the acceptance criteria with respect to QC samples and calibration standards were not met. However, a second re-analysis could not be performed as there was not enough sample matrix left for this purpose. Thus, the results are non-valid and marked using *italic writing* in the result table. n.d. = no data; n.a. = not applicable

Individual serum concentrations of betamethasone 17-propionate in humans after multiple dermal dosing with DOVOBET/DAIVOBET Ointment and DOVOBET/DAIVOBET gel once daily for 55 days.

APPEARS THIS WAY
ON ORIGINAL

| Visit 11, Day 55 | | Approximate use of drug product (g), week 5 - week 8 | | | concentration of betamethasone 17-propionate (pg/mL) | | | | | | |
|------------------|-----|--|-------|-------|--|---|---|---|---|---|--|
| Sample ID | Sex | Ointment | Gel | total | time (hours) | | | | | | |
| | | | | | 0 | 1 | 2 | 3 | 5 | 7 | |
| U001 | M | 218.0 | 30.2 | 248.2 | | | | | | | |
| U002* | M | 211.8 | 72.9 | 284.7 | | | | | | | |
| U003* | M | 150.9 | 82.3 | 233.2 | | | | | | | |
| U005 | M | 237.2 | n.d. | n.a. | | | | | | | |
| U031 | M | 98.7 | 48.1 | 146.8 | | | | | | | |
| U044* | M | 199.8 | 91.9 | 291.7 | | | | | | | |
| U059 | M | 231.1 | 100.5 | 331.6 | | | | | | | |
| U021 | F | n.d. | n.d. | n.d. | | | | | | | |
| U024 | F | n.d. | 108.2 | n.a. | | | | | | | |
| U036* | F | 206.5 | 114.2 | 320.7 | | | | | | | |
| U053 | F | 191.7 | 101.9 | 293.6 | | | | | | | |
| U094* | F | 83.8 | 129.7 | 213.5 | | | | | | | |

b(4)

* The samples were analyzed and re-analyzed in two analytical runs in which the acceptance criteria with respect to QC samples and calibration standards were not met. However, a second re-analysis could not be performed as there was not enough sample matrix left for this purpose. Thus, the results are non-valid and marked using *italic writing* in the result table above.

n.d. = no data; n.a. = not applicable

No difference between genders in the measured concentrations or percentage of measurements above LLOQ of Calcipotriol, BDP and B17P could be observed whereas the percentage of samples with concentrations of MC1080 above LOQ was higher for female than for male subjects. However, the ratio between the numbers of male and female subjects was 9 females vs. 25 males on Day 27 and 5 females vs. 7 males on Day 55 and given the high interindividual variability in concentrations, and the imbalance in the number of male and female subjects on both days, the existence of true gender differences could neither be proven nor excluded.

Summary of Serum Concentrations of MC1080 and B17P

| Day | MC1080 | B17P |
|-----|--|--|
| 27 | 20-46 pg/mL for males (n=6) 23-39 pg/mL for females (n=4) | 30-92 pg/mL for males (n=14) 30-170 pg/mL for females (n=5) |
| 55 | 37-75 pg/mL for males (n=2) 21-50 pg/mL for females (n=3) | 30-106 pg/mL for males (n=4) 30-100 pg/mL for females (n=3) |

The applicant stated that no correlation between the measured concentrations of MC1080 and B17P and the estimated individual usages of DOVOBET/DAIVOBET gel and DOVOBET/DAIVOBET Ointment during week 1-4 and week 5-8 was given. This observation might reflect that variation of the systemic exposure is primarily due to interindividual differences in the diffusion barrier and/or the rate of metabolism and excretion.

No pharmacokinetic parameters could be calculated due to high variability within patients and due to several patients having values below or close to the detection limit. In addition, most patients only had a few values above the lower limit of quantification which were insufficient to provide a full profile.

Reviewer's comments: This reviewer concurs with the applicant's findings with regards to the HPA axis suppression component, the calcium metabolism component and the pharmacokinetic evaluation. However, revisions to the proposed labeling are recommended (refer to section 4.2 for labeling recommendations) for the following reasons:

b(4)

/ / / / /

Vasoconstriction Study

Study # MBL 0403 FR

Title of study: In vivo bioequivalence study of betamethasone dipropionate in Daivobet®/Dovobet gel and Diprosone® ointment according to the FDA guideline for vasoconstrictor bioassay

Investigator: _____

b(4)

Study Center(s): _____

Studied Period: The study was conducted in 2 parts as follows:

Pilot Part: First subject enrolled on March 7th, 2005; last subject completed on March 18th, 2005

Pivotal Part: First subject enrolled on May 2nd, 2005; last subject completed on June 17th, 2005

Objectives: The aim of the study was to establish the potency of DAIVOBET/DOVOBET gel using the model according to FDA's Guidance for Industry: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence.

Secondary Objective: To assess the overall tolerability of the trial products in both the pilot phase and the pivotal phase of the study.

Methodology / Study design: This was a randomized, controlled, investigator-blinded, single centre, bioequivalence study according to the FDA guidelines on vasoconstrictor bioassay for corticosteroids in healthy subjects. Both the pilot and pivotal parts of the study were conducted in "responder" subjects. Sensitivity in the pivotal study was established through dosing the reference product calibrators at two dose durations, D₁ (the dose duration corresponding to approximately half

(0.25-0.5 times) ED₅₀) and D₂ (the dose duration corresponding to approximately two (2-4 times) ED₅₀) determined from the pilot study.

The Pilot Phase

Objective: To determine the dose-duration/response relationship of the reference product, thus providing ED₅₀, D₁ and D₂ to be used in the pivotal part as well as an estimate of the number of subjects expected to meet the D₁/D₂ ratio of AUC values in the pivotal part (“detector” subjects). *A “detector” subject is a subject whose AUEC_{0-24h} value at D₁ and D₂ are both negative and that meets the following criterion: AUEC_{0-24h} at D₂/AUEC_{0-24h} at D₁ ≥ 1.25. D₁ being the dose-duration corresponding to 0.5 times ED₅₀, D₂ the dose-duration corresponding to 2 times ED₅₀. (ED₅₀ is the dose-duration corresponding to approximately half maximal blanching response).*

Study Design: Single center, randomized, double-blind study

Study Population: 12 healthy subjects (responders) between 18 and 45 years of age. All subjects who withdrew were replaced. *A “responder” subject is a subject who shows a visual reading of at least one unit (i.e. slight blanching based on the visual scoring scale)) two hours after a dose duration of 4-6 hours during the screening period.*

Test Sites: Twelve sites (2.2 cm diameter) were used on the anterior side of the forearms (6 sites per forearm). For all sites, a baseline colorimetric evaluation was performed prior to the first drug application (i.e. within one hour before T₀ minus 6 hours).

The study was performed with staggered applications and synchronized removal: The study treatment was applied to skin sites at eight different times (8 dose durations) and was removed at the same time for all dose durations (T₀). Eight different dose durations from 0.25 to 6 hours were tested. Untreated control sites (2 on each forearm) allowed for the correction of the active drug skin sites for spontaneous circadian color changes during the study unrelated to drug exposure. Application to each subject of the 8 dose durations and 4 untreated sites were randomized. The 2 evaluators/readers were blinded to the randomization scheme. After drug removal (T₀), skin blanching assessment was performed both subjectively using a 5-point (0-4) visual assessment scale and objectively with the Chromameter over a 24h period. The dose duration corresponding to half maximal response (ED₅₀) was determined. Then, determination of D₁ and D₂ was performed.

Treatments: Only the Reference product, Diprosone® ointment, (betamethasone dipropionate 0.5 mg/g) [Schering-Plough Laboratories; Lot No: 4015/Exp. 09/2007] was applied during the pilot part of the study.

A single application of 10 microliter was administered under non-occlusive conditions on eight dose-duration sites on the ventral forearms (corresponding to durations of 0.25, 0.5, 0.75, 1, 1.5, 2, 4, and 6 hours) with applications done at *staggered times but with synchronized removal*. Two untreated sites on each forearm served as the control.

Selection of Dose: The dose of 10 microliter of reference or test product corresponds to 5.3 mg/cm². This dose was chosen based on results from previous similar studies.

Criteria for Evaluation: Skin blanching (vasoconstriction) was assessed using the Chromameter over a 24 hour period to measure the chromametric a* value (primary) and a 5-point (0-4) visual assessment scale (secondary). Assessment times were baseline (T=0), 10 min, 2, 4 and 6 hours after the drug removal on Day 1; and 19 and 24 hours after drug removal on Day 2.

Chromametric Measurements:

The chromameter used was the _____ with an opening diameter of 8 mm. The _____ Chromameter is a portable instrument with a flexible hand-held probe which can be moved very easily from one site to another. The measured area is 8 mm in diameter. This reflected light colorimeter offers five different color systems for measuring absolute chromaticity. The L* a* b* system is recommended by the CIE.

b(4)

Color is expressed in a three dimensional space. The L* value (luminance) gives the relative brightness ranging from total black (L*=0) to total white (L*=100). The a* value represents the balance between the red (positive values) and the green (negative values). The b* value represents the balance between the yellow (positive values) and the blue (negative values). The skin blanching effect leads to an increase of the L* value and a decrease of the a* value compared to baseline. The b* value is not modified by the blanching phenomena and will not be taken into account for the study analysis (b* reflects mainly pigmentation changes rather than vascular changes).

Visual Scoring:

The visual scoring scale was as follows:

0: no change in skin color, 1: slight blanching (barely visible), 2: obvious blanching, 3: intense blanching, 4: blanching judged to be maximal

Intermediate scores (half units) were used when needed (e.g. 0.5 for a doubtful blanching). At each evaluation time, 2 visual score values (one per trained evaluator) were recorded for each test site.

Safety: Adverse events were recorded when reported spontaneously by the subject or observed by the investigator.

Data Analysis: Chromameter Data: The primary criterion was the colorimetric parameter a*. The mean of two successive measurements performed on each test site was used. The variable subjected to analysis was denoted Δa^* and was computed by first subtracting the baseline values i.e. the a* values immediately after removal of the application. Then, in this new data set, the mean values at the untreated control sites were subtracted separately for each arm. The area under the effect curve from 0 to 24 hours (AUEC_{0-24h}) for Δa^* (baseline adjusted and untreated control site corrected values) was calculated by the trapezoidal method for each individual test site. In the computation, theoretical, not actual, time points were used. The dose duration-response data were analyzed using a non-linear least square regression to determine the population ED₅₀ value which served as the approximate dose duration for the bioequivalence comparison in the pivotal study. In accordance with the FDA guidance for Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, the D₁ and D₂ were also estimated.

The AUEC (0-24) data for the 12 subjects for each of the treatment duration was fitted simultaneously to the following equation: $E = E_{max} * D / (ED_{50} + D)$ [*E = effect, the AUEC for a given dose; E_{max} = maximum observed effect; D = Dose, the duration of application of cream; ED₅₀ = the dose that causes a half-maximal effect*]

Visual Scoring Data: For the visual blanching score, analyzed variables were the mean of the visual blanching scores (from 0 to 4) between the two evaluators, for each time. For each vasoconstriction time profile, the area under the curve was computed using the trapezoidal rule. The dose-duration-response data was fitted as described above. The ED₅₀, D₁ and D₂ were then determined.

Results of the Pilot Phase:

Eighteen subjects were enrolled, of which 6 (CRF=102, 103, 105, 109, 114, 117) were withdrawn since they were non-responders, therefore 12 subjects were randomized.

Demographic Characteristics:

| | N (%) or Mean + SD (range) |
|--------------------|----------------------------|
| Number of subjects | 12 |
| Gender | |
| Male | 4 (33.3%) |
| Female | 8 (66.7%) |
| Race | all 12 were Caucasian |
| Age | 30.9 + 5.9 (23-40) |
| Weight (kg) | 68.1 ± 15.1 (49-100) |
| Height (cm) | 167.8 ± 6.6 (156-178) |

Chromameter Results:

Table: Mean AUEC_{0-24h} for Δa* (baseline adjusted and untreated control site corrected) by treatment: per protocol analysis set, pilot phase

| Dose Duration (h) | 0.25 | 0.5 | 0.75 | 1 | 1.5 | 2 | 4 | 6 |
|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Mean | -17.88 | -21.63 | -21.33 | -22.99 | -26.85 | -27.44 | -30.06 | -31.35 |
| Std | 15.69 | 12.51 | 16.34 | 16.99 | 17.80 | 17.90 | 22.65 | 16.90 |
| Min | -38.52 | -43.99 | -45.35 | -55.52 | -64.84 | -59.26 | -83.24 | -61.79 |
| Max | 8.20 | -6.30 | 0.00 | 3.19 | -3.54 | -1.68 | -6.77 | -7.81 |
| N | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |

Table: Parameter estimates from E_{max} model fitted by nonlinear least squares regression, pilot phase

| | | | |
|------------------------|----------------------------|--------------------------|--------------------------|
| E_{max} | ED₅₀ (h) | D₁ (h) | D₂ (h) |
| -31.11 | 0.24 | 0.12 | 0.48 |

The applicant stated that, for practical reasons, the values that were actually used were: ED₅₀=20 min (0.33h), D₁=5 min (0.08h), D₂=60 min (1.00h). This is in accordance with the FDA guideline, which allows for a choice of D₁ between 0.25 to 0.5 times ED₅₀ and of D₂ between 2-4 times ED₅₀.

Table : Mean chromatometer a* AUEC_{0-24h} by dose duration. Estimated detector status based on estimated AUEC_{0-24h} at D₁ and D₂, pilot phase

| CRF No. | D1 (h) | AUEC(D1) | D2 (h) | AUEC(D2) | AUEC(D2)/ AUEC(D1) | Detector (Y/N) |
|---------|--------|----------|--------|----------|-----------------------|-------------------|
| 101 | 0.08 | 1.10 | 1.00 | -16.97 | -15.43 | No |
| 104 | 0.08 | -2.65 | 1.00 | -14.73 | 5.56 | Yes |
| 106 | 0.08 | -11.32 | 1.00 | -8.72 | 0.77 | No |
| 107 | 0.08 | -9.86 | 1.00 | -41.92 | 4.25 | Yes |
| 108 | 0.08 | -8.73 | 1.00 | -55.52 | 6.36 | Yes |
| 110 | 0.08 | -9.94 | 1.00 | 3.19 | -0.32 | No |
| 111 | 0.08 | -12.84 | 1.00 | -43.63 | 3.40 | Yes |
| 112 | 0.08 | -4.04 | 1.00 | -9.06 | 2.24 | Yes |
| 113 | 0.08 | 2.73 | 1.00 | -20.36 | -7.45 | No |
| 115 | 0.08 | -2.60 | 1.00 | -26.43 | 10.15 | Yes |
| 116 | 0.08 | -10.81 | 1.00 | -28.57 | 2.64 | Yes |
| 118 | 0.08 | -2.59 | 1.00 | -13.21 | 5.09 | Yes |

Visual Scoring Results:

Table: Mean AUEC_{0-24h} for visual score (untreated control site corrected) by treatment: per protocol analysis set, pilot phase

| Dose duration (h) | 0.25 | 0.5 | 0.75 | 1 | 1.5 |
|-------------------|-------|-------|-------|-------|-------|
| Mean | 30.36 | 27.51 | 29.10 | 30.17 | 29.46 |
| Std | 11.82 | 10.55 | 13.82 | 11.92 | 17.18 |
| Min | 9.74 | 7.63 | 10.43 | 9.27 | 4.89 |
| Max | 55.21 | 42.00 | 51.02 | 52.81 | 65.98 |
| N | 12 | 12 | 12 | 12 | 12 |

Continued...

| Dose duration (h) | 2 | 4 | 6 |
|-------------------|-------|-------|-------|
| Mean | 32.94 | 39.73 | 40.66 |
| Std | 15.11 | 13.49 | 15.58 |
| Min | 17.81 | 19.01 | 16.84 |
| Max | 70.29 | 54.73 | 65.35 |
| N | 12 | 12 | 12 |

Table: Parameter estimates from Emax model fitted by nonlinear least squares regression with AEUC_{0-24h} of the visual score as dependent variable, pilot phase

| Emax | ED50 (h) | D1 (h) | D2 (h) |
|-------|----------|--------|--------|
| 36.42 | 0.11 | 0.05 | 0.22 |

A dose duration-response curve was fitted. As a sensitivity analysis, ED₅₀, D₁ and D₂ were estimated. Even though ED₅₀, D₁ and D₂ were estimated separately for the secondary response criterion, for practical reasons, the same application times as for the primary criterion were used when the visual score was assessed, i.e. ED₅₀=20 min (0.33h), D₁=5 min (0.08h), D₂=60 min (1.00h).

Pivotal Phase

Objective: The pivotal phase of this study was intended to compare the pharmacodynamic activity (skin blanching effect due to vasoconstriction) of DAIVOBET/DOVOBET gel (formulation containing betamethasone dipropionate and calcipotriol) to the commercially available reference product DIPROSONE ointment in order to document the *in vivo* bio-equivalence of the DAIVOBET/DOVOBET gel formulation to the reference product.

Study Design: Single center, randomized (application sites), investigator blinded, intra-subject comparison study

Study Population: 70 healthy subjects (responders) between 18 and 45 years of age. All subjects who withdrew were replaced. Selection of the responders was done using the same procedure as that of the pilot study.

A “responder” subject is a subject who shows a visual reading of at least one unit (i.e. slight blanching) two hours after dose duration of 4-6 hours during the screening period.

A “detector” subject is a subject whose AEUC_{0-24h} value at D₁ and D₂ are both negative and that meets the following criterion: AEUC_{0-24h} at D₂/AEUC_{0-24h} at D₁ ≥ 1.25

Test Sites: Sixteen test sites (2.2 cm diameter on the anterior side of the forearms (8 sites per forearm) were delimited by the investigator. For all sites, a baseline colorimetric evaluation was performed prior to the first drug application.

Treatments:

Test Product: Daivobet® gel (calcipotriol 50 mcg/g with betamethasone dipropionate 0.5 mg/g) [Leo Pharmaceutical Products, Ltd; Lot No: 04259601, Expiry date: 08/2006] and the

Reference Product: Diprosone® ointment, (betamethasone dipropionate 0.5 mg/g) [Schering-Plough Laboratories; Lot No: 4015, Expiry date: 09/2007]

A single application of 10 microliter of the test and reference product was applied under non-occlusive conditions according to the following dose-durations for each arm:

- Four sites (2 on each forearm) were untreated
- Four sites received the test product for a duration equal to ED 50
- Four sites received the reference product for a duration equal to ED 50
- Two sites received the reference product for a duration equal to D1
- Two sites received the reference product for a duration equal to D2

These applications were performed at *staggered times but with synchronized removal (i.e. removed at the same time for all dose durations (T0)*. Application of the study drugs to each subject were done according to a randomized application list without the presence of both evaluators/readers.

Selection of Dose: The dose of 10 microliter of reference or test product corresponds to 5.3 mg/cm². This dose was chosen based on results from previous similar studies.

Criteria for Evaluation: The **Efficacy** (vasoconstriction) and **Safety** (adverse events) criteria was the same as the pilot study.

Data Analysis:

Chromameter Data: Same as the pilot study with the following additions

- The 90 % confidence interval was calculated for the ratio of the average AUC response of the test product and the reference product using Locke’s method
- The bioequivalence assessment was based only on the data of “detector subjects”. However, the data of “non detectors” was also documented in this report

Visual Scoring Data: Same as the pilot study and removal times are the same as described above for the chromameter readings.

Results of the Pivotal Part:

Demographics

| Characteristics | N (%) or Mean ±SD (range) |
|--------------------|---------------------------|
| Number of subjects | 70 |
| Gender | |
| Male | 12 (17.1) |
| Female | 58 (82.9) |

| | |
|-------------|-----------------------|
| Age | 28.0 ± 5.7 (19-41) |
| Weight (kg) | 61.1 ± 11.1 (43-95) |
| Height (cm) | 167.7 ± 9.9 (150-203) |

Of the 70 randomized responder subjects, only 27 subjects fulfilled the criterion of detectors and were included in the per protocol analysis set.

Reviewer's Comments: Guidance recommends 40 to 60 evaluable subjects i.e. subjects who meet the "responder" and "detector" criteria. However, in this case this reviewer agrees that twenty-seven subjects may be considered acceptable to still provide the required statistical power based on the sponsor's calculation using data from the pilot phase of the study. The pivotal study report shows that 27 subjects (39%) out of 70 were "detectors" therefore approximately 61 % of all subjects who participated in the study could not differentiate D1 (32 minutes) application from D2 (128-minute) application. The applicant provided the following possible theoretical explanations for the observed difference.

Values for population ED₅₀ decreases with increase in corticosteroid product potency. For potent corticosteroid formulations, the ED₅₀ values are very short so that D₁ and D₂ are very close to each other and only a small number of responder subjects have a D₂/D₁ AUECs ratio ≥ 1.25. The responder status is determined by the ability of a subject to express a clear-cut visually assessed blanching effect. Highly reactive subjects may thus be selected by the investigator but such subjects can be a posteriori poor detectors.

The screening procedure discards subjects who are poor responders (absence of blanching) as opposed to be non-detectors (those who meet the ratio of AUC 0-24h at D₁ and D₂ being ≥ 1.25).

Moreover, for potent corticosteroids the screening procedure with dose durations equal to 4-6 hours does not seem appropriate when compared to the bioequivalence study in which dose durations are very short (less than one hour).

Pharmacodynamic Assessments:

Chromametric a* Parameter:

Table: Mean AUEC for Δa* (baseline adjusted and untreated control site corrected) by treatment: per protocol analysis set, pivotal phase

**APPEARS THIS WAY
ON ORIGINAL**

| | DAIVOBET/ DOVOBET gel ED50 | DIPROSONE ointment ED50 | DIPROSONE ointment D1 | DIPROSONE ointment D2 |
|------|----------------------------------|-------------------------------|-----------------------------|-----------------------------|
| Mean | -10.03 | -12.89 | -10.84 | -18.54 |
| Std | 10.87 | 12.87 | 10.10 | 12.21 |
| Min | -44.77 | -59.14 | -36.02 | -47.59 |
| Max | 15.89 | 25.07 | 6.02 | -0.19 |
| N | 108 | 108 | 54 | 54 |

Table: Results of the statistical analysis of bioequivalence based on chromameter a*: per protocol analysis set, pivotal phase

| ratio | 90% confidence interval (Locke's method) |
|-------|---|
| 0.78 | (0.64, 0.95) |

The table above has the results of a statistical analysis using Locke's method to estimate a confidence interval for the ratio of the expected AUEC_{0-24h} for the treatment group and the expected AUEC_{0-24h} for the untreated group.

Bioequivalence cannot be claimed from the results of this study. The estimate of the ratio was 0.78, with a 90% confidence interval of (0.64, 0.95). Since the interval is entirely below 1, this suggests that DAIVOBET/DOVOBET gel has *less blanching effect* than the reference ointment.

Visual Scoring (secondary criterion):

Table 33: Mean AUEC_{0-24h} for visual score (untreated control site corrected) by treatment: per protocol analysis set, pivotal phase

| | DAIVOBET/ DOVOBET gel ED50 | DIPROSONE ointment ED50 | DIPROSONE ointment D1 | DIPROSONE ointment D2 |
|------|----------------------------------|-------------------------------|-----------------------------|-----------------------------|
| Mean | 16.0 | 19.9 | 19.6 | 24.3 |
| Std | 8.6 | 10.8 | 9.3 | 12.0 |
| Min | -6.1 | -7.4 | -2.4 | 1.6 |
| Max | 39.8 | 45.0 | 38.3 | 46.3 |
| N | 108 | 108 | 54 | 54 |

As shown in the table above, the results of the visual score also indicate that skin blanching after DAIVOBET/DOVOBET gel administration is less than after DIPROSONE ointment.

Reviewer's Comments: The calculated parameter G (= 0.053923) was inferior to 1, the study met the bioequivalence requirements and the 90% confidence interval could be calculated. G= the ratio of the standard deviation of the reference product divided by the mean of the reference product multiplied by the square of the 95th percentile of the distribution for n-1 degrees of freedom. G < 1 is required to have proper confidence intervals.

However on the basis of the study data, it can be concluded that the betamethasone dipropionate in DAIVOBET/DOVOBET gel did not prove to be bioequivalent with the reference product DIPROSONE ointment.

This result was expected as DAIVOBET/DOVOBET gel showed a significantly lower antipsoriatic effect than DAIVOBET/DOVOBET ointment (for which bioequivalence to DIPROSONE ointment has been demonstrated in a psoriasis plaque test study).

Applicant's Conclusions:

The study was conclusive and demonstrated that DAIVOBET/DOVOBET gel was not bioequivalent to DIPROSONE ointment regarding AUEC_{0-24h} for the colorimetric parameter Δa^* (baseline adjusted and untreated control site corrected). DAIVOBET/DOVOBET gel induced less skin blanching than DIPROSONE ointment, suggesting that DAIVOBET/DOVOBET gel can be considered a weaker (less clinically potent) topical corticosteroid than DIPROSONE ointment.

Reviewer's Comments: This reviewer concurs with the applicant's findings.

Calcium Metabolism in Phase 3 Clinical Studies:

A synopsis of the studies with special emphasis on serum calcium measurements is provided below. This reviewer only focused on the serum calcium measurements component of the study. A detailed review of the efficacy and safety components of the studies is currently being reviewed by the medical reviewer (Dr. B. Carr)

Study # MBL 0405 INT

Title of study: 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

International Co-ordinating Investigator: Dr. Gregor Jemec, Medical department, Roskilde Amtssygehus, Køgevej 7-13, DK-4000, Roskilde, Denmark.

Centre details: Multicenter study conducted at 101 centers (Canada 15; Denmark 4; France 25; Norway 10; Portugal 2; Spain 10; Sweden 11; United Kingdom 24).

Study period details: First patient included on 17 November 2004; Last patient attended last visit on 08 September 2005

Phase of development: Phase III

Objectives: To compare the efficacy and safety of once daily treatment for up to 8 weeks of calcipotriol plus betamethasone dipropionate gel (henceforth referred to as

DAIVOBET/DOVOBET gel) with betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle alone in patients with scalp psoriasis.

Study methodology: An international, multicenter, prospective, randomized, double-blind, 4-arm, parallel group, 8-week study in patients with scalp psoriasis. Patients were randomized in a 4:4:2:1 ratio to receive once daily treatment for up to 8 weeks with either 1) DAIVOBET/DOVOBET gel or 2) betamethasone dipropionate in the gel vehicle or 3) calcipotriol in the gel vehicle or 4) gel vehicle. Visits were performed on day 0 (Visit 1) and after 7 (Visit 2), 14 (Visit 3), 28 (Visit 4), 42 (Visit 5) and 56 (Visit 6) days. A follow-up visit took place 14 days after the patient's last on-treatment visit if a treatment related (possible, probable or not assessable relationship to treatment) adverse event was ongoing.

Efficacy assessments including the Investigator's Global Assessment of disease severity, extent of scalp psoriasis, and assessment of the clinical signs (redness, thickness and scaliness) were performed at all visits (1 to 6) and the patient's overall assessment of response to treatment at visits 2 to 6.

Safety assessments were performed at all post-baseline visits. Blood samples for analysis of serum calcium and albumin were taken at baseline and at Weeks 1 and 4 (Visits 2 and 4). Laboratory data (total serum calcium, serum albumin and albumin corrected serum calcium) were used for individual patient safety monitoring. Laboratory data were evaluated using absolute change in laboratory values from baseline (Visit 1) to Week 1 (Visit 2) and Week 4 (Visit 4).

Number of patients enrolled: A total of 1485 patients were planned (DAIVOBET/DOVOBET gel 540, betamethasone dipropionate in the gel vehicle 540, calcipotriol in the gel vehicle 270 and gel vehicle 135). A total of 1506 patients were enrolled and 1505 were randomized; 541 patients to DAIVOBET/DOVOBET, 556 to betamethasone dipropionate in the gel vehicle, 272 to calcipotriol in the gel vehicle and 136 to the gel vehicle.

Results:

Results of calcium measurements:

The table below summarizes actual change from baseline. It should be noted that the laboratory reference ranges (serum calcium =2.25 to 2.67 mmol/L and albumin-corrected serum calcium = 2.12 to 2.56 mmol/L) used in the database were for patients aged 18 years old and above and that there was one patient identified with a minor protocol violation (being 17 rather than 18 years old). The reference ranges used for this patient were those for an 18 year old but this is not considered likely to impact the interpretation of these data.

Reviewer's Comments: What is the difference between the reference range for a 17 year old and an 18 year old?

Week 1

Examination of the shifts from baseline to Week 1 (Visit 2) showed 1 (0.2%) patient in the DAIVOBET/DOVOBET gel group experienced a shift from normal corrected calcium at baseline to abnormally high corrected calcium. In the betamethasone dipropionate in gel vehicle group, 4 (0.7%) patients experienced a shift to high corrected calcium. Two (0.8%) patients in the

calcipotriol in gel vehicle group experienced a shift to high corrected calcium. No patients in the gel vehicle group experienced a shift from normal at baseline to abnormally high corrected calcium at Week 1.

Week 4

The corresponding results for shifts from normal at baseline to abnormally high corrected calcium at Week 4 (Visit 4) were 1 (0.2%) patient in the DAIVOBET/DOVOBET gel group, 3 (0.5%) patients in the betamethasone dipropionate in gel vehicle group, 1 (0.3%) patient in the calcipotriol in gel vehicle group and, 1 (0.7%) patient in the gel vehicle group.

The mean actual changes reported were small. Changes from baseline to Week 1 (Visit 2) and to Week 4 (Visit 4), in albumin corrected calcium were similar for all four treatment groups (i.e. DAIVOBET/DOVOBET gel group, betamethasone dipropionate in gel vehicle group, calcipotriol in gel vehicle group and gel vehicle group). The mean changes ranged between 0.00 and -0.01 at Week 1 and between -0.01 and -0.02 at Week 4.

Individual Patient Data

Week 1

However, in terms of changes in individual patients there were two patients in the DAIVOBET/DOVOBET gel group who had a value above the upper reference limit at Week 1 (Visit 2). One of these (CRF=1229) also had a high value at baseline and no increase compared with baseline was observed. One patient (CRF=1219) shifted from a normal value at baseline to a value just above the upper reference limit at Week 1 (Visit 2).

In the betamethasone dipropionate in gel vehicle group there were 10 patients who had values above the upper reference limit at Week 1 (Visit 2). Six of these (CRF=1173, 2211, 1806, 1560, 2334, 2614) also had high values at baseline. The largest increase was from 2.69 mmol/l to 2.78 mmol/l (CRF=1560). Four patients (CRF=2241, 1771, 1621, 2373) shifted from a normal value at baseline to a value above the upper reference limit at Week 1 (Visit 2).

In the calcipotriol in gel vehicle group, there were two patients (CRF=2260 and 1866) who had a value above the upper reference limit at Week 1 (Visit 2). Both shifted from a normal value at baseline to a value above the upper reference limit at Week 1 (Visit 2).

In the gel vehicle group, one patient (CRF=2505) had similarly high values up to 2.70 mmol/l at baseline, visit 2 and visit 4.

In the gel vehicle group, one patient (CRF=2505) had similarly high values up to 2.70 mmol/l at baseline and Week 1 (visit 2).

Week 4

Two patients had a value above the upper reference limit at Week 4 (Visit 4) in the DAIVOBET/DOVOBET gel group. One of these patients (CRF=1229) also had a similarly high value at baseline (3.07 mmol/l). The patient was a 60-year-old female with no concurrent diagnoses

or concomitant medication at baseline. During the study, she had adverse events involving upper and lower respiratory tract infections, which were treated with Flovent and resolved. The patient was withdrawn from the study after Week 4 (Visit 4) due to the high calcium value. This patient had a slightly higher value (3.13 mmol/l) at the 2-week follow-up testing 2 weeks after treatment discontinuation. At follow-up the investigator stated that the value should be considered an adverse event, but no such adverse event was reported as it occurred after discontinuation of study treatment. The patient used 13.28g of DAIVOBET/DOVOBET gel in Week 1, 14.08g in Week 2, 43.06g during Weeks 3 and 4, and the week between Week 4 (Visit 4) and withdrawal the patient used 38.46 g of DAIVOBET/DOVOBET gel.

The second patient (CRF=2622) shifted from a normal value at baseline to a value (2.75 mmol/l) above the upper reference limit (at Week 4 (Visit 4)). The value was reported as an adverse event of mild intensity but the patient continued study treatment. An on-treatment follow-up value was normal. This patient used 1.58g of DAIVOBET/DOVOBET gel in Week 1, 11.58g in Week 2, and 49.96g during Weeks 3 and 4.

In the betamethasone dipropionate in gel vehicle group there were seven patients who had values above the upper reference limit at Week 4 (Visit 4). Four of these (CRF=1173, 1806, 1560 and 2428) also had high values at baseline. The largest increase was from 2.69 mmol/l to 2.87 mmol/l (CRF=2428). Three patients shifted from a normal value at baseline to a value above the upper reference limit (CRF=2255, 1621 and 1989).

In the calcipotriol in the gel vehicle group there was one patient (CRF=2260) who had a value above the upper reference limit at Week 4 (Visit 4).

In the gel vehicle group, one patient (CRF=2505) had high values up to 2.70 mmol/l at baseline, Week 4 (visit 4). One patient (CRF=2789) shifted from a normal value at baseline to a value above the upper reference limit (2.73 mmol/l) at Visit 4.

Patients were not permitted to use concomitant vitamin D analogues on the body and it was confirmed that none of the patients with abnormal shifts in corrected calcium in the DAIVOBET/DOVOBET gel or calcipotriol in the gel vehicle groups had taken such disallowed medication.

Actual Change in Laboratory Parameters from Baseline to Visits 2 and 4: safety analysis set

| Laboratory parameter | Daivobet Gel (n=530) | Betamethasone (n=548) | Calcipotriol (n=266) | Gel Vehicle (n=135) |
|--|-------------------------|--------------------------|-------------------------|------------------------|
| Change from baseline to visit 2 (Week 1) | | | | |
| Albumin | | | | |
| Mean | 0.0 | -0.3 | -0.5 | -0.6 |
| SD | 2.1 | 2.1 | 2.2 | 2.1 |
| Minimum | -9 | -7 | -8 | -6 |
| Maximum | 11 | 6 | 5 | 3 |

| | | | | |
|--|-------|-------|-------|-------|
| Number | 518 | 528 | 260 | 130 |
| Change from baseline to visit 2 | | | | |
| Calcium | | | | |
| Mean | -0.01 | -0.01 | -0.01 | -0.02 |
| SD | 0.09 | 0.09 | 0.10 | 0.09 |
| Minimum | -0.38 | -0.32 | -0.35 | -0.26 |
| Maximum | 0.26 | 0.27 | 0.53 | 0.19 |
| Number | 517 | 528 | 260 | 130 |
| Calcium (albumin corrected) | | | | |
| Mean | -0.01 | -0.01 | 0.00 | -0.01 |
| SD | 0.08 | 0.08 | 0.09 | 0.07 |
| Minimum | -0.34 | -0.24 | -0.25 | -0.20 |
| Maximum | 0.27 | 0.24 | 0.59 | 0.15 |
| Number | 517 | 528 | 260 | 130 |
| Change from baseline to visit 4 (Week 4) | | | | |
| Albumin | | | | |
| Mean | -0.5 | -0.5 | -0.4 | -0.8 |
| SD | 2.2 | 2.1 | 2.5 | 2.0 |
| Minimum | -9 | -8 | -8 | -7 |
| Maximum | 8 | 6 | 10 | 4 |
| Number | 469 | 492 | 219 | 118 |
| Change from baseline to visit 4 (Week 4) | | | | |
| Calcium | | | | |
| Mean | -0.03 | -0.03 | -0.02 | -0.04 |
| SD | 0.09 | 0.09 | 0.10 | 0.09 |
| Minimum | -0.32 | -0.42 | -0.34 | -0.36 |
| Maximum | 0.22 | 0.31 | 0.48 | 0.16 |
| Number | 469 | 491 | 219 | 118 |
| Calcium (albumin corrected) | | | | |
| Mean | -0.02 | -0.02 | -0.01 | -0.02 |
| SD | 0.08 | 0.09 | 0.09 | 0.08 |
| Minimum | -0.30 | -0.32 | -0.33 | -0.30 |
| Maximum | 0.21 | 0.31 | 0.54 | 0.17 |
| Number | 469 | 491 | 219 | 118 |

Applicant's Conclusions: The changes in corrected serum calcium from baseline were small and not of clinical significance in all four groups.

Reviewer's Comments: Data indicates that some patients did experience some increase in calcium levels, therefore hypercalcemia may develop during the use of Taclonex Scalp gel when used according to the recommended dosing regimen. It is recommended that this finding should be communicated in the label.

Study # MBL 0406 INT

Title of study: Calcipotriol plus Betamethasone Dipropionate Gel Compared to Betamethasone Dipropionate in the Gel Vehicle and Calcipotriol in the Gel Vehicle in Scalp Psoriasis

International Co-ordinating Investigator: Peter van de Kerkhof, MD, Afdeling Dermatologie, Universitair Medisch, Centrum St. Radboud, Postbus 9101, NL-6525 GL Nijmegen, The Netherlands

Centre details: Multicenter study conducted at 98 centers (Belgium: 11; Canada: 6; Finland: 7; France: 7; Germany: 14; Ireland: 4; Netherlands: 8; United Kingdom: 41).

Study period details: date of first enrolment, date of last patient completed:

First patient included on 08 December 2004, Last patient attended last visit on 12 September 2005

Phase of development: Phase III

Objectives: To compare the efficacy and safety of once daily treatment for up to 8 weeks of calcipotriol plus betamethasone dipropionate gel (henceforth referred to as DAIVOBET/DOVOBET gel) with betamethasone dipropionate in the gel vehicle and calcipotriol in the gel vehicle in patients with scalp psoriasis

Study methodology: An international, multicenter, prospective, randomized, double-blind, 3-arm, parallel group, 8-week study in patients with scalp psoriasis. Patients were randomized in a 2:2:1 ratio to receive once daily treatment for up to 8 weeks with either 1) DAIVOBET/DOVOBET gel or 2) betamethasone dipropionate in the gel vehicle or 3) calcipotriol in the gel vehicle. Visits were performed at baseline (Visit 1) and after 7 (Visit 2), 14 (Visit 3), 28 (Visit 4), 42 (Visit 5) and 56 (Visit 6) days. A follow-up visit took place 14 days after the patient's last on-treatment visit if a treatment related adverse event (possible, probable or not assessable relationship to treatment) was ongoing.

Efficacy assessments: The Investigator's Global Assessment of Disease Severity, extent of scalp psoriasis and assessment of the clinical signs (redness, thickness and scaliness) were performed at all visits (1 to 6). At Visits 2 to 6 the patients made an overall assessment of their treatment response compared to baseline.

Safety assessments: These were performed at all post-baseline visits (Visits 2 to 6 and follow-up). Blood samples for albumin corrected calcium measurements were taken at baseline and at weeks 1 and 4 (Visits 2 and 4). Laboratory data (total serum calcium, serum albumin and albumin corrected serum calcium) were used for individual patient safety monitoring. Laboratory data were evaluated using absolute change in laboratory values from baseline (Visit 1) to Week 1 (Visit 2) and Week 4 (Visit 4).

Number of patients enrolled: A total of 1350 patients were planned (DAIVOBET/DOVOBET gel 540, betamethasone dipropionate in the gel vehicle 540, calcipotriol in the gel vehicle 270). A total of 1418 patients were enrolled and 1417 were randomized: 568 to DAIVOBET/DOVOBET gel 563 to betamethasone dipropionate in the gel vehicle and 286 to calcipotriol in the gel vehicle.

Investigational product, dose, method of administration, lot numbers:

DAIVOBET/DOVOBET gel: calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) gel applied topically to affected areas on the scalp once daily to a maximum of 100 g per week. Lot numbers: 04 225 6101, 04 224 6101, 04 257 6101, 04 259 6101 and 04 219 6101

Reference product, dose, method of administration, lot numbers:

Betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle. Lot numbers: 04 217 6101 and 04 260 6101; Calcipotriol 50 mcg/g in the gel vehicle. Lot numbers: 04 271 6101, 04 264 6101, 04 272 6101, 04 265 6101 and 04 273 6101. Both reference products were applied topically to affected areas on the scalp once daily.

Duration of treatment: Up to 8 weeks.

Results of calcium measurements:

The applicant stated that an examination of the shifts from baseline to week 1 (Visit 2) showed none of the patients in the DAIVOBET/DOVOBET gel group experienced a shift from normal corrected calcium at baseline to abnormally high corrected calcium. In the betamethasone dipropionate in the gel vehicle group three patients (0.5%) experienced such a shift and in the calcipotriol in the gel vehicle group one patient (0.4%) experienced such a shift.

The corresponding results for shifts from normal at baseline to abnormally high corrected calcium at week 4 (Visit 4) were 3 (0.5%) patients in the DAIVOBET/DOVOBET gel group, 2 (0.4%) patients in the betamethasone dipropionate in the gel vehicle group and 1 (0.4%) patient in the calcipotriol in the gel vehicle group.

Actual change in laboratory parameters from baseline to visits 2 and 4: safety analysis set [study0406]

| Laboratory parameter | Daivobet Gel (n=563) | Betamethasone (n=556) | Calcipotriol (n=282) |
|--|-------------------------|--------------------------|-------------------------|
| Change from baseline to visit 2 Albumin | | | |
| Mean | -0.1 | -0.0 | -0.3 |
| SD | 2.0 | 2.2 | 2.0 |
| Minimum | -7 | -10 | -6 |
| Maximum | 7 | 6 | 5 |
| Number | 547 | 533 | 269 |

| | | | |
|------------------------------------|-------|-------|-------|
| Calcium | | | |
| Mean | -0.01 | -0.01 | -0.02 |
| SD | 0.10 | 0.10 | 0.10 |
| Minimum | -0.35 | -0.51 | -0.33 |
| Maximum | 0.30 | 0.31 | 0.23 |
| Number | 547 | 533 | 269 |
| Calcium (albumin corrected) | | | |
| Mean | -0.01 | -0.01 | -0.02 |
| SD | 0.09 | 0.09 | 0.09 |
| Minimum | -0.31 | -0.43 | -0.30 |
| Maximum | 0.33 | 0.29 | 0.21 |
| Number | 547 | 533 | 269 |
| Change from baseline to visit 4 | | | |
| Albumin | | | |
| Mean | -0.5 | -0.2 | -0.4 |
| SD | 2.2 | 2.2 | 1.8 |
| Minimum | -9 | -8 | -6 |
| Maximum | 8 | 7 | 5 |
| Number | 502 | 483 | 254 |
| Calcium | | | |
| Mean | -0.03 | -0.02 | -0.04 |
| SD | 0.10 | 0.10 | 0.10 |
| Minimum | -0.39 | -0.33 | -0.36 |
| Maximum | 0.29 | 0.31 | 0.25 |
| Number | 502 | 482 | 254 |
| Calcium (albumin corrected) | | | |
| Mean | -0.02 | -0.02 | -0.03 |
| SD | 0.09 | 0.08 | 0.09 |
| Minimum | -0.36 | -0.26 | -0.35 |
| Maximum | 0.42 | 0.23 | 0.26 |
| Number | 502 | 482 | 254 |

The mean actual changes from baseline reported were small. Changes from baseline to week 1 (Visit 2) and to week 4 (Visit 4) in albumin-corrected calcium were similar for all three treatment groups (i.e. DAIVOBET/DOVOBET gel group, betamethasone dipropionate in the gel vehicle group and calcipotriol in the gel vehicle group). The actual changes ranged between -0.43 and 0.33 at week 1 and between -0.36 and 0.42 at week 4.

Individual Patient Data:

Week 1

In terms of individual cases there were three patients (CRF= 4857, 4514 and 4599) in the DAIVOBET/DOVOBET gel group who had a serum corrected calcium value above the upper reference limit at week 1 (Visit 2). All of these also had a high value at baseline and one patient (CRF =4599) showed an increase from baseline (from 2.81 to 2.98 mmol/l).

In the betamethasone dipropionate in gel vehicle group there were eleven patients who had a serum corrected calcium value above the upper reference limit at week1 (Visit 2). Eight of these (CRF= 4036, 4080, 5899, 4772, 5027, 5351, 5155, 5418) also had a high value at baseline. All values at week 1 (Visit 2) were similar or lower than at baseline (maximum increase 0.04 mmol/l in CRF= 4772). Three patients (CRF= 4495, 4652, 5277) shifted from a normal value at baseline to a value just above the upper reference limit at week 1 (Visit 2). The values were 2.66 mmol/l for CRF=4652 and 2.65 mmol/l for the other 2 patients).

In the calcipotriol in gel vehicle group there were four patients who had a serum corrected calcium value above the upper reference limit at week 1 (Visit 2). Three of these (CRF= 4078, 4097 and 4452) also had a high value at baseline. All values at week 1 (Visit 2) were similar to baseline. One patient (CRF= 4701) shifted from a normal value at baseline (2.51 mmol/l) to a value above the upper reference limit (2.69 mmol/l) at week 1 (Visit 2). The amount of medication used by this patient during week 1 was 9.0g. The patient did not use concomitant vitamin D analogues on the body.

Week 4

In the DAIVOBET/DOVOBET gel group, five patients had a value above the upper reference limit at week 4 (Visit 4). Two of these (CRF= 4857 and 4599) also had a high value at baseline and no increase versus baseline was shown. Three patients shifted from a normal value at baseline to a value above the upper reference limit (CRF=5225, 5214 and 5316). None of these patients used concomitant vitamin D analogues on the body. The amount of medication used by CRF=5225 was 4.88g in week 1, 5.78g in week 2 and 13.86g in weeks 3 and 4 (a total of 24.52g during the first 4 weeks). The amount used by CRF= 5316 was 22.08g in week 1, 27.18g in week 2 and 44.66g during weeks 3 and 4 (a total of 93.92g during the first 4 weeks). **Patient CRF=5214 did not return all dispensed tubes so the amount used by this patient was not available. An adverse event of mild hypercalcemia was reported for this patient who remained in the study and had a normal value at week 6 (Visit 5).**

In the betamethasone dipropionate in gel vehicle group there were eight patients who had values above the upper reference limit at week 4 (Visit 4). Six of these (CRF=5899, 4636, 4772, 5027, 5351 and 5155) also had a high value at baseline. All values were similar or lower than at baseline. Two patients shifted from a normal value at baseline to a value above the upper reference limit (CRF= 4091 and 4652).

In the calcipotriol in gel vehicle group there were four patients who had a value above the upper reference limit at week 4 (Visit 4). Three of these (CRF= 4078, 4450 and 4452) also had a high value at baseline. CRF= 4450 had an increase from 2.65 mmol/l at baseline to 2.73 mmol/l at Visit 4 but the other two patients had values similar or lower than at baseline. One patient (CRF= 4724) shifted from a normal value at baseline to a value just above the upper reference limit. This patient

used a total of 199.9g during the first 4 weeks (54.8g in week 1, 41.4g in week 2 and 103.7g during weeks 3 and 4). The patient did not use concomitant vitamin D analogues on the body.

Week 1 and 4

One more patient (CRF=5291) reported an adverse event of increased serum calcium levels. This patient had a serum calcium above the upper reference limit at weeks 1, 4 and follow-up. The albumin corrected calcium, however, was within the reference range throughout the study.

I

Applicant's Conclusion:

There were no changes of clinical concern in serum corrected calcium.

Reviewer's Comments: This reviewer does not concur with the applicant's conclusions. The results indicate that some patients did experience some increase in calcium levels, therefore hypercalcemia may develop during the use of Taclonex Scalp gel when used according to the recommended dosing regimen. This finding should be communicated in the label.

Study # MBL 0502 US

Title of study: Calcipotriene plus betamethasone dipropionate gel compared to the gel vehicle in scalp psoriasis, in patients receiving calcipotriene plus betamethasone dipropionate ointment for psoriasis vulgaris of trunk/limbs.

International Co-ordinating Investigator: Dr S Tying, Consultant Dermatologist, Centre for Clinical Studies, Houston, Texas, USA.

Centre details: 18 centers in the US.

Study period details: First patient enrolled on 27-Dec-2005, last patient visit in double-blind phase on 05-Sep-2006

Phase of development: III

Objectives: To compare the efficacy and safety of 8 weeks treatment with DAIVOBET/DOVOBET gel with that of gel vehicle in scalp psoriasis.

Study methodology: Patients were randomized on a double-blind basis in a 3:1 ratio to 8 weeks treatment of scalp psoriasis with either DAIVOBET/DOVOBET gel or gel vehicle. Randomization was stratified by ethnicity (Hispanic/Latino patients, non-Hispanic/Latino patients). In addition, all patients received DAIVOBET/DOVOBET ointment as treatment for psoriasis of trunk/limbs. Patients were assessed every 2 weeks in the double-blind phase.

Efficacy Assessments: Global assessment of severity of scalp psoriasis (6 point scale, from clear to very severe), extent of scalp psoriasis (as a percentage of total scalp area), clinical signs of scalp psoriasis (redness, thickness and scaliness, each scored on a 5-point scale, from 0 (none) to 4 (very severe)), global assessment of severity of psoriasis of trunk/limbs (6-point scale, from clear to very severe)

Safety assessments: adverse events, blood pressure at all visits and laboratory assessments at weeks 0, 2 and 4 (calcium, albumin, blood urea nitrogen, creatinine, urinalysis). Laboratory data (total serum calcium, serum albumin and albumin corrected serum calcium) were used for individual patient safety monitoring. Laboratory data were evaluated using absolute change in laboratory values from baseline (Visit 1) to Week 2 (Visit 2) and Week 4 (Visit 4). Changes in laboratory parameters were presented by shift tables of the values at Visit 2 and at Visit 4 to the value at baseline. Shift tables by treatment group show the baseline values against the values at Visit 2 and at Visit 4, each categorized as low, normal or high (i.e. below, within, or above the reference ranges, respectively). The absolute change from baseline to Visit 2 and to Visit 4 was tabulated by treatment group.

Number of patients enrolled: A total of 178 patients were enrolled, of whom 177 were randomized, 135 to DAIVOBET/DOVOBET gel and 42 to gel vehicle.

Investigational product, dose, method of administration, lot numbers: DAIVOBET/DOVOBET gel applied topically once daily, Lot numbers 05 175 61 01 and 05 174 61 01. DAIVOBET/DOVOBET ointment applied topically once daily when required, Lot numbers 05 207 61 and 05 207 62.

Reference product, dose, method of administration, lot numbers: Gel vehicle applied topically once daily, lot number 05 173 61 01.

Duration of treatment: 8 weeks

Results of calcium measurements:

The change in serum calcium (total) with respect to the reference range (2.12 - 2.56 mmol/L) is presented in the table below. One patient in the DAIVOBET/DOVOBET gel group (CRF 4126) had a value that was just normal at baseline (2.56 mmol/L) and high at the end of the double-blind phase (2.64 mmol/L) hence the increase was 0.08 mmol/L. In the gel vehicle group, serum calcium (total) was within the reference range for all patients at the end of the double-blind phase.

Change in serum calcium (total) from baseline with respect to reference range: safety analysis set

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| Visit | Baseline category ¹ | DAIVOBET gel (n=128) | | | Gel vehicle (n=38) | | |
|---------------------------------|--------------------------------|-----------------------------|--------|------|-----------------------------|--------|------|
| | | Visit category ² | | | Visit category ² | | |
| | | Low | Normal | High | Low | Normal | High |
| Visit 2 | Baseline low | 1 | 0 | 0 | 0 | 0 | 0 |
| | Baseline normal | 1 | 109 | 2 | 0 | 32 | 0 |
| | Baseline high | 0 | 0 | 0 | 0 | 0 | 1 |
| Visit 3 | Baseline low | 1 | 0 | 0 | 0 | 0 | 0 |
| | Baseline normal | 0 | 109 | 2 | 0 | 33 | 0 |
| | Baseline high | 0 | 0 | 0 | 0 | 1 | 0 |
| End of double-blind phase | Baseline low | 1 | 0 | 0 | 0 | 0 | 0 |
| | Baseline normal | 0 | 122 | 1 | 0 | 35 | 0 |
| | Baseline high | 0 | 0 | 0 | 0 | 1 | 0 |

1) Number of patients with calcium below, within or above the reference range.
2) Calcium at visit 2, visit 3 or end of double blind phase as appropriate.

The change in albumin-corrected serum calcium with respect to the reference range (2.12 to 2.56 mmol/L) is presented in the table below. One patient in the DAIVOBET/DOVOBET gel group (CRF 4126) had an albumin-corrected serum calcium that was normal at baseline (2.50 mmol/L) and high at Visit 3 (week 4) (2.58 mmol/L). Hence the increase was 0.08 mmol/L. This visit 3 value was carried forward to be the value for the end of the double-blind phase. This was the same patient with the high value for serum calcium (total) at the end of the double-blind phase. In the gel vehicle group, albumin-corrected serum calcium was within the reference range for all patients at the end of the double-blind phase.

Change in albumin-corrected serum calcium from baseline with respect to reference range: safety analysis set

**APPEARS THIS WAY
ON ORIGINAL**

| Visit | Baseline category ¹ | DAIVOBET gel (n=128) | | | Gel vehicle (n=38) | | |
|---------------------------|--------------------------------|-----------------------------|--------|------|-----------------------------|--------|------|
| | | Visit category ² | | | Visit category ² | | |
| | | Low | Normal | High | Low | Normal | High |
| Visit 2 | Baseline low | 0 | 3 | 0 | 0 | 0 | 0 |
| | Baseline normal | 3 | 107 | 0 | 0 | 33 | 0 |
| Visit 3 | Baseline low | 0 | 2 | 0 | 0 | 0 | 0 |
| | Baseline normal | 1 | 108 | 1 | 1 | 33 | 0 |
| End of double-blind phase | Baseline low | 0 | 3 | 0 | 0 | 0 | 0 |
| | Baseline normal | 1 | 119 | 1 | 0 | 36 | 0 |

1) Number of patients with albumin-corrected serum calcium within or below the reference range.
2) Albumin-corrected serum calcium at visit 2, visit 3 or end of double blind phase as appropriate.

Absolute Change in serum calcium

The absolute change in serum calcium (total) is presented in the table below. In the DAIVOBET/DOVOBET gel group, the mean change from baseline to end of the double-blind phase was -0.02 mmol/L (range: -0.26 to 0.20), and in the gel vehicle group it was -0.01 mmol/L (range: -0.18 to 0.14).

Absolute change in serum calcium (total) from baseline: safety analysis set

| Visit | DAIVOBET gel (n=128) | Gel vehicle (n=38) |
|----------------------------------|----------------------|--------------------|
| Change in serum calcium (mmol/L) | | |
| Baseline | | |
| Mean | 2.35 | 2.36 |
| SD | 0.10 | 0.09 |
| Median | 2.34 | 2.38 |
| Min | 1.98 | 2.14 |
| Max | 2.56 | 2.60 |
| Number | 126 | 36 |
| Change to Visit 2 | | |
| Mean | -0.01 | -0.01 |
| SD | 0.08 | 0.10 |
| Median | -0.02 | 0.00 |
| Min | -0.20 | -0.20 |

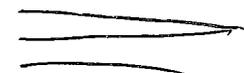
| | | |
|-------------------------------------|-------|-------|
| Max | 0.22 | 0.24 |
| Number | 113 | 33 |
| Change to Visit 3 | | |
| Mean | -0.03 | -0.01 |
| SD | 0.09 | 0.09 |
| Median | -0.02 | 0.00 |
| Min | -0.26 | -0.16 |
| Max | 0.20 | 0.14 |
| Number | 112 | 34 |
| Change to end of double-blind phase | | |
| Mean | -0.02 | -0.01 |
| SD | 0.09 | 0.09 |
| Median | -0.02 | -0.01 |
| Min | -0.26 | -0.18 |
| Max | 0.20 | 0.14 |
| Number | 124 | 36 |

Applicant's Conclusions: There were no changes of clinical significance in the laboratory values.

Reviewer's Comments: This reviewer does not concur with the applicant's conclusions. The results of the albumin corrected serum calcium levels in all 3 studies indicate that some patients did experience some increase in calcium levels, therefore hypercalcemia may develop during the use of Taclonex Scalp gel when used according to the recommended dosing regimen. This finding should be included in the label.

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OCPB Filing form:

| | | | | |
|--|--|--------------------------------|---|----------------------|
| Office of Clinical Pharmacology and Biopharmaceutics <i>New Drug Application Filing and Review Form</i> | | | | |
| General Information about the Submission | | | | |
| | Information | | Information | |
| NDA Number | 22-185 | Brand Name | Taclonex Scalp [®] Gel | |
| OCPB Division (I, II, III) | DCP3 | Generic Name | Calcipotriene hydrate (0.005%=50 mcg/g) and Betamethasone dipropionate (0.05% = 0.5 mg/g) | |
| Medical Division | HFD-540 | Drug Class | Corticosteroid and Synthetic Vitamin D analogue | |
| OCPB Reviewer | Abi Adebowale, Ph.D. | Indication(s) | Treatment of Psoriasis Vulgaris of the Scalp in adults 18 years of age and older. | |
| OCPB Team Leader | Lydia Velazquez, Pharm.D. | Dosage Form | Gel | |
| | | Dosing Regimen | Apply to the affected area of the scalp once daily for up to 8 weeks.  The maximum daily dose should not exceed 100 g. | |
| Date of Submission, Internal Filing Date | June 19 th , 2007 August 27 th , 2007 | Route of Administration | Topical | |
| Estimated Due Date of OCPB Review | February 28th, 2008 | Sponsor | Leo Pharmaceuticals Products | |
| PDUFA Due Date | April 28th, 2008 | Priority Classification | 4S | |
| Clinical Division Due Date | March 2nd, 2008 | IND Number | 67,835 | |
| Clinical Pharmacology and Biopharmaceutics Information | | | | |
| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Study Numbers If any |
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |
| Tabular Listing of All Human Studies | X | | | |
| HPK Summary | X | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | X | | | Report No VR/05/08 |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Studies using other Human Biomaterials | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |

b(4)

| | | | | |
|---|---|---|---|--|
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | X | 1 | | MBL 0404 FR (HPA axis suppression, calcium metabolism and exploratory PK sampling) |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |
| Ethnicity/race: | X | 1 | | MBL 0502 US (measured serum calcium)-Phase 3 Study |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD (HEALTHY OR PATIENTS): | | | | |
| Phase 1 or 2: | | | | |
| Phase 3: | | | | |
| PK/PD (HEALTHY OR PATIENTS): | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | X | 1 | | MBL 0405 INT and MBL 0406 INT (measured serum calcium) |
| Population Analyses - | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability: | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | X | 1 | | MBL 0403 FR (Using the vasoconstrictor assay) |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | | | | |
| Dissolution: | | | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Other (in vitro percutaneous absorption study) | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | X | 5 | 5 | |
| Fileability and QBR comments | | | | |

| | | |
|--|--|--|
| | "X" if yes X | Comments Sent following information request to sponsor on?: Please provide or direct me to the location of the validation report No. VR/05/08 (2) for the quantification of calcipotriol, MC1080, betamethasone dipropionate and betamethasone 17-propionate in serum samples originating from the GCP study: <i>Effect of Dovobet/Daivobet gel on the HPA Axis and Calcium metabolism in Patients with Extensive Scalp Psoriasis</i> . Applicant responded on August 29th, 2007. The assay method was located in module 4 (Pharm/Tox section) as per the response. |
| Application filable ? | X (provided the sponsor commits to submitting the full validation report) | Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? |
| Comments sent to firm? | Yes | Comments have been sent to firm (or attachment included). FDA letter date if applicable. Comments are to be sent to the firm on 08/16/2007. |
| QBR questions (key issues to be considered) | Does betamethasone affect the systemic exposure of calcipotriene and vice versa when used in combination for psoriasis of the scalp? Was there any correlation between the serum concentrations and HPA axis suppression? | |
| Other comments or information not included above | | |
| Primary reviewer Signature and Date | Abi Adebowale 08/15/07 | |
| Secondary reviewer Signature and Date | Lydia Velazquez | |

CC: NDA 22-185, HFD-850 (P.Lee), HFD-540 (M. Bauerlien), DCP3 (L.Velazquez, A.Adebowale, H. Ahn, D. Bashaw)

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

/s/

Abi Adebawale
3/14/2008 11:56:53 AM
BIOPHARMACEUTICS

Lydia Velazquez
3/19/2008 06:25:45 PM
BIOPHARMACEUTICS