



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for calcipotriol and betamethasone (as dipropionate)

Proprietary Product Name: Daivobet 50/500

Sponsor: Leo Pharma Pty Ltd

Date of First Round CER: 30 June 2012

Date of Second Round CER: 30 November 2012

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
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List of abbreviations

Abbreviation	Meaning
ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotrophic hormone
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ANOVA	Analysis of Variance
APC	Antigen presenting cell
AUC _{0-t}	Area under the curve to last measureable concentration
AUC _{0-∞}	Area under the curve to infinity
BSA	Body surface area
CI	Confidence interval
C _{max}	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel test
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
EOT	End of Treatment
EU	European Union
FDA	Food and Drug Administration (USA)
g/gms	grams

Abbreviation	Meaning
GCP	Good Clinical Practice
HPA	Hypothalamic-pituitary-adrenal axis
ICH	International Conference on Harmonisation
IGA	Investigator's Global Assessment of disease severity
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MUSE	Maximum use systemic exposure
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PGA	Patient's Global Assessment of disease severity
PK	Pharmacokinetic
PI	Product Information
PTH	Parathyroid hormone
PUVA	Psoralen plus Ultraviolet light A
RDC	Remote Data Capture
SAE	Serious Adverse Event
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCS	Total Clinical Score
T _{max}	Time to maximum plasma concentration
T _½	Apparent elimination half-life
UVA	Ultraviolet light A
UVB	Ultraviolet light B

Abbreviation	Meaning
VAS	Visual Analogue Scale
WHO	World Health Organisation

Definitions

Skin type

The skin type of the subjects was recorded using the following classification:

Skin Type	Skin Colour (unexposed skin)	History -(to first 30 to 45 minutes of sun exposure after a winter season of no sun exposure)
I	White	Always burns easily; never tans
II	White	Always burns easily; tans minimally
III	White	Burns moderately; tans gradually (light brown)
IV	White	Burns minimally; always tans well (moderate brown)
V	Brown	Rarely burns; tans profusely (dark brown)
VI	Black	Never burns, deeply pigmented

Investigator's Global Assessment of disease severity (IGA)

This assessment represents the **average** lesion severity on the trunk, arm and legs. The assessment is based on the condition of the disease at the time of evaluation, and not in relation to the condition at the previous visit.

There was a slight difference between the scales used in the pivotal studies (LEO80185-G23 and LEO80185-G21) and the supportive comparative study (MBL0202INT). For the purposes of the pooled-analysis these were considered comparable.

Term	Description
Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling LEO80185-G23: Erythema = none (no residual red colouration but post-inflammatory hyperpigmentation may be present)

Term	Description
	LEO80185-G21: Erythema = none or hyperpigmentation or residual red colouration. MBL0202INT: Erythema = none or slight (hyperpigmentation or residual red colouration)
Almost clear	Plaque thickening = none or possible thickening but difficult to ascertain whether there is a slight elevation above normal skin level Scaling = none or residual surface dryness and scaling Erythema = light pink colouration MBL0202INT: Erythema: up to mild (up to light red or pink colouration)
Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions Erythema = light red colouration MBL0202INT: Erythema = up to moderate (up to definite red colouration)
Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red colouration
Severe	Plaque thickening = marked elevation typically with hard or sharp edges Scaling = non-tenacious scale predominates, covering most or all of the lesions Erythema = very bright red colouration
Very severe	Plaque thickening = very marked elevation typically with hard or sharp edges Scaling = thick tenacious scale covers most or all of the lesions Erythema = extreme red colouration; deep red colouration

'Controlled disease' = 'clear' or 'almost clear' according to IGA.

Psoriasis Area and Severity Index (PASI)

PASI is based on the investigator's assessment of extent (E) and severity of the disease locally (on trunk, arms and legs) in terms of three clinical signs: redness (R), thickness (T) and scaliness (S). The subject was scored for each of the three areas: arms, trunk and legs and calculated using the following formula:

Arms 0.2 (R + T + S)E = X

Trunk 0.3 (R + T + S)E = Y

Legs 0.4 (R + T + S)E = Z

The sum of X + Y + Z gives the total PASI which can range from 0 to 64.8. The PASI used in both pivotal studies was modified to exclude assessment of the head, as study treatment was not used here.

There was a minor difference between the studies in that the buttocks were to be included as part of the legs in the pivotal studies (LEO80185-G23 and LEO80185-G21) but as part of the trunk in the supportive comparative study (MBL0202INT).

Modified PASI Scale (excluding scalp, face and flexures)

Extent
0 = non involvement
1 = <10%
2 = 10-29%
3 = 30-49%
4 = 50-69%
5 = 70-89%
6 = 90-100%

Severity		
Redness	Thickness	Scaliness
0 = none (no erythema)	0 = none (no plaque elevation)	0 = none (no scaling)
1 = mild (faint erythema, pink to very light red)	1 = mild (slight, barely perceptible elevation)	1 = mild (sparse, fine scale lesions, only partially covered)
2 = moderate (definite light red erythema)	2 = moderate (definite elevation but not thick)	2 = moderate (coarser scales, most of lesions covered)
3 = severe (dark red erythema)	3 = severe (definite elevation, thick plaque with sharp edge)	3 = severe (entire lesion covered with coarse scales)
4 = very severe (very dark red erythema)	4 = very severe (very thick plaque with sharp edge)	4 = very severe (very thick coarse scales, possibly)

Severity		
Redness	Thickness	Scaliness
		fissured)

In study MBL0202INT the wording of the severity of the signs of redness, thickness and scaliness was slightly different to that used in the pivotal studies (LEO80185-G23 and LEO80185-G21) but was considered equivalent to those above:

0 = absent

1 = slight

2 = moderate

3 = severe

4 = severest possible

Investigator's assessment of body surface area (BSA) involvement of extent of disease at baseline

The total psoriatic involvement on the arms, legs and trunk was recorded as a percentage of the total body surface area (BSA), estimating that the surface of the full, flat palm (including the five digits) correlates to approximately 1% of the total BSA. The purpose was to obtain an estimate of the total area to be treated with study medication.

Patient's global assessment of disease severity (PGA)

The subject's assessment was made prior to the investigator assessments.

Clear	No psoriasis symptoms at all
Very mild	Very slight psoriasis symptoms, does not interfere with daily life
Mild	Slight psoriasis symptoms, interferes with daily life only occasionally
Moderate	Definite psoriasis symptoms, interferes with daily life frequently
Severe	Intense psoriasis symptoms, interferes or restricts daily life very frequently

Patient's assessment of plaque discomfort

This assessment was based on the condition of the disease at the time of evaluation and used a visual analogue scale. This assessment was made prior to the IGA and used the subject's mark on an arbitrary scale of 0=100 graduated in 10 unit intervals.

Quality of life assessment

The scale used for this assessment was the Dermatology Life Quality Index (DLQI) which is a validated dermatology specific questionnaire.

Total clinical score (Study PLQ-001)

All assessments for a subject were to be made by the same investigator. The severity of the symptoms was rated on Day 1 (baseline), 4, 8, 11, 15, 18, 22 (end of treatment) according to the following 0-3 with half point grading scale.

Score	Intensity	Erythema Description	Scaling Description	Infiltration Description
0	No evidence	Normal skin colour	No scaling	
0.5	Doubtful or very mild			
1.0	Mild	Pink or light red	Slight roughness, mainly fine scales	Slight definite infiltration
1.5	Mild to moderate			
2.0	Moderate	Red	Coarse scaling	Moderate infiltration
2.5	Moderate to severe			
3.0	Severe	Intense red	Coarse, thick scales	Very marked Infiltration

The Total Clinical Score was defined as the sum of erythema plus scaling plus thickness scores and therefore ranges from 0 (all symptoms absent) to 9 (all symptoms severe).

1. Clinical rationale

Calcipotriol and betamethasone have been used by dermatologists in combination for the treatment of psoriasis vulgaris. The development of the Daivobet ointment provided a fixed dose combination which has been approved for the treatment of non-scalp psoriasis vulgaris. It has been shown that the betamethasone dipropionate counteracts the local skin irritation that calcipotriol exhibits in some subjects, thereby allowing calcipotriol to exert its beneficial effects. Calcipotriol may also reduce the amount of corticosteroid required due to a positive additive effect and thus reduce the risk of steroid-related adverse effects. The previous clinical development program for Daivobet ointment is said to have demonstrated an additive/synergistic effect on the trunk and limbs, while the safety profile is similar or better than the single constituents given alone.

The cosmetic properties of a formulation are important for patient acceptability and greasy ointments can be a barrier to patient compliance leading to a disappointing clinical effect. Since compliance remains a critical factor in achieving effective treatment of psoriasis, patient preferences regarding agents and vehicles are an integral part of therapy selection. Daivobet gel was developed to complement Daivobet ointment. Daivobet gel contains the same active components as Daivobet ointment but in a gel vehicle that has the advantages of the combination treatment while allowing once daily application with a cosmetically acceptable formulation. The gel formulation was originally developed for use on the scalp but its physical properties also make it a suitable alternative treatment for psoriasis lesions on non-scalp areas of the body. The favourable cosmetic properties of a non-greasy gel may improve patient

compliance. Thus the objective of the clinical development program was to demonstrate sufficient evidence to include the treatment of psoriasis vulgaris on non-scalp areas of the body.

1.1. Guidance

The TGA has adopted the following EU Guideline with amendment: "Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis. (CHMP/EWP/2454/02)". This guideline became effective in Europe in June 2004 and in Australia in July 2005.

The key points of this guideline are:

- There are no validated diagnostic criteria for psoriasis, the diagnosis being clinical and histological confirmation not necessary.
- In previously treated patients a washout period is necessary to avoid unnecessary rebound of psoriasis.
- Inter-individual comparison with parallel groups is the recommended study design.
- A duration of 8 to 12 weeks is generally sufficient to show short term efficacy with specified assessments at a minimum of 0, 4, 8 and 12 weeks.
- A least one confirmatory trial should include an observation period of at least 2 months in order to explore the duration of remission/response, rebound and time to relapse.
- Psoriasis is a seasonal, chronic relapsing disease and so one-year intermittent or prolonged use is recommended.
- Body surface area (BSA) affected by psoriasis and Psoriasis Area and Severity Index (PASI) scores are recommended methods to assess psoriasis severity. Physician global assessment (PGA) of psoriasis severity is also used. Training of investigators prior to study start may decrease inter-observer variability.
- PASI alone is not sufficient to evaluate psoriasis severity at baseline and on treatment. It is recommended to use at least 2 endpoints to assess efficacy: a validated, standardised global scale (eg PGA) in conjunction with PASI.
- The best evidence of efficacy is the percentage of patients who achieve the result of "clear or almost clear" (PASI >90%) on treatment.
- >50% and >75% improvements compared to baseline have been considered as clinically meaningful. Clear or almost clear has been defined as an improvement of PASI >90%.
- A reduction in the PASI score <50% is currently not considered as an acceptable demonstration of treatment response.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The clinical dossier documented a development program of pharmacodynamic, pivotal and other clinical trials relating to the proposed extension of indication.

The submission contained the following clinical information:

Module 5:

- 1 x clinical pharmacology study (LE080185-G24), which aimed to provide pharmacodynamic and pharmacokinetic data
- 2 x pivotal comparative efficacy/safety studies (LE080185-G23 and LE080185-G21)
- 2 x other efficacy/safety studies (MBL0202INT and PLQ-001)
- 3 x PSURs, Integrated Summary of Efficacy (which was identical to the Module 2 Summary of Clinical Efficacy), Integrated Summary of Safety (which was identical to the Module 2 Summary of Clinical Safety)

Module 1:

Application letter, application form, draft Australian PI and CMI, FDA-proposed product label, European Summary of Product Characteristics as approved in the Netherlands, Sweden and the UK and Pre-Submission Details. No Risk Management Plan was included. No explanation is given for its absence.

Module 2:

Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

The clinical studies were conducted in the USA, EU and Canada. All studies were conducted in accordance with Good Clinical Practice and with the principles of the Declaration of Helsinki as adopted in 1964 and subsequent amendments and with national regulatory requirements. The protocols were reviewed by institutional or independent ethics committees and all patients signed written informed consent prior to study participation.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

No pharmacokinetic (PK) data was provided in the submission.

One study (LE080185-G24) aimed to collect PK data but none of the PK parameters could be calculated because only a minority of patients had values above the lower detection limit. This study also collected PD data.

3.2. Evaluator's overall conclusions on pharmacokinetics

No information is provided on the dose selection or how the gel is applied to the skin (eg thickness). No information is provided on drug interactions – reference is made to the previously approved ointment formulation.

No information is provided in the study reports on how or when the patients applied the cream. The study protocols only provided the information – “To be applied once daily on psoriasis vulgaris lesions on the trunk, arms and legs”. There were no specific instructions as to time of day for dosing.

The instructions to the patients outlined in the protocols are similar for the clinical trials (eg, LE080185-G23).

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

The table below shows the studies relating to each pharmacodynamic (PD) topic. Only one new pharmacodynamic study was included in this submission.

Table 1. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	Primary Aim of Study
Primary Pharmacology	Effect on HPA axis and calcium metabolism	LEO80185-G24	HPA suppression
Secondary Pharmacology		No Study	
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	No Study	
	Effect of age	No Study	
PD Interactions		No Study	
Population PD and PK-PD analyses	Healthy subjects	No Study	
	Target§ population	No Study	

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

The pharmacodynamic study did not have deficiencies that excluded its results from consideration.

4.2. Summary of pharmacodynamics

The information in the following summary is derived from one conventional pharmacodynamic study in humans. The Module 2 summaries do not provide even an overview of the pharmacokinetics or pharmacodynamics of the combination gel. The individual study reports provide brief information on the pharmacodynamics of the individual components of the product.

Calcipotriol

Calcipotriol is a Vitamin D analogue which acts to reverse the signs and symptoms associated with psoriasis due to its main effects of inhibition of cell proliferation, stimulation of cell proliferation, stimulation of cell differentiation and regulation of inflammatory response.

Overdosage with calcipotriol can cause systemic side effects in the form of hypercalcaemia, attributable to the effects of Vitamin D analogues on the calcium metabolism.

Betamethasone dipropionate

Betamethasone dipropionate is a synthetic fluorinated corticosteroid classified as a potent (WHO Group III) steroid. It has been available worldwide for many years for the treatment of various dermatological disorders including psoriasis vulgaris. Like other corticosteroids it exerts its effect by suppressing various components of the inflammatory reaction of the disease. Betamethasone dipropionate has been shown to have metabolic and toxicological effects typical for corticosteroids. Adverse events with topical corticosteroids are generally local and include itching, skin atrophy, and striae of the skin. Excessive and prolonged use may result in suppression of the hypothalamic-pituitary-adrenal (HPA) axis which is generally reversible.

Calcipotriol / Betamethasone dipropionate Combination product

Using calcipotriol and betamethasone dipropionate in combination as an ointment has been shown to result in an additive effect in the treatment of psoriasis vulgaris on the trunk and limbs. By simultaneous use of the two active components it is expected that betamethasone dipropionate could counteract the local skin irritation that calcipotriol exhibits in some subjects, thereby allowing calcipotriol to exert its beneficial effects. On the other hand calcipotriol may reduce the amount of corticosteroid required due to a possible additive effect and thus reduce the risk of steroid-related adverse effects. Combining the two compounds in a gel vehicle with favourable cosmetic properties might improve subject compliance resulting in a better treatment response.

Study LE080185-G24 was a multicentre, prospective, non-controlled, open, 8 week study in subjects with extensive psoriasis covering 15-30% of the total BSA (excluding psoriasis on the face, genitals and skin folds). The primary objective was to evaluate the effect of once daily use of Daivobet gel on the HPA axis and calcium metabolism. Subjects left the study after the 4 week period at Day 28 if the psoriasis on the body was judged as 'clear' according to the investigator's global assessment of disease severity (IGA). Subjects who had psoriasis lesions remaining continued treatment for another 4 week period. Adrenal function was determined by measuring serum cortisol before and at 30 and 60 minutes after stimulation by a rapid standard dose adrenocorticotrophic hormone (ACTH) (Cortrosyn) challenge test. The ACTH tests were performed within 7 days of baseline and after 4 and 8 weeks of treatment (Days 28 and 56). If the cortisol level at 30 days after ACTH stimulation was $\leq 18 \mu\text{g/dL}$, the subject was withdrawn from treatment and the test was repeated 28 days after treatment was stopped. Evaluation of calcium metabolism was performed after 3 days of an individual standardised calcium diet at baseline and at Day 28 and 56.

A total of 43 subjects received treatment (mean age 46 years, 77% male, 84% white, 65% 'moderate and 35% severe disease severity with psoriatic lesions on mean 21% BSA). The average weekly use of Daivobet gel ranged from 7.64 to 92.95 g with a mean amount of 52.27 g.

Three (7%) subjects had a serum cortisol $\leq 18 \mu\text{g/dL}$ 30 minutes after the ACTH stimulation test at Day 28. None of the subjects who continued to Day 56 had a 30 minutes serum cortisol $\leq 18 \mu\text{g/dL}$. Of the three subjects 2 were considered to show signs of adrenal suppression – one was considered borderline and the other had clear signs of adrenal suppression. This subject also showed signs of a possibly clinically relevant increase in 24 hour urinary excretions but calcipotriol and its main metabolites were below the lower limit of quantification (LLOQ) in the PK samples. There were no clinically relevant mean changes in albumin-corrected serum calcium, 24 hour urine calcium excretion or the urine calcium:creatinine ratio. No subject had albumin-corrected serum calcium values above the reference range at any visit. Two subjects were identified with a possibly clinically relevant increase in 24 hour urine calcium excretion. Calcipotriol and its metabolite (MC1080) were not detected in any of the PK samples from these subjects.

4.2.1. Evaluator's overall conclusions on pharmacodynamics

No new data is presented on the pharmacodynamics of the product. No summary of the pharmacodynamics is provided in the submission.

Study LE080185-G24 was a small study which assessed the effect of Daivobet gel on HPA axis suppression and calcium metabolism in patients with moderate to severe psoriasis. HPA axis suppression was seen in approx 3/43 (7%) of subjects. Another study (MBL0404FR evaluated in a previous submission) in which patients used Daivobet gel on the scalp and Daivobet ointment on the body showed that 5 of 32 (15.6%) patients had serum cortisol $\leq 18 \mu\text{g/dL}$ (all five had values $> 17 \mu\text{g/dL}$) 30 minutes after ACTH challenge at Week 4. Two of the 11 (18.2%) patients who continued to Week 8 had serum cortisol $\leq 18 \mu\text{g/dL}$ at 30 minutes. All patients had

serum cortisol >18 µg/dL at 60 minutes both at Weeks 4 and 8. The results of the new study appear consistent with the previous study.

5. Dosage selection for the pivotal studies

No explanation is provided as to the dose selection for the clinical studies.

The justification for the dose given in the protocols is: "A once daily treatment regimen has been chosen as this is considered more convenient for the subject and has been shown to be effective in previous studies. It decreases drug exposure and time spent on application and thus, probably enhances subject compliance."

6. Clinical efficacy

6.1. Indication: Psoriasis of the body (non-scalp)

6.1.1. Pivotal efficacy studies

Comment: In the pooled analysis (see section on *Analyses performed across trials (pooled analyses and meta-analyses*, below) the company has included all the comparative studies (LEO80185-G23, LEO80185-G21 and MBL0202INT) but in the report of the pooled analysis only study LEO80185-G23 is called a "pivotal" study. No explanation is provided for not considering study LEO80185-G21 a pivotal study. While the active comparator drug (tacalcitol) is not approved in Australia the study does provide comparison to the gel vehicle and is therefore included here as a pivotal study.

Study MBL0202INT was previously submitted as a supportive study in the application for treatment of psoriasis of the scalp presumably to provide safety data. It is summarised here to include the efficacy data.

6.1.1.1. Study LEO80185-G23

Calipotriol plus Betamethasone Dipropionate Topical Suspension Compared to Betamethasone Dipropionate in the Topical Suspension Vehicle, Calcipotriol in the Topical Suspension Vehicle and the Topical Suspension Vehicle Alone in Psoriasis Vulgaris.

6.1.1.1.1. Study design, objectives, locations and dates

Primary Objective: to compare the efficacy of once daily treatment for up to 8 weeks of Daivobet gel with betamethasone gel, calcipotriol gel and the gel vehicle alone in subjects with psoriasis vulgaris on the non-scalp regions of the body (trunk and/or limbs).

Secondary objective: to compare the safety of Daivobet gel with betamethasone gel, calcipotriol gel and gel vehicle alone in subjects with psoriasis vulgaris on the non-scalp regions of the body (trunk and/or limbs).

Study Design: The study was a multicentre, prospective, randomised, double-blind, 4-arm, parallel group, 8 week study conducted in 59 centres in the USA from September 2010 to March 2011.

The study consisted of 3 phases:

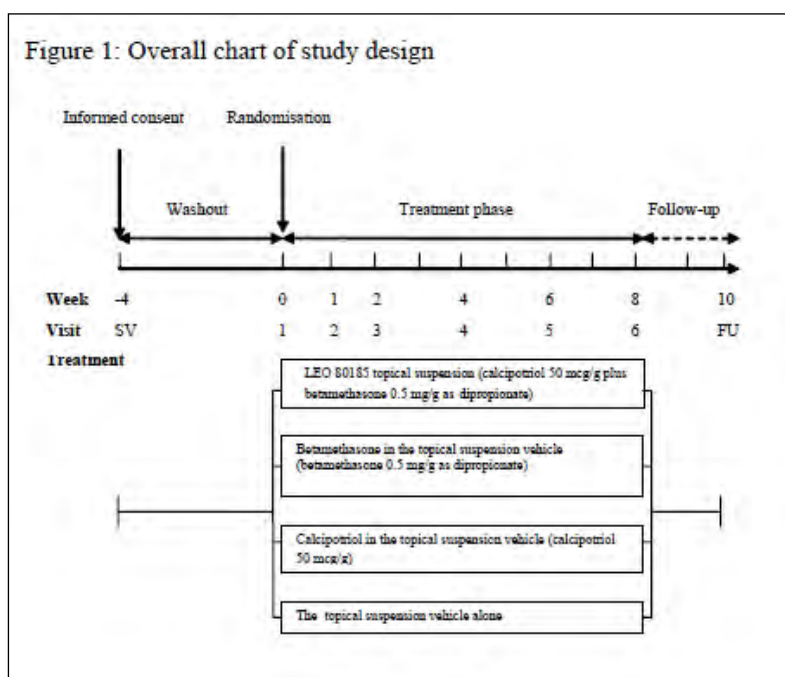
Washout phase: prior to randomisation the subject entered a washout phase (if required) where anti-psoriatic treatments and other relevant medication were discontinued as defined by the exclusion criteria. The washout was limited to a maximum of 4 weeks depending on which treatment the subject was receiving.

Treatment phase: The treatment phase started on Day 0 (Visit 1, baseline) when the subject was randomised to one of four treatment groups. The treatment period was 56 days (8 weeks) and included 6 visits: Day 0, 7 (± 2), 14 (± 2), 28 (± 2), 42 (± 2), and 56 (± 2) (Visits 1-6).

Subjects classified as 'clear' according to the IGA at any of the Visits 2-5 were allowed to stop treatment at the (sub)investigator's discretion. The subjects remained in the study and attended all scheduled visits. Investigational product was dispensed and subjects were advised to reinstate treatment if required based on the subject's own judgement, due to reappearance of psoriasis vulgaris on the treatment areas. More than one discontinuation/restart was allowed. The subject was not allowed to discontinue treatment themselves between study visits. Study treatment was only stopped on the advice of the (sub)investigator at a scheduled visit.

Follow-up phase: a follow-up phase took place if there was an ongoing serious or non-serious AE at the last on-treatment visit. The follow-up visit occurred 14 (± 2) days after the last on-treatment visit.

Figure 1. Study LE080185-G23 Overview of study design



6.1.1.1.2. Inclusion and exclusion criteria

Inclusion:

- Patients aged 18 years or above, of either sex, with a clinical diagnosis of stable plaque psoriasis vulgaris of at least 6 months duration involving the non-scalp regions of the body (trunk and/or limbs) amenable to treatment with a maximum of 100 g of topical medication per week. The trunk and limbs included the arms (including hands), and/or trunk (including neck) and/or the legs (including buttocks and feet). The scalp, face, flexures and genitals were not treated with the investigation product or assessed as part of the efficacy analysis.
- An IGA of mild or moderate on the body (trunk and/or limbs) at Day 0 (Visit 1)
- A minimum modified PASI score for extent of 2 in at least one body region (ie psoriasis affecting at least 10% of arms, and/or 10% of trunk, and/or 10% of legs).
- Females of childbearing potential had to have a negative pregnancy test at Day 0 and agree to use a highly effective method of birth control (implants, injectables, combined oral contraceptives, IUCD, sexual abstinence or vasectomised partner) during the study.

Exclusion:

- Recent treatment with biologics other than etanercept that required more than a 4 week washout period
- Systemic treatment with biological therapies with a possible effect on psoriasis vulgaris with the following time periods prior to randomisation:
 - Etanercept – within 4 weeks prior to randomisation
 - Adalimumab, alefacept, infliximab – within 2 months prior to randomisation
 - Ustekinumab – within 4 weeks prior to randomisation
- Experimental products – within 4 weeks / 5 half-lives (whichever is longer) prior to randomisation
- Systemic treatment with all other therapies with a possible effect on psoriasis vulgaris (eg corticosteroids, retinoids, methotrexate, cyclosporin and other immunosuppressives) within 4 weeks of randomisation
- PUVA or Grenz ray therapy within 4 weeks prior to randomisation
- UVB therapy within 2 weeks prior to randomisation
- Any topical treatment of the trunk and/or limbs (except for emollients) within 2 weeks prior to randomisation
- Topical treatment for other relevant skin disorders on the face and flexures (eg facial and flexural psoriasis, eczema) with class 1-5 corticosteroids or Vitamin D analogues within 2 weeks prior to randomisation
- Planned initiation of, or changes to, concomitant medication that could affect psoriasis vulgaris (eg beta blockers, anti-malarials, lithium, ACE inhibitors) during the study
- Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis
- Presence of any of the following conditions present on the treatment area: viral (herpes or varicella) lesions of the skin, fungal and bacterial skin infections, rosacea, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, ulcers and wounds
- Known or suspected disorders of calcium metabolism associated with hypercalcaemia
- Known or suspected severe renal insufficiency or severe hepatic disorders.
- Planned excessive exposure to the sun during the study that could affect the psoriasis vulgaris

6.1.1.1.3. Study treatments

Subjects were randomised to receive one the following treatments:

- Daivobet gel (calcipotriol 50 µg/g plus betamethasone 0.5 mg/g as dipropionate)
- Betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle
- Calcipotriol 50 µg/g in the gel vehicle
- The gel vehicle alone

No details of dosing are provided other than the treatments were applied topically once daily for 8 weeks.

The following concomitant therapies were allowed during the study:

- Inhaled steroids, bath oils and moisturising soaps
- Unlimited use of emollients for face, flexures (skin folds) and scalp
- All topical medications for face, flexures and scalp except Class 1 to 5 corticosteroids, vitamin D analogues and prescription shampoos for the scalp.

No information is provided in study report on how treatment is to be applied. The study protocol contains directions on use for the patient. This states that the patient should not use more than 100 g (2 bottles) per week. The treatment directions from the protocol are included in the dossier.

6.1.1.1.4. *Efficacy variables and outcomes*

Primary efficacy outcome: the percentage of patients with ‘controlled disease’ according to the Investigator’s Global Assessment (IGA) at Weeks 4 and 8 (both LOCF). [See Definitions for details of scoring scales].

‘Controlled disease’ is defined as ‘clear’ or ‘almost clear’ for subjects with moderate disease at baseline and ‘clear’ for subjects with mild disease at baseline.

The primary analysis was to test for superiority of Daivobet gel versus betamethasone gel, calcipotriol gel and the gel vehicle using the full analysis set (ITT). To be considered superior, all three tests had to be statistically significant.

Other efficacy outcomes included:

The percentage change in PASI from baseline to Week 4 and Week 8

- The percentage of subjects who achieved ‘controlled disease’ according to the IGA at Weeks 1, 2, 4, 6 and 8 by treatment group
- The percentage of subjects at each visit who achieved at least 75% reduction in PASI from baseline
- The percentage of subjects at each visit who achieved at least 50% reduction in PASI from baseline
- The percentage of subjects who achieved ‘controlled disease’ according to the patient’s global assessment of disease severity at Week 1, 2, 4, 6 and 8 by treatment group
- The change in discomfort score (actual) from baseline to each visit

6.1.1.1.5. *Randomisation and blinding methods*

Eligible subjects were randomised, using a central Interactive Web Response System (IWRS) to receive one daily treatment for up to 8 weeks. The IWRS system stratified the randomisation of subjects according to baseline disease severity (mild:moderate) as determined by the IGA. Randomisation of treatment arms took place in a 5:5:1:1 ratio within each stratum of baseline disease severity.

The study was double-blinded as the packaging and labelling of the investigational products contained no evidence of their identity.

6.1.1.1.6. *Analysis populations*

All randomised subjects were included in the full analysis set (intention to treat (ITT) analysis set) and analysed for efficacy.

All subjects who received any treatment with trial medication and for whom the presence or confirmed absence of AEs was available were included in the safety analysis set and analysed for safety.

The per protocol analysis set was defined by excluding subjects from the full analysis set who received no treatment with trial medication, who provided no efficacy data following start of treatment, who were known to have taken the wrong trial medication throughout the treatment phase of the trial and/or who did not fulfil the disease defining inclusion criteria.

6.1.1.1.7. *Sample size*

The sample size calculation was based on the following assumptions: the subjects having 'controlled disease' at Week 8 according to the IGA was approximately 30% in the Daivobet gel group, 20% in the betamethasone gel group, 13% in the calcipotriol gel group and 0% in the group treated with gel vehicle alone for subjects with mild or moderate disease severity at baseline. The assumptions were 20%, 10%, 4.5% and 3% respectively at Week 4. These estimates were taken from the results of a Phase 2 study (study report not included in submission but publication provided). A further assumption was that the ratio of mild:moderate (IGA) was approximately 1:3.

Based on these assumptions, with 480 subjects in the Daivobet gel group as well as the betamethasone gel group, Fisher's Exact Test would have 90% power to reject the null hypothesis of no difference between the two treatment groups regarding the primary response criterion of subjects with 'controlled disease' according to the IGA at Week 8 and more than 90% power for the endpoint of Week 4. With 480 subjects in the Daivobet gel and betamethasone groups the sample size of the calcipotriol and the vehicle groups was fixed at 96. The test of no difference between the Daivobet gel and the calcipotriol groups in the primary response criterion has a power of at least 89%.

Each centre was to recruit a minimum of 12 subjects and no centres were allowed to recruit more than 100 subjects (approximately 10% of the total sample size).

6.1.1.1.8. *Statistical methods*

The primary efficacy response was analysed for the full analysis set and the per protocol analysis set. The analysis of the primary response criteria consisted of testing the defined hypotheses at each time point (Week 4 and 8) using the Hochberg correction to control for multiplicity in terms of testing primary response criteria. The percentage of subjects who achieved 'controlled disease' according to the IGA at Week 4 and 8 (both LOCF) were compared between Daivobet gel and each of the other 3 treatments using the Cochran-Mantel-Haenszel test adjusting for the effect of (pooled) centre. The Cochran-Mantel-Haenszel adjusted odds ratio (odds of 'controlled disease' for Daivobet gel relative to that for betamethasone, calcipotriol and vehicle gel), corresponding to 95% CI and p values were calculated. The Breslow-Day test for homogeneity of the odds ratio across (pooled) centres was performed at a 10% level; if significant, a sensitivity analysis omitting centres with the smallest and highest odds ratios respectively was performed to identify possible extreme centres.

The percentage of subjects who achieved 'controlled disease' at Weeks 4 and 8 were tabulated by treatment group, by age groups, sex, ethnicity, race and baseline disease severity according to the IGA. The number and percentage of subjects in each of the six categories (clear to very severe) was tabulated for each of the treatments pooling all centres together. These tabulations were intended for descriptive purposes only and no statistical analysis of these data was undertaken.

The percentage change in PASI from baseline to Week 4 and 8 were expected to be approximately normally distributed. Thus the treatment groups were compared using analysis of variance (ANOVA) including centre, baseline disease severity and treatment in the model as design variables. The presence of a treatment by centre interaction was tested but not included in the model. For each of the treatment comparisons, the difference (Daivobet gel – betamethasone / calcipotriol / vehicle gel), its 95% CI and a p value were calculated from the ANOVA.

The percentage of subjects who achieved 'controlled disease' according to the IGA and PGA were tabulated at Weeks 1, 2, 4, 6 and 8 by treatment group, pooling all centres together.

The change in PASI scores (actual and percentage) and patients assessment of plaque discomfort from baseline to each visit was summarised as mean, median, SD, minimum and maximum for each of the treatments pooling all centres.

All significance tests were two-sided. All efficacy data was tabulated by visit using an observed cases approach (ie involving only those subjects who attended each specific visit). Last observation carried forward (LOCF) data at relevant visits was used for efficacy data that was statistically analysed (using the last non-missing value for subjects with missing data at a particular visit). As a supplement to the LOCF handling of missing data for the primary efficacy criterion, three sensitivity analyses were to be carried out: 1) all missing set to 'controlled disease', 2) all missing set to 'non-controlled disease' and 3) all missing in the Daivobet gel treatment group set to 'non-controlled disease' and in the other treatment groups set to 'controlled disease'.

6.1.1.1.9. Participant flow

Enrolled = 1423

- 271 did not meet inclusion and/or exclusion criteria

Randomised = 1152

- Daivobet gel = 482
- Betamethasone gel = 479
- Calcipotriol gel = 96
- Gel vehicle = 95

Completed study (Week 8) = 1020

- Daivobet gel = 444
- Betamethasone gel = 417
- Calcipotriol gel = 82
- Gel vehicle = 77

ITT analysis set = 1152

Per protocol analysis set = 1111

Safety analysis set = 1152

Additional details of reasons for withdrawals are provided in the dossier.

6.1.1.1.10. Major protocol violations/deviations

There were no major protocol violations/deviations. The most common protocol deviation (67 subjects) was failure to meet the visit window (± 2 days) which resulted in the exclusion of some data from a similar percentage of subjects in all the treatment groups.

6.1.1.1.11. Baseline data

Table 2. Study LE080185-G23 Baseline data

	All randomised subjects (n=1152)	Daivobet gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Vehicle (n=95)
Age (years)					
Mean	48.6	48.7	48.5	48.0	49.4
SD	13.5	13.4	13.8	13.7	13.0
Median	49.0	49.0	50.0	48.0	49.0
Minimum	18	18	19	18	22
Maximum	88	82	88	82	76
Sex (No, %)					
Male	690 (59.9)	284 (58.9)	286 (59.7)	60 (62.5)	60 (63.2)
Female	462 (40.1)	198 (41.1)	193 (40.3)	36 (37.5)	35 (36.8)
Race					
White	1027 (89.1)	435 (90.2)	425 (88.7)	83 (86.5)	84 (88.4)
Black or African American	71 (6.2)	27 (5.6)	28 (5.8)	9 (9.4)	7 (7.4)
Asian	30 (2.6)	11 (2.3)	15 (3.1)	1 (1.0)	3 (3.2)
American Indian or Alaska Native	4 (0.3)	2 (0.4)	1 (0.2)	1 (1.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	4 (0.3)	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
Other	16 (1.4)	5 (1.0)	8 (1.7)	2 (2.1)	1 (1.1)
Ethnicity					
Hispanic or Latino	169 (14.7)	69 (14.3)	64 (13.4)	20 (20.8)	16 (16.8)
Not Hispanic or Latino	983 (85.3)	413 (85.7)	415 (86.6)	76 (79.2)	79 (83.2)

	All randomised subjects (n=1152)	Daivobet gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Vehicle (n=95)
Total	1152 (100.0)	482 (100.0)	479 (100.0)	96 (100.0)	95 (100.0)
Skin type					
I	66 (5.7)	30 (6.2)	20 (4.2)	10 (10.4)	6 (6.3)
II	319 (27.7)	134 (27.8)	148 (30.9)	19 (19.8)	18 (18.9)
III	369 (32.0)	158 (32.8)	144 (30.1)	30 (31.3)	37 (38.9)
IV	268 (23.3)	109 (22.6)	117 (24.4)	21 (21.9)	21 (22.1)
V	82 (7.1)	33 (6.8)	29 (6.1)	13 (13.5)	7 (7.4)
VI	48 (4.2)	18 (3.7)	21 (4.4)	3 (3.1)	6 (6.3)
Duration of Psoriasis					
Mean	16.8	17.8	15.8	15.9	17.8
SD	13.1	13.3	12.5	13.3	14.4
Median	14.0	15.0	12.0	10.5	13.0
Minimum	1	1	1	1	1
Maximum	71	71	63	56	60
IGA at baseline					
Mild	253 (22.0)	107 (22.2)	105 (21.9)	20 (20.8)	21 (22.1)
Moderate	899 (78.0)	375 (77.8)	374 (78.1)	76 (79.2)	74 (77.9)
PSAI at baseline					
Mean	7.9	7.9	7.8	8.5	7.8
SD	3.5	3.4	3.7	3.5	2.9
Median	7.2	7.2	7.2	7.9	7.6
Minimum	1	1	1	2	2
Maximum	28	26	28	20	16
BSA at baseline					

	All randomised subjects (n=1152)	Daivobet gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Vehicle (n=95)
Mean	12.2	12.3	12.2	12.6	11.1
SD	10.8	10.4	11.9	9.9	7.4
Median	10.0	10.0	10.0	10.0	9.0
Minimum	1	2	2	1	2
Maximum	90	90	84	60	40

The groups were also balanced for weight, height and blood pressure at baseline.

6.1.1.1.12. Results for the primary efficacy outcome

Only results for ITT (full analysis set) are provided. Per protocol analysis was similar for all parameters

Table 3. Study LE080185-G23 Percentage of patients with 'controlled disease' at Week 4 and 8

	Daivobet gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Vehicle (n=95)
Week 4				
Controlled Disease	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)
Controlled	64 (13.3)	60 (12.5)	5 (5.2)	2 (2.1)
Non-controlled	418 (86.7)	419 (87.5)	91 (94.8)	93 (97.9)
Total	482 (100.0)	479 (100.0)	96 (100.0)	95 (100.0)
Statistical analysis				
Difference (%)		0.8	8.1	11.2
95% CI		-3.5 to 5.0	2.7 to 13.4	7.0 to 15.4
Odds ratio ¹		1.0	3.0	8.4
95% CI		0.7 to 1.5	1.1 to 7.6	1.9 to 37.1
CMH test p-value ²		0.82	0.019	0.001
Breslow-Day test p-value ³		0.65	0.43	0.96
Week 8				

	Daivobet gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Vehicle (n=95)
Controlled	140 (29.0)	103 (21.5)	14 (14.6)	6 (6.3)
Non-controlled	342 (71.0)	376 (78.5)	82 (85.4)	89 (93.7)
Total	482 (100.0)	479 (100.0)	96 (100.0)	95 (100.0)
Statistical analysis				
Difference (%)		7.5	14.5	22.7
95% CI		2.1 to 13.0	6.3 to 22.6	16.4 to 29.1
Odds ratio ¹		1.5	2.8	7.5
95% CI		1.1 to 2.0	1.5 to 5.3	3.0 to 18.8
CMH test p-value ²		0.008	0.002	<0.001
Breslow-Day test p-value ³		0.56	0.94	0.98

1) Cochran-Mantel-Haenszel odds ratio for Controlled disease (Daivobet gel relative to Betamethasone gel /Calcipotriol gel/Vehicle) adjusted for pooled centre

2) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1

3) Breslow-Day test for homogeneity of odds ratios across pooled centres

At Week 4 Daivobet gel was statistically significantly more effective than calcipotriol gel and the gel vehicle. Because of the lack of statistical significance in the comparison with betamethasone, a formal claim of superiority could not be made at Week 4 for any of the three pair-wise comparisons.

At Week 8 Daivobet gel was statistically significantly more effective than betamethasone gel, calcipotriol gel and the gel vehicle.

For all the analysis, the Breslow-Day test to investigate the consistency of the response across centres was not statistically significant at the 10% level which means that no treatment by centre interactions were found indicating a consistent response among centres.

Comment: The primary efficacy endpoint was the percentage of patients who achieved 'controlled disease according to the IGA at Week 4 and 8 and the primary analysis was to test for superiority of Daivobet gel versus betamethasone gel, calcipotriol gel and the gel vehicle using the full analysis set (ITT). To be considered superior, all three tests had to be statistically significant.

This study did not achieve the preset primary efficacy endpoint. Daivobet gel was superior to betamethasone gel, calcipotriol gel and the gel vehicle at 8 weeks but at Week 4 it was not superior to betamethasone gel. Daivobet gel was superior to calcipotriol gel and the gel vehicle at Week 4.

6.1.1.1.13. Results for other efficacy outcomes

Statistical analysis was only provided for percentage change in PSAI at Weeks 4 and 8. The remaining results are only presented descriptively.

Percentage change in PSAI at Weeks 4 and 8:

Table 4. Study LE080185-G23 Percentage change in PSAI at Week 4 and 8

Percentage change in PASI	Daivobet gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Vehicle (n=95)
Week 4				
Mean	-46.4	-42.7	-32.2	-17.4
SD	30.2	29.4	27.3	36.8
Median	-50.0	-42.6	-33.3	-16.7
Minimum	-100	-100	-94	-98
Maximum	73	62	59	173
Number	482	479	96	95
Statistical analysis				
Difference ^{1,2}		-3.9	-16.3	-28.9
95% CI		-7.6 to -0.2	-22.7 to -9.8	-35.4 to -22.5
P-value ³		0.038	< 0.001	< 0.001
Week 8				
Mean	-55.8	-48.6	-43.6	-20.9
SD	34.4	35.8	34.1	49.1
Median	-63.0	-53.7	-45.9	-20.3
Minimum	-100	-100	-100	-100
Maximum	73	83	59	173
Number	482	479	96	95
Statistical analysis				
Difference ^{1,2}		-7.6	-14.9	-34.2
95% CI		-12.1 to -3.1	-22.7 to -7.0	-42.0 to -26.4

Percentage change in PASI	Daivobet gel (n=482)	Betamethasone gel (n=479)	Calcipotriol gel (n=96)	Vehicle (n=95)
P-value ³		<0.001	<0.001	<0.001

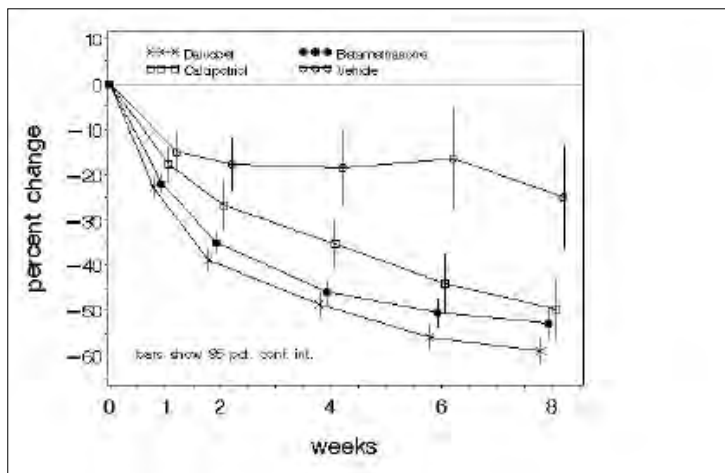
- 1) Daivobet gel minus Betamethasone gel/Calcipotriol gel/Vehicle
- 2) Adjusted for the effect of centre and baseline disease severity
- 3) T-test for adjusted difference

Daivobet gel was superior to betamethasone gel, calcipotriol gel and gel vehicle at both Week 4 ($p \leq 0.038$) and Week 8 ($p \leq 0.038$).

The mean percentage change in PASI at Weeks 1, 2, 4, 6 and 8

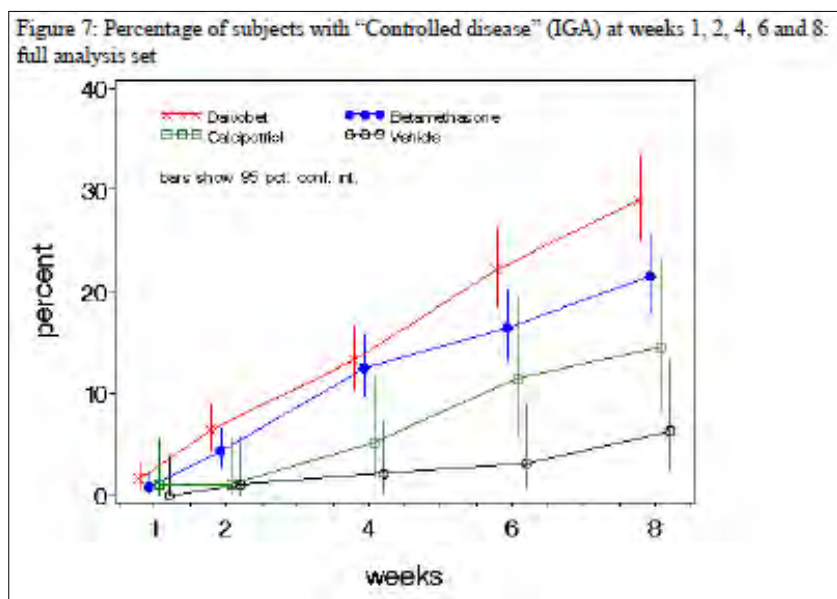
The mean percentage change in PASI increased as the study progressed: from -23.0 at Week 1 to -58.9 at week 8 in the Daivobet gel group, from -22.0 to -52.8 in the betamethasone gel group, and from -17.8 to -49.5 in the calcipotriol gel group. In the gel vehicle group, the mean percentage change in the PASI was similar at Weeks 1, 2, 4, and 6 ranging between -15.1 and -18.6 but slightly greater at Week 8 (-25.0).

Figure 2. Study LEO80185-G23 Summary of percentage change in PASI from baseline to weeks 1, 2, 4, 6 and 8: full analysis set



The percentage of subjects who achieved 'controlled disease' according to the IGA at Weeks 1, 2, 4, 6 and 8 by treatment group

Figure 3. Study LEO 80185-G23 Percentage of subjects with 'Controlled disease' (IGA) at weeks 1, 2, 4, 6 and 8: full analysis set



The percentage of subjects at each visit who achieved at least 75% reduction in PASI from baseline to Week 4 and 8

Table 5. Study LEO80185-G23 PASI 75 from baseline to Week 4 and 8

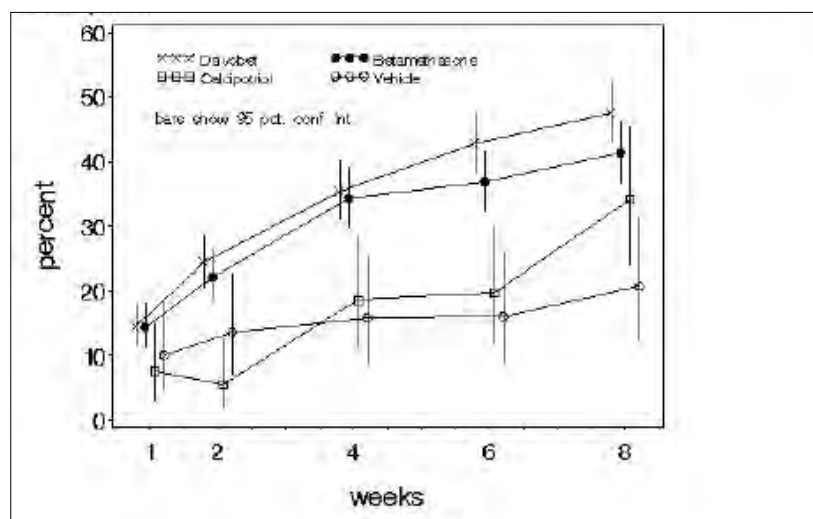
Visit PASI 75	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)
Week 4				
≥ 75% PASI reduction	103 (23.1)	78 (18.1)	5 (5.9)	2 (2.4)
< 75% PASI reduction	343 (76.9)	353 (81.9)	80 (94.1)	80 (97.6)
Total	446 (100.0)	431 (100.0)	85 (100.0)	82 (100.0)
Week 8				
≥ 75% PASI reduction	181 (40.8)	146 (34.9)	17 (20.7)	12 (15.6)
< 75% PASI reduction	263 (59.2)	272 (65.1)	65 (79.3)	65 (84.4)
Total	444 (100.0)	418 (100.0)	82 (100.0)	77 (100.0)

The percentage of subjects at each visit who achieved at least 50% reduction in PASI from baseline to Week 4 and 8

Table 6. Study LE080185-G23 PASI 50 from baseline to Week 4 and 8

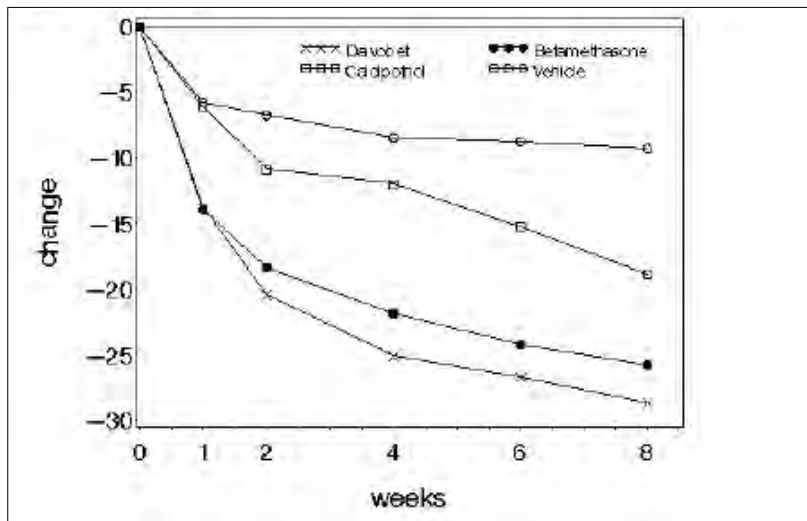
Visit PASI 50	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)
Week 4				
≥ 50% PASI reduction	239 (53.6)	199 (46.2)	27 (31.8)	20 (24.4)
< 50% PASI reduction	207 (46.4)	232 (53.8)	58 (68.2)	62 (75.6)
Total	446 (100.0)	431 (100.0)	85 (100.0)	82 (100.0)
Week 8				
≥ 50% PASI reduction	298 (67.1)	245 (58.6)	45 (54.9)	26 (33.8)
< 50% PASI reduction	146 (32.9)	173 (41.4)	37 (45.1)	51 (66.2)
Total	444 (100.0)	418 (100.0)	82 (100.0)	77 (100.0)

The percentage of subjects who achieved 'controlled disease' according to the patient's global assessment of disease severity at Week 1, 2, 4, 6 and 8 by treatment group

Figure 4. Study LE080185-G23 - Percentage of subjects with 'controlled disease' (PGA) at weeks 1, 2, 4, 6 and 8: full analysis set

The change in discomfort score (actual) from baseline to each visit

Figure 5. Study LE080185-G23 - Summary of change in plaque discomfort score from baseline to week 1, 2, 4, 6 and 8: full analysis set



6.1.1.2. Study LE080185-G21

Efficacy and Safety of Calcipotriol plus Betamethasone Gel Compared with Tacalcitol Ointment and the Gel Vehicle Alone in Patients with Psoriasis Vulgaris.

Comment: Tacalcitol is a vitamin D3 derivative, which inhibits keratinocyte hyper-proliferation and induces differentiation of these cells. Tacalcitol ointment was approved in the EU in 2006 but does not appear to have been approved in Australia.

6.1.1.2.1. Study design, objectives, locations and dates

Primary objective was to compare the efficacy of once daily treatment for up to 8 weeks of Daivobet gel with tacalcitol ointment and the gel vehicle alone in subjects with psoriasis vulgaris on the body.

Secondary objectives were:

- Compare safety of once daily treatment for up to 8 weeks of Daivobet gel with tacalcitol ointment and the gel vehicle alone in subjects with psoriasis of the body
- To investigate the occurrence of and the time to relapse and occurrence of rebound after the end of treatment in subjects with 'controlled disease'
- To obtain data on the quality of life of subjects treated with Daivobet gel, tacalcitol ointment and the gel vehicle alone, using quality of life questionnaires.

Study design

This was a multicentre, prospective, randomised, investigator blind, active and vehicle controlled, 3 arm, parallel group, 8 week phase 3 clinical study conducted in 18 centres in Canada. The study was conducted from April 2008 to February 2009.

The study consisted of the following 4 phases:

Washout phase – prior to randomisation the subject entered a washout phase (if required) where anti-psoriatic treatments and other relevant medication were discontinued as defined by exclusion criteria. The duration of the washout period varied from 2 weeks to up to 4 weeks depending on which treatment the subject received. A subject was not eligible for the study if they had been treated with biologics recently and required more than 28 days washout period.

Treatment phase – subject was randomised on Day 0 and the treatment period continued for 56 days (8 weeks) and included 6 visits: Day 0, 7 (± 2), 14 (± 2), 28 (± 2), 42 (± 2) and 56 (± 2). If

the subject cleared according to the IGA before 8 weeks of treatment, the subject continued in the study and used study medication as required until the end of week 8.

Observation phase – the treatment phase was followed by an observation period of 8 weeks for subjects with ‘controlled disease’ according to the IGA at week 8. During this treatment-free observation period the subject was evaluated at Week 10, 12 and 16 to investigate the occurrence and the time to relapse if a subject relapsed or experienced rebound and needed to reinstate treatment between two scheduled visits. Subjects who experienced relapse/rebound, as verified by the investigator, completed the study and were given treatment according to the investigator’s discretion.

Follow-up phase – subjects with ongoing (serious or non serious) AEs at the last on-treatment visit had a follow up contact. This may have been a regular clinic visit or a telephone contact according to the investigator’s discretion 14 (± 2) days after the last on treatment visit. Serious AE were followed up until a final outcome of the event was determined.

6.1.1.2.2. *Inclusion and exclusion criteria*

Inclusion:

- Patients aged 18 years and above, of either sex and any ethnic origin who had a clinical diagnosis of psoriasis vulgaris involving the trunk and/or arms and/or legs amenable to treatment with a maximum of 100 gms of Daivobet gel per week or 10 gms per day of tacalcitol ointment
- Disease severity graded moderate, severe or very severe according to the Investigators’ global assessment (IGA) of disease severity
- A minimum PASI score for extent of 2 in at least one body region (ie psoriasis affecting at least 10% of arms, and/or of trunk, and/or of legs)

Exclusion:

- Systemic treatment with biological therapies with a possible effect on psoriasis vulgaris (eg alefacept, efalizumab, etanercept, infliximab, adalimumab) within 3 months prior to randomisation
- Systemic treatment with any therapy with a possible effect on psoriasis vulgaris (eg corticosteroids, retinoids, immunosuppressants) within 4 weeks prior to randomisation
- Systemic treatment with Vitamin D preparations above 500 IU per day
- PUVA or Grenz ray therapy within 4 weeks prior to randomisation
- UVB therapy within 2 weeks prior to randomisation
- Any topical treatment of the trunk/limbs (except for emollients) within 2 weeks prior to randomisation
- Topical treatment for other relevant skin disorders on the face and flexures (eg facial psoriasis, flexural psoriasis, eczema) with potent or very potent corticosteroids or vitamin D analogues within 2 weeks prior to randomisation
- Planned initiation of, or changes to concomitant medication that could affect psoriasis vulgaris (eg beta blockers, ACE inhibitors, anti-malarial drugs, lithium) during the study
- Current diagnosis of erythrodermic, exfoliative or pustular psoriasis
- Patients with any of the following conditions present on the treatment area: viral (eg herpes or varicella) lesions, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, rosacea, perioral dermatitis, acne

vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, ulcers and wounds

- Known or suspected: disorders of calcium metabolism associated with hypercalcaemia, severe renal insufficiency or severe hepatic disorders or hypersensitivity to any of the components of the investigational products
- Planned exposure to sun during the study that may affect psoriasis vulgaris
- Females of child bearing potential wishing to become pregnant during the study, or breast feeding, or not using adequate method of contraception during the study, or returning positive pregnancy test at Visit 1

6.1.1.2.3. Study treatments

Subjects were randomised in a 2:2:1 ratio to one of the following treatments:

- Daivobet gel (calcipotriol 50 µg/g as hydrate plus betamethasone 0.5 mg/g as dipropionate)
- Curaderm ointment (tacalcitol 4 µg/g as monohydrate)
- Gel vehicle

Subjects were instructed to apply the treatment once daily on affected areas on the trunk and/or limbs.

The following concomitant therapies were allowed during the study:

- Treatments for conditions other than psoriasis vulgaris (with no potential effect on psoriasis vulgaris) without change in dosage whenever possible
- Unlimited use of emollients for face, flexures (skin folds) and scalp
- All topical medications for face, skin folds/flexures and scalp except very potent WHO group IV corticosteroids and vitamin D analogues

6.1.1.2.4. Efficacy variables and outcomes

The primary efficacy outcome was subjects with 'controlled disease' according to IGA at week 8.

Other efficacy outcomes included:

- Subjects with 'controlled disease' according to IGA at week 4
- Percentage change in PASI from baseline to week 4 and 8
- Subjects with relapse during the study and time to relapse
- Subjects with rebound during the study
- Change in quality of life baseline to week 4 and 8 using SF-36 (v2) and Skindex-16
- Subjects with 'controlled disease' according to the IGA at week 6
- Subjects with 'controlled disease' according to the patients global assessment at week 8
- Subjects with PASI 75 (at least 75% reduction in PASI from baseline) at each visit
- Subjects with PASI 50 (at least 50% reduction in PASI from baseline) at each visit

See Definitions for details of the scoring systems

6.1.1.2.5. Randomisation and blinding methods

Randomisation was in a 2:2:1 ratio to the treatments Daivobet gel: tacalcitol: vehicle. Treatment assignment was pre-planned according to a computer generated randomisation schedule.

Due to difference in formulation and packaging, it was not considered possible to double blind the investigational products. In order to keep the study investigator blinded, packing and labelling of the outer box was identical for all treatments. The Investigational products were either packed in bottles (Daivobet gel and gel vehicle) or in tubes (tacalcitol ointment). Handling of the individual bottles/tubes was handled by a designated third person. Individual bottles/tubes of investigational products were inaccessible to the (sub)investigator(s) and other study staff involved in the evaluation of subjects and conduct of the study.

6.1.1.2.6. *Analysis populations*

Full analysis set = ITT = all randomised subjects

Safety analysis set = all subjects who received any treatment with trial medication and for whom the presence or confirmed absence of adverse events was available

Per protocol analysis set = all randomised subjects excluding those who received no treatment with trial medication, who provided no efficacy data following start of treatment, who were known to have taken the wrong trial medication throughout the treatment phase of the study and/or who did not fulfil the disease defining inclusion criteria.

6.1.1.2.7. *Sample size*

The response rate for Daivobet was estimated based on a phase 2 study (MBL202INT) and the tacalcitol was based on a study with tacalcitol ointment in which the average reduction in PASI was 40%. Based on studies where both PASI and IGA were assessed this is assumed to correspond to a 'controlled disease' of 11-15%.

The sample size calculation assumed that 28% of subjects in the Daivobet gel treatment group, 15% of the subjects in the tacalcitol ointment treatment group and 5% of the subjects in the gel vehicle treatment group had 'controlled disease' and that a two-tailed significance level, α of 0.05 was used. Each centre aimed to recruit a minimum of 15 subjects and no centre was to recruit more than 45 subjects.

With 180 subjects in the Daivobet gel and tacalcitol treatment groups a chi-square test would have 82% power to reject the null hypothesis of no difference between the two groups regarding the primary response criterion. Likewise, with 90 subjects in the gel vehicle treatment group a chi-square test would have 99% power to reject the null hypothesis of no difference between the Daivobet gel treatment group and the gel vehicle treatment group. Thus the overall power was approximately 81%.

6.1.1.2.8. *Statistical methods*

The primary response criterion was analysed for the full analysis set and the per protocol analysis set. The other response criteria were only analysis for the full analysis set. Two hypotheses were tested in sequential order: 1) Daivobet gel was superior to gel vehicle and 2) Daivobet gel was superior to tacalcitol ointment, for the proportion of subjects with 'controlled disease' at week 8 according to the IGA. The second hypothesis was only tested if the first test was significant ($p < 0.05$). Testing was conducted at the 5% level of significance using the Cochran-Mantel-Haenszel (CMH) test adjusting for the effect of centre.

The secondary response criteria using IGA and PASI scores used a Bonferroni corrected level of significance of 0.0167 (0.05/3) to account for multiplicity.

For the secondary response criteria, the proportion of subjects with 'controlled disease' at week 4 according to the IGA was compared between the treatment groups using the CMH test. Analysis of variance (ANOVA) was used to compare the treatment groups for the percentage change in PASI at week 4 and 8 and quality of life measurements at week 4 and 8. Paired t-tests were used to analyse the change in quality of life within treatment groups.

The proportion of subjects who experienced relapse and rebound were tabulated by treatment group and by centre. The time until relapse was plotted for each treatment group as a Kaplan-Meier plot. If relapse had not occurred within the observation period, the subject was censored (at the date of last visit). The median time to relapse with lower and upper quartiles was calculated for each treatment group.

6.1.1.2.9. *Participant flow*

Enrolled = 458

Randomised = 458

- Daivobet gel = 183
- Tacalcitol ointment = 184
- Gel vehicle = 91

Withdrawals during treatment = 60:

Reason for withdrawal	Daivobet = 12	Tacalcitol = 21	Gel vehicle = 27
Exclusion criteria emerging	2	0	0
Lost to follow up	4	3	1
Other reasons	1	0	0
Unacceptable AE	3	4	4
Treatment failure	2	12	20
Voluntary (and no other reason)	0	2	2

Completed Treatment phase = 398

- Daivobet gel = 171
- Tacalcitol ointment = 163
- Gel vehicle = 64

Entered Observation Phase = 108

- Daivobet gel = 68
- Tacalcitol ointment = 35
- Gel vehicle = 5

Withdrawals during observation phase = 59:

Reason for withdrawal	Daivobet = 45	Tacalcitol = 14	Gel vehicle = 5
Experienced relapse/rebound	36	4	0

Reason for withdrawal	Daivobet = 45	Tacalcitol = 14	Gel vehicle = 5
Lost to follow up	0	1	0
Other reasons	5	6	5
Voluntary (and no other reason)	4	3	0

Completed observation phase = 49

Daivobet gel = 23

Tacalcitol ointment = 21

Gel vehicle = 5

6.1.1.2.10. Major protocol violations/deviations

The percentages of patients with protocol deviations were generally similar among the treatment groups. The most common deviation was “disallowed medication started after baseline” and “violation of visit window” but each accounted for less than 5% of patients.

6.1.1.2.11. Baseline data

Table 7. Study LE0801855-G21 Baseline data

	All randomised subjects (n=458)	Daivobet gel (n=183)	Tacalcitol ointment (n=184)	Vehicle (n=91)
	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)
Age (years)				
Mean	51.6	50.9	51.7	52.8
SD	14.0	14.3	13.4	14.9
Median	52.0	51.0	53.0	54.0
Minimum	18	18	18	18
Maximum	82	79	82	82
Sex (No, %)				
Male	285 (62.2)	117 (63.9)	115 (62.5)	53 (58.2)
Female	173 (37.8)	66 (36.1)	69 (37.5)	38 (41.8)
Race				

	All randomised subjects (n=458)	Daivobet gel (n=183)	Tacalcitol ointment (n=184)	Vehicle (n=91)
	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)
White	430 (93.9)	173 (94.5)	171 (92.9)	86 (94.5)
Black or African American	4 (0.9)	2 (1.1)	2 (1.1)	0 (0.0)
Asian	5 (1.1)	1 (0.5)	2 (1.1)	2 (2.2)
American Indian or Alaska Native	2 (0.4)	1 (0.5)	0 (0.0)	1 (1.1)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0 (0.5)	0 (0.0)	0 (0.0)
Other	16 (3.5)	5 (2.7)	9 (4.9)	2 (2.2)
Skin type				
I	12 (2.6)	5 (2.7)	6 (3.3)	1 (1.1)
II	146 (31.9)	56 (30.6)	65 (35.3)	25 (27.5)
III	167 (36.5)	66 (36.1)	64 (34.8)	37 (40.7)
IV	106 (23.1)	47 (25.7)	39 (21.2)	20 (22.0)
V	22 (4.8)	7 (3.8)	8 (4.3)	7 (7.7)
VI	5 (1.1)	2 (1.1)	2 (1.1)	1 (1.1)
Duration of Psoriasis				
Mean	19.8	21.2	19.1	18.5
SD	13.3	13.2	12.9	14.3
Median	18.0	20.0	17.0	16.0
Minimum	0	1	0	0

	All randomised subjects (n=458)	Daivobet gel (n=183)	Tacalcitol ointment (n=184)	Vehicle (n=91)
	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)
Maximum	70	58	60	70
IGA at baseline				
Moderate	313 (68.3)	130 (71.0)	119 (64.7)	64 (70.3)
Severe	135 (29.5)	50 (27.3)	58 (31.5)	27 (29.7)
Very Severe	10 (2.2)	3 (1.6)	7 (3.8)	0 (0)
Investigators assessment of extent				
Mean	9.3	9.0	9.5	9.4
SD	8.2	7.7	9.6	6.2
Median	7.0	7.0	7.0	8.0
Minimum	2	2	3	2
Maximum	84	72	84	41
PGA				
Very mild	16 (3.5)	8 (4.4)	6 (3.3)	2 (2.2)
mild	68 (14.9)	24 (13.1)	32 (17.5)	12 (13.3)
Moderate	264 (57.9)	111 (60.7)	92 (50.3)	61 (67.8)
Severe	108 (23.7)	40 (21.9)	53 (29.0)	15 (16.7)

6.1.1.2.12. Results for the primary efficacy outcome

The primary efficacy outcome was subjects with 'controlled disease' according to IGA at week 8.

The proportion of subjects who achieved 'controlled disease' at week 8 (LOCF) in the Daivobet gel group was 39.9% compared with 5.5% in the gel vehicle group and 17.9% in the tacalcitol group. Daivobet gel was statistically significantly more effective than the gel vehicle (OR 13.9, 95% CI 4.99 to 38.7; $p < 0.001$) and the sequential test versus tacalcitol also showed that Daivobet gel was statistically significantly more effective (OR 3.42, 95% CI 2.05 to 5.70; $p < 0.001$). There was no treatment by centre interaction ($p > 0.10$).

Table 8. Study LE080185-G21 'Controlled disease' at Week 8

Controlled disease	Daivobet Gel (n=183) Number of Subjects (%)	Tacalcitol (n=184) Number of Subjects (%)	Gel Vehicle (n=91) Number of Subjects (%)
Controlled	73 (39.9)	33 (17.9)	5 (5.5)
Non-controlled	110 (60.1)	151 (82.1)	86 (94.5)
Total	183 (100.0)	184 (100.0)	91 (100.0)
Odds ratio ¹		3.42	13.9
95% CI		2.05 to 5.70	4.99 to 38.7
CMH test ²		<0.001	<0.001
Breslow-Day test ³		0.99	0.88

1) Cochran-Mantel-Haenszel Odds for Controlled disease (Daivobet Gel relative to Tacalcitol/Gel vehicle) adjusted for centre

2) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1

3) Test for homogeneity of odds ratios across centres

6.1.1.2.13. Results for other efficacy outcomes

Subjects with 'controlled disease' according to IGA at week 4

The proportion of subjects who achieved 'controlled disease' at week 4 (LOCF) in the Daivobet gel group was 18.6% compared with 6.5% in the tacalcitol group and 1.1% in the gel vehicle group. Daivobet gel was statistically significantly more effective than tacalcitol (OR 3.51, 98.33% CI 1.46 to 8.40; $p < 0.001$) and the gel vehicle (OR 32.9, 98.33% CI 2.07 to 522; $p < 0.001$). There was no treatment by centre interaction ($p > 0.10$).

Table 9. Study LE080185-G21 'Controlled disease' at Week 8

Controlled disease	Daivobet Gel (n=183) Number of Subjects (%)	Tacalcitol (n=184) Number of Subjects (%)	Gel Vehicle (n=91) Number of Subjects (%)
Controlled	34 (18.6)	12 (6.5)	1 (1.1)
Non-controlled	149 (81.4)	172 (93.5)	90 (98.9)

Controlled disease	Daivobet Gel (n=183) Number of Subjects (%)	Tacalcitol (n=184) Number of Subjects (%)	Gel Vehicle (n=91) Number of Subjects (%)
Total	183 (100.0)	184 (100.0)	91 (100.0)
Odds ratio ¹		3.51	32.9
95% CI		1.46 to 8.40	2.07 to 522
CMH test ²		< 0.001	< 0.001
Breslow-Day test ³		0.21	0.99

1) Cochran-Mantel-Haenszel Odds for Controlled disease (Daivobet Gel relative to Tacalcitol/Gel vehicle) adjusted for centre

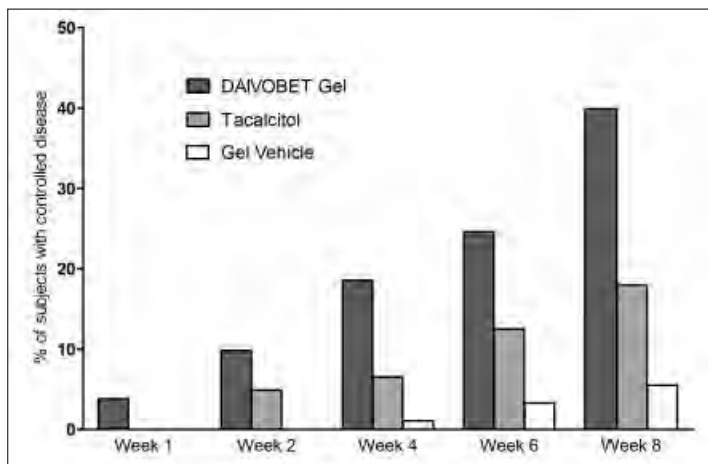
2) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1

3) Test for homogeneity of odds ratios across centres

Development of controlled disease according to the IGA

The percentage of subjects with 'controlled disease' according to the IGA at weeks 1, 2, 4, 6 and 8 is shown in figure below.

Figure 6. Study LE080185-G21 Development of 'Controlled disease' during study



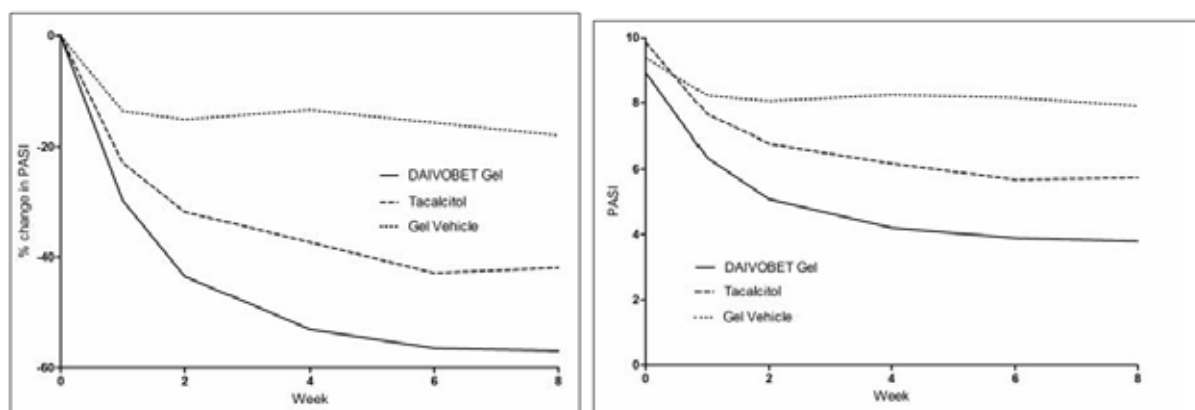
Percentage change in PASI from baseline to week 4 and 8

Table 10. Study LE080185-G21. Percentage change in PASI from baseline to week 4 and 8

Percentage change in PASI	Daivobet Gel (n=183)	Tacalcitol (n=184)	Gel Vehicle (n=91)
WEEK 4			
Least squares mean ¹	-53.6	-38.1	-13.8
Mean	-53.1	-37.3	-13.3
SD	27.4	26.4	27.7
Median	-56.3	-40.0	-11.2
Minimum	-100	-96	-77
Maximum	102	29	58
Difference ²		-15.5	-39.8
98.33% CI		-22.1 to -8.95	-47.8 to -31.7
P-value		<0.001	<0.001
WEEK 8			
Least squares mean ¹	-57.0	-42.3	-17.9
Mean	-57.0	-41.9	-17.9
SD	29.6	33.4	35.3
Median	-63.6	-43.0	-20.0
Minimum	-100	-100	-100
Maximum	87	47	69
Difference ²		-14.7	-39.1
98.33% CI		-22.6 to -6.90	-48.7 to -29.5
P-value		<0.001	<0.001

1) Adjusted for effect of centre

2) Daivobet gel minus tacalcitol/gel vehicle, adjusted for effect of centre

Figure 7. Study LE080185-G21 Percentage and actual change in PASI during study*Subjects with relapse during the study and time to relapse*

'Relapse' is defined as a reduction in PASI improvement from baseline by at least 50% among subjects with 'controlled disease' at week 8. The time to relapse was defined as the number of days from the last on-treatment visit (could be before week 8 if a subject cleared before week 8) until relapse.

At the end of the treatment phase 67 subjects in the Daivobet gel group, 31 in the tacalcitol group and 5 subjects in the gel vehicle group had 'controlled disease' and entered the observation phase.

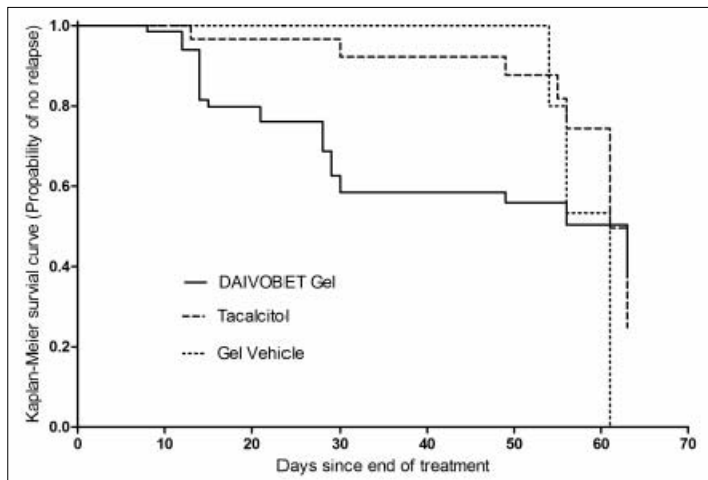
Table 11. Study LE080185-G21 Development of relapse during observation period

	Daivobet Gel (n=67)	Tacalcitol (n=31)	Gel Vehicle (n=5)
Relapse¹	Number of Subjects (%)	Number of Subjects (%)	Number of Subjects (%)
Relapse	28 (41.8)	7 (22.6)	3 (60.0)
No Relapse	39 (58.2)	24 (77.4)	2 (40.0)
Kaplan-Meier estimates²			
Median time to relapse (days)	63	61	61
Lower quartile (days)	28	56	56
Upper quartile (days) ²		63	61

1) 7 patients had controlled disease but withdrew after week 8; these patients were not included in this table

2) Upper quartile in the Daivobet group cannot be estimated due to the large number of censored patients (ie patients who had not relapsed when leaving the study)

Figure 8. Study LE080185-G21 Time to relapse: those subjects in the full analysis set who achieved 'controlled disease' according to the IGA at week 8



Subjects with rebound during the study

Rebound is defined as worsening of psoriasis to a PASI >125% of the baseline value among subjects with 'controlled disease' according to IGA at week 8.

No subjects experienced rebound during the observation period.

Subjects with 'controlled disease' according to the patients global assessment (PGA) at weeks 1, 2, 4, 6 and 8

Table 12. Study LE080185-G21 Subjects with 'controlled disease' according to the PGA at each visit

	Daivobet Gel (n=183)	Tacalcitol (n=184)	Gel Vehicle (n=91)
Controlled disease	Number of Subjects (%)	Number of Subjects (%)	Number of Subjects %
Day 0			
Controlled	8 (4.48)	6 (3.3)	2 (2.2)
Non-controlled	175 (95.6)	177 (96.7)	88 (97.8)
WEEK 1			
Controlled	17 (9.4)	8 (4.4)	3 (3.3)
Non-controlled	163 (90.6)	174 (95.6)	87 (96.7)
WEEK 2			
Controlled	31 (17.5)	15 (8.4)	9 (1.5)
Non-controlled	146 (82.5)	164 (91.6)	77 (89.5)
WEEK 4			

	Daivobet Gel (n=183)	Tacalcitol (n=184)	Gel Vehicle (n=91)
Controlled disease	Number of Subjects (%)	Number of Subjects (%)	Number of Subjects %
Controlled	52 (29.7)	21 (12.0)	7 (8.6)
Non-controlled	123 (70.3)	154 (88.0)	74 (91.4)
WEEK 6			
Controlled	57 (33.5)	27 (16.3)	7 (10.1)
Non-controlled	113 (66.5)	139 (83.7)	62 (89.9)
WEEK 8			
Controlled	69 (40.4)	35 (21.5)	14 (21.9)
Non-controlled	102 (59.6)	128 (78.5)	50 (78.1)

Subjects with PASI 75 (at least 75% reduction in PASI from baseline) at each visit

Table 13. Study LE080185-G21 Subjects with PASI 75 at each visit

	Daivobet Gel (n=183)	Tacalcitol (n=184)	Gel Vehicle (n=91)
PASI 75	Number of Subjects (%)	Number of Subjects (%)	Number of Subjects (%)
WEEK 1			
≥ 75% PASI reduction	5 (2.8)	0 (0.0)	1 (1.1)
< 75% PASI reduction	175 (97.2)	182 (100.0)	89 (98.9)
WEEK 2			
≥ 75% PASI reduction	23 (13.0)	8 (4.5)	1 (1.2)
< 75% PASI reduction	154 (87.0)	171 (95.5)	85 (98.8)
WEEK 4			
≥ 75% PASI reduction	36 (20.5)	19 (10.9)	1 (1.2)

	Daivobet Gel (n=183)	Tacalcitol (n=184)	Gel Vehicle (n=91)
PASI 75	Number of Subjects (%)	Number of Subjects (%)	Number of Subjects (%)
< 75% PASI reduction	140 (79.5)	156 (89.1)	80 (98.8)
WEEK 6			
≥ 75% PASI reduction	54 (31.8)	28 (16.9)	2 (2.9)
< 75% PASI reduction	116 (68.2)	138 (83.1)	67 (97.1)
WEEK 8			
≥ 75% PASI reduction	59 (34.5)	42 (25.8)	5 (7.8)
< 75% PASI reduction	112 (65.5)	121 (74.2)	59 (92.2)

Subjects with PASI 50 (at least 50% reduction in PASI from baseline) at each visit

Table 14. Study LE080185-G21 Subjects with PASI 50 at each visit

	Daivobet Gel (n=183)	Tacalcitol (n=184)	Gel Vehicle (n=91)
PASI 50	Number of Subjects (%)	Number of Subjects (%)	Number of Subjects (%)
WEEK 1			
≥ 50% PASI reduction	38 (21.1)	17 (9.3)	4 (4.4)
< 50% PASI reduction	142 (78.9)	165 (90.7)	86 (95.6)
WEEK 2			
≥ 50% PASI reduction	74 (41.8)	40 (22.3)	6 (7.0)
< 50% PASI reduction	103 (58.2)	139 (77.7)	80 (93.0)
WEEK 4			

	Daivobet Gel (n=183)	Tacalcitol (n=184)	Gel Vehicle (n=91)
PASI 50	Number of Subjects (%)	Number of Subjects (%)	Number of Subjects (%)
≥ 50% PASI reduction	109 (61.9)	54 (30.9)	11 (13.6)
< 50% PASI reduction	67 (38.1)	121 (69.1)	70 (86.4)
WEEK 6			
≥ 50% PASI reduction	120 (70.6)	83 (50.0)	13 (18.8)
< 50% PASI reduction	50 (29.4)	83 (50.0)	56 (81.2)
WEEK 8			
≥ 50% PASI reduction	119 (69.6)	80 (49.1)	15 (23.4)
< 50% PASI reduction	52 (30.4)	83 (50.9)	49 (76.6)

Change in quality of life baseline to week 4 and 8 using SF-36 (v2) and Skindex-16

In the SF-36 (v2) general health questionnaire the scores for the Physical Component Summary and Mental Component Summary were similar among the groups. When comparing response within the Daivobet gel group, there were no significant changes from baseline in the Physical Component Summary but the change from baseline in the Mental Component Summary score was statistically significant at Weeks 4 and 8 (p=0.002 and p=0.012 respectively).

For the skin disease specific questionnaire (Skindex-16) the changes from baseline within each treatment group were statistically significant for total score in all treatment groups at Week 4 and 8 (p<0.001 for both timepoints). There were statistically significant differences in favour of Daivobet gel at Weeks 4 and 8 compared with tacalcitol (p=0.010 and p=0.007 respectively) and also compared with the gel vehicle (p<0.001) at both timepoints.

6.1.2. Other efficacy studies

6.1.2.1. Study MBL0202INT

6.1.2.1.1. Study design, objectives, locations and dates

Calcipotriol Plus Betamethasone Dipropionate Gel Compared to Betamethasone Dipropionate in the Gel Vehicle, Calcipotriol in the Gel Vehicle Alone in Psoriasis Vulgaris.

Objectives

To compare the efficacy and safety of once daily treatment for up to 8 weeks of Daivobet gel (calcipotriol plus betamethasone dipropionate) with betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle alone in patients with psoriasis vulgaris on the trunk and/or limbs.

Methodology

Design: an international, multicentre, prospective, randomised, double blind, 4 arm, parallel group, 8 week study conducted at 19 centres (Canada 6; Germany 4; Ireland 1; Sweden 3; UK 5) between December 2005 and May 2006.

Visits occurred at baseline and after 7, 14, 28, 42 and 56 days. A follow up visit took place 14 days after the last on-treatment visit if a treatment related AE was ongoing. Prior to randomisation a washout period was completed if the patients received anti-psoriatic treatments or other relevant medication as defined in the exclusion criteria.

Entry criteria: patients of either sex, aged 18 years and above, with a diagnosis of psoriasis vulgaris on the trunk and/or limbs amenable to treatment with a maximum of 100 mg of topical medication per week and a disease severity of at least mild according to the IGA.

Treatments: Patients were randomised in a 4:2:2:1 ratio to receive once daily treatment for up to 8 weeks to one of the following four treatment groups:

- Daivobet gel (calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g)
- Betamethasone dipropionate 0.50 mg/g in the gel vehicle
- Calcipotriol 50 µg/g in the gel vehicle
- Gel vehicle

Treatment was applied once daily to the affected area on the trunk and/or limbs for 8 weeks.

Data collection and analysis: efficacy assessments including the investigator's (IGA) and the patient's (PGA) global assessment of disease severity and the investigator's assessment (PASI) of extent and clinical signs (redness, thickness and scaliness) were performed at all visits. Safety assessments were performed at all post-randomisation visits. There was no pre-set margin of superiority.

Study participants

Enrolled: 374

Randomised: 364

- Daivobet gel: 162
- Betamethasone gel: 83
- Calcipotriol gel: 79
- Gel vehicle: 40

Completed: 328

- Daivobet gel: 149
- Betamethasone gel: 78
- Calcipotriol gel: 73
- Gel vehicle: 28

Analysed: 364 patients analysed in full analysis set (ITT) and the safety analysis set.

Overall age was similar in all four treatment groups and ranged from 50.1 years in the Daivobet gel group to 52.6 years in the calcipotriol gel group. The overall distribution of sex was similar in all treatment groups and agreed with the overall distribution of 58.8% males and 41.2% females. The majority of the population (98.1%) was of Caucasian origin. The percentage of Caucasians was 97.5% in all groups except the betamethasone gel group in which 100% were Caucasian. Overall the mean duration of disease was similar in all treatment groups and ranged

between 18.5 years and 19.5 years. The distribution of the baseline IGA, PASI and PGA was similar in the four groups. The majority of patients (over 50%) had moderate disease (IGA and PGA) at baseline; the mean PASI ranged between 7.7 and 7.9.

6.1.2.1.2. Results

Controlled disease according to the IGA at weeks 4 and 8

Table 15. Study MBL0202INT Patients with 'controlled disease' according to IGA at week 4 and 8 and results of statistical analysis: full analysis set

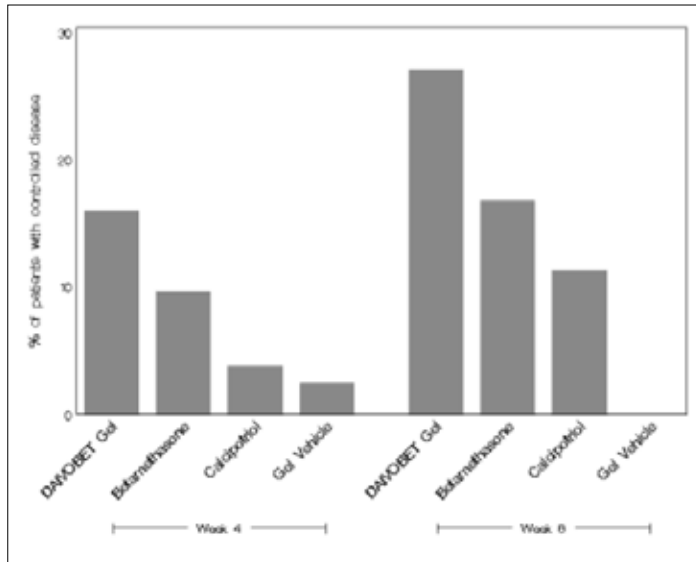
Controlled disease	Daivobet Gel	Betamethasone	Calcipotriol	Gel Vehicle
	(n=162)	(n=83)	(n=79)	(n=40)
	No. (%)	No. (%)	No. (%)	No. (%)
Week 4 (LOCF)				
Controlled disease	26 (16.0)	8 (9.6)	3 (3.8)	1 (2.5)
Non-controlled disease	136 (84.0)	75 (90.4)	76 (96.2)	39 (97.5)
Odds ratio		2.02	5.98	10.83
95% CI		0.84 to 4.82	1.53 to 23.34	1.04 to 112.73
CMH test ¹ (p value)		0.11	0.006	0.027
Breslow-Day test ²		0.39	0.92	1.00
Week 8 (LOCF)				
Controlled disease	44 (27.2)	14 (16.9)	9 (11.4)	0 (0)
Non-controlled disease	118 (72.8)	69 (83.1)	70 (88.6)	40 (100.0)
Odds ratio		2.40	2.89	
95% CI		1.11 to 5.20	1.31 to 6.38	
CMH test ¹ (p value)		0.027	0.006	< 0.001
Breslow-Day test ²		0.88	0.29	

1. Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1

2. Test for homogeneity of odds ratios across centres

Daivobet gel was statistically significantly more effective than betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle at Week 8 but at Week 4, the comparison with betamethasone dipropionate in gel vehicle did not reach statistical significance.

Figure 9. Study MBL0202INT Percentage of patients with 'controlled disease' at week 4 and 8 by treatment: full analysis set



Psoriasis Area and Severity Index (PASI)

Figure 10. Study MBL0202INT Mean PASI over time by treatment group: full analysis set

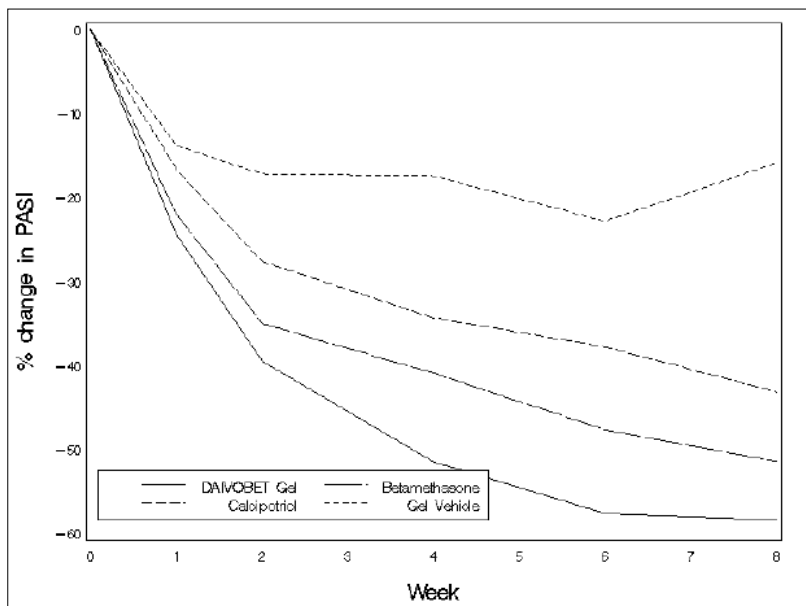


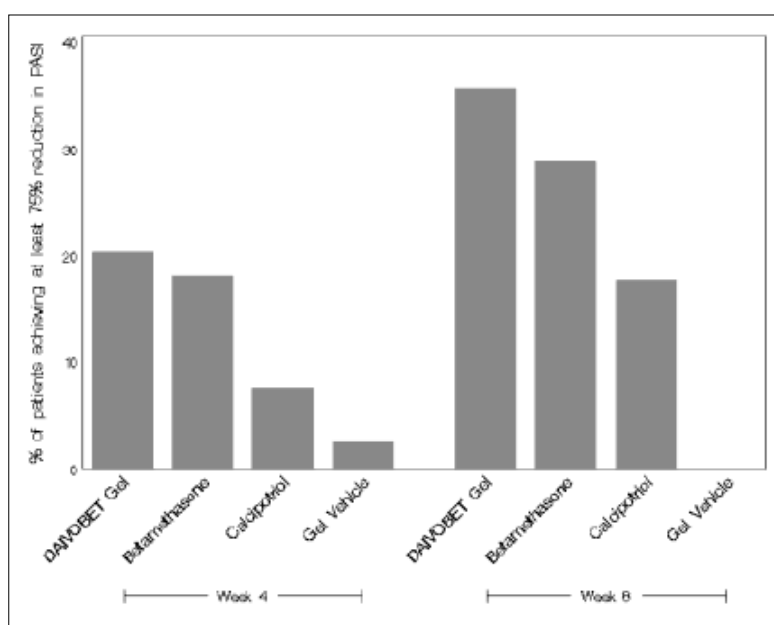
Table 16. Study MBL0202INT Percentage change in PASI from baseline to weeks 4 and 8 and statistical analysis: full analysis set

Percentage change in PASI	Daivobet Gel (n=162)	Betamethasone (n=83)	Calcipotriol (n=79)	Gel Vehicle (n=40)
Week 4 (LOCF)				
Mean	-48.1	-40.9	-32.7	-16.9
SD	32.0	32.3	22.9	30.9
Median	-50	-39	-29	-17
Minimum	-100	-100	-92	-89
Maximum	119	29	4	67
Difference		-7.85	-15.4	-30.8
95% CI		-15.2 to -0.5	-22.8 to -7.9	-40.4 to -21.2
p-value		0.04	<0.001	<0.001
Week 8 (LOCF)				
Mean	-55.3	-49.8	-41.2	-11.9
SD	33.3	34.0	31.0	28.6
Median	-62	-49	-40	-6
Minimum	-100	-100	-100	-61
Maximum	62	29	21	67
Difference		-6.16	-13.9	-43.1
95% CI		-14.2 to 1.9	-22.0 to -5.7	-53.6 to -32.6
p-value		0.13	<0.001	<0.001

Daivobet gel was statistically significantly more effective than betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle at Week 4 but at Week 8, the comparison with betamethasone dipropionate in gel vehicle did not reach statistical significance.

PASI 75 at weeks 4 and 8

No statistical analysis was performed on these results.

Figure 11. Study MBL0202INT Percentage of subjects with PASI 75 at week 4 and 8

Patient's Global Assessment of Disease Severity (PGA)

Controlled disease at Weeks 4 and 8

At week 4 and 8 Daivobet gel was statistically significantly more effective than calcipotriol in the gel vehicle and gel vehicle but not compared to betamethasone dipropionate in the gel vehicle.

Table 17. Study MBL0202INT Patients with 'controlled disease' according to PGA at week 4 and 8 and statistical results: full analysis set

Controlled disease according to PGA.	Daivobet Gel (n=162) No (%)	Betamethasone (n=83) No (%)	Calcipotriol (n=79) No (%)	Gel Vehicle (n=40) No (%)
Week 4 (LOCF)				
Controlled disease	48 (29.6)	23 (27.7)	11 (13.9)	3 (7.5)
Non-controlled disease	114 (70.4)	60 (72.3)	68 (86.1)	37 (92.5)
Odds ratio		1.15	2.99	6.82
95% CI		0.6 to 2.2	1.4 to 6.5	1.8 to 26.5
CMH test ¹ (p value)		0.66	0.005	0.002
Breslow-Day test ²		0.25	0.31	0.69
Week 8 (LOCF)				
Controlled disease	69 (42.6)	35 (42.2)	16 (20.3)	4 (10.0)

Controlled disease according to PGA.	Daivobet Gel (n=162) No (%)	Betametha- sone (n=83) No (%)	Calcipotriol (n=79) No (%)	Gel Vehicle (n=40) No (%)
Non-controlled disease	93 (57.4)	48 (57.8)	63(79.7)	36 (90.0)
Odds ratio		1.07	3.05	8.28
95% CI		0.6 to 1.9	1.6 to 6.0	2.4 to 28.5
CMH test ¹ (p value)		0.81	<0.001	<0.001
Breslow-Day test ²		0.81	0.20	0.59

1. Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1

2. Test for homogeneity of odds ratios across centres

6.1.2.2. Study PLQ-001

A Plaque Test Comparing Three Marketed Products and Two Investigational Products and a Vehicle Control for the Treatment of Psoriasis Vulgaris.

6.1.2.2.1. Study design, objectives, locations and dates

Objectives

To evaluate the psoriasis plaque test using two investigational products:

- LEO 80185 gel (calcipotriol 50 µg/g as hydrate plus betamethasone 0.5 mg/g as dipropionate)
- LEO 80190 ointment (calcipotriol 25 µg/g as hydrate plus hydrocortisone 10 mg/g)

Three active marketed reference products:

- Daivonex ointment - (calcipotriol 50 µg/g as hydrate)
- Daivonex cream - (calcipotriol 50 µg/g as hydrate)
- Daivobet ointment (calcipotriol 50 µg/g as hydrate plus betamethasone 0.5 mg/g as dipropionate)

One reference product as control:

- Daivobet ointment vehicle

Secondary objectives were to validate the use of immunohistochemical scoring of biopsy material in conjunction with clinical scoring of the treated areas in the evaluation of treatment effects in psoriatic skin in the subjects and to obtain safety information for each of the treatments.

Methodology

Design: single centre, investigator blinded, within subject randomised, active and vehicle controlled, repeat dose, translational study at one centre in France between February 2008 and March 2009.

The study consisted of a screening visit, a wash-out period if needed, a treatment period of 21 days. At the final treatment visit (Day 22) 48 biopsies were taken after the last assessment and sutures were removed 10 days later. If applicable a follow-up visit was performed. A biopsy scheme was employed that ensured that an equal amount of biopsies were available for each of the treatment regimens. No individual subject had more than 2 biopsies taken.

Entry criteria: subjects were either sex, 18 years of age or above with a diagnosis of stable psoriasis vulgaris with lesions on the arms, legs and trunk. Subjects with psoriasis lesions (plaques) assessed by a Total Clinical Score (sum of scores of erythema, scaling and infiltration) of 4 to 9 inclusive but each individual item ≥ 1 .

Treatments: Six (6) test sites of 2-cm diameter were selected on predetermined lesions, marked with a disposable circular device and mapped on a drawn figure. The investigational products were applied once daily (50 μ L per application) 6 days a week (not Sundays) for three weeks (21 days) – for total of 18 application days per patient.

Data collection and analysis:

Absolute change in clinical symptom score (erythema, scaling, infiltration) compared to baseline

Change in Total Clinical Score (TCS) at individual visits compared to baseline;

Ultrasonography (lesion thickness measured by ultrasonography);

Histology and Immunohistochemistry (T-cell markers, epidermal differentiation and epidermal proliferation) and pathology of lesions; were done but only compared ointments and ointment vehicles. Results are not relevant to this application and are not presented in this report.

See Definitions for details of scoring systems

Study participants

Enrolled: 27

Completed: 24 completed (2 subjects withdrew due to exclusion criteria)

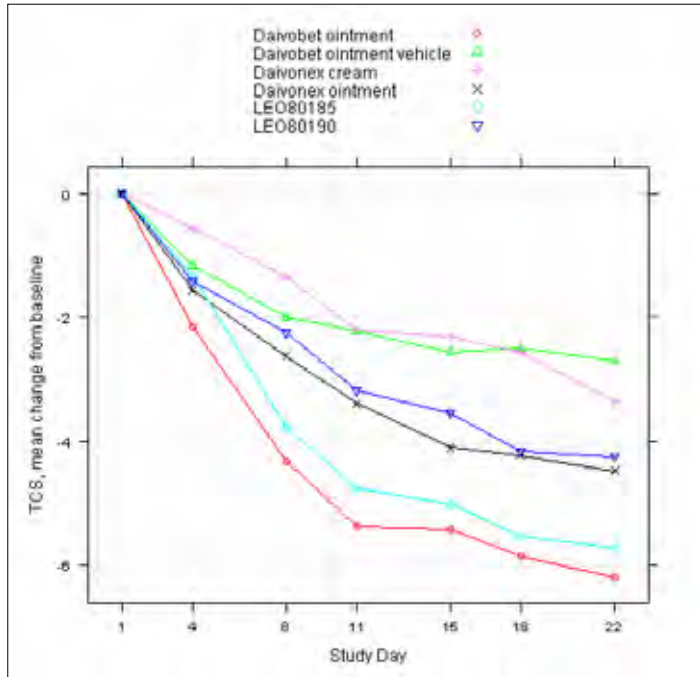
Analysed: 24 (each patient served as own control)

18 out of 24 (75%) were male. The mean age was 53.1 years, and no subject was under 37 years. Out of the 24, 22 (91.7%) had skin type III and the remaining two had skin type II. The mean duration of disease was 26.8 years (SD 12.5).

6.1.2.2.2. Results

Primary response outcome – absolute change in TCS for the different treatments

Figure 12. Study PLQ-001 Absolute change in TCS for the different treatments: full analysis set



The six treatments divide into three groups:

1. Daivobet ointment and LEO 80185 (Daivobet gel) with largest reductive effect on TCS
2. Calcipotriol ointment and LEO 80190
3. Daivobet ointment vehicle and calcipotriol cream

The differences between the three groups are statistically significant as shown below:

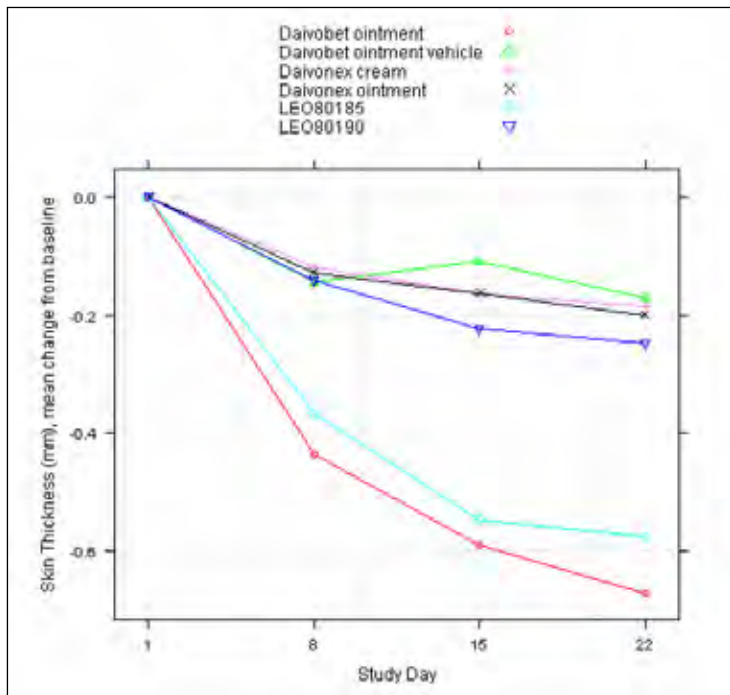
Table 18. Study PLQ-001 Pair-wise t-tests comparing the absolute change in Total Clinical Score from baseline to end of treatment: full analysis set

P-value Student's T-test	LEO80190	Daivobet gel LEO80185	Daivonex cream	Daivonex ointment	Daivobet ointment
Daivobet ointment					
Ointment vehicle	0.003	<0.001	0.12	<0.001	<0.001
LEO80190		<0.001	0.030	0.53	<0.001
Daivobet gel			<0.001	<0.001	0.23
Calcipotriol cream				0.004	<0.001

P-value Student's T-test	LEO80190	Daivobet gel LEO80185	Daivonex cream	Daivonex ointment	Daivobet ointment
Calcipotriol ointment					<0.001

Table 19. Study PLQ-001 Pair-wise Wilcoxon's signed rank tests comparing absolute change in TCS from baseline to end of treatment: full analysis set

P-value, Wilcoxon's signed rank test	LEO80190	Daivobet Gel (LEO80185)	Daivonex cream	Daivonex ointment	Daivobet ointment
Daivobet ointment					
Ointment vehicle	0.003	<0.001	0.043	<0.001	<0.001
LEO80190		<0.001	0.029	0.85	<0.001
Daivobet gel			<0.001	<0.001	0.21
Calcipotriol cream				0.004	<0.001
Calcipotriol ointment					<0.001

*Ultrasound measurements of skin thickness***Figure 13. Study PLQ-001 Absolute change from baseline in ultrasound measurements of skin thickness: randomised patients**

Ultrasound measurements of skin thickness confirms the impression from the analysis of the TCS that Daivobet ointment and Daivobet gel were the two most effective treatments.

Table 20. Study PLQ-001 Absolute change in ultrasound measurements of skin thickness from baseline to end of treatment: full analysis set

Thickness - Absolute change from baseline to end of treatment (mm)	Daivobet ointment vehicle	LEO80190	Daivobet gel LEO80185	Daivonex cream	Daivonex ointment	Daivobet ointment
Mean	-0.17	-0.25	-0.58	-0.19	-0.20	-0.67
SD	0.32	0.25	0.32	0.29	0.26	0.30
Median	-0.19	-0.25	-0.53	-0.13	-0.21	-0.68
Min	-1.00	-0.69	-1.32	-0.63	-0.66	-1.13
Max	0.42	0.13	-0.04	0.36	0.30	-0.02
N	24	24	24	24	24	24

Table 21. Study PLQ-001 Pair-wise t-tests comparing absolute change in ultrasound measurements of skin thickness from baseline to end of treatment

P-value, Student's T test	LE080190	Daivobet gel LE080185	Daivonex cream	Daivonex ointment	Daivobet ointment
Daivobet ointment					
Ointment vehicle	0.31	<0.001	0.81	0.66	<0.001
LE080190		<0.001	0.39	0.47	<0.001
Daivobet gel (LE080185)			<0.001	<0.001	0.20
Daivonex cream				0.87	<0.001
Daivonex ointment					<0.001

Table 22. Study PLQ-001 Pair-wise Wilcoxon's signed rank test comparing absolute change in Ultrasound measurements of skin thickness from baseline to end of treatment

P-value, Wilcoxon's signed rank test	LE080190	Daivobet gel LE080185	Daivonex cream	Daivonex ointment	Daivobet ointment
Daivobet ointment					
Ointment vehicle	0.58	<0.001	0.76	0.75	<0.001
LE080190		<0.001	0.54	0.70	<0.001
Daivobet gel (LE080185)			<0.001	<0.001	0.16
Daivonex cream				1.00	<0.001
Daivonex ointment					<0.001

Histology and immunohistochemistry

The results of the studies comparing the ointments and ointment vehicles showed that calcipotriol (in Daivonex), in contrast to steroids (in Daivobet), primarily have effect on cell

differentiation (strong effect on morphology), and only modest effect on the inflammation in psoriasis, whereas the opposite is true for steroids. The results also demonstrated a good correlation between the selected biomarkers and TCS in the psoriasis lesions.

6.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

Comment: The applicant has presented a report called a “pooled analysis” of the comparative studies: LEO80185-G23, LEO80185-G21 and MBL0202INT. In parts of the submission this is also called a “meta-analysis” of the three comparative studies however the statistical report does not refer to a meta-analysis. The pooled analysis is not a true meta-analysis as it does not follow the appropriate approved EU guideline for meta-analysis.

It is reasonable to pool the comparative studies as the study design, the inclusion/exclusion criteria and outcome parameters are similar (see details of scoring scales under Definitions, above).

The report of the pooled analysis is very poorly written and the report is identical to the Module 2 Summary of Clinical Efficacy. In the report only Study LEO80185-G23 is called ‘pivotal’ and the results of the other two studies are compared to the ‘pivotal’ study. No explanation is given for this classification of the studies. Also there is no discussion of the results of the pooled analysis compared to the individual studies for the primary response criteria of ‘controlled disease’ at 4 and 8 weeks.

The analysis was done for the full analysis set which includes all subjects randomised in all three studies and the subset of patients who had ‘mild’ or ‘moderate’ disease at baseline (all subjects in study LEO80185-G23 and subsets of patients from LEO80185-G21 and MBL0202INT. The statistical analysis plan and statistical report for the meta-analysis is included in the submission.

Full analysis set

In the all studies pooled population, subjects had a mean age of 49.8 years, 60.2% were male and the majority were white (91.9%). The mean duration of psoriasis was 17.9 years, mean BSA of total psoriasis involvement at baseline was 11.4% (only assessed in Study LEO80185-G23 and LEO80185-G21) and mean baseline PASI was 8.23. According to the IGA the majority of patients (72.2%) were assessed as having “moderate” disease at baseline, 17.0% had “mild” disease and 10.1% were assessed as “severe”. Very few subjects (0.7%) had “very severe” disease.

The demographic and baseline characteristics were largely similar in the individual studies. In Study LEO80185-G21 there were no subjects with “mild” disease as these were excluded in the protocol. Likewise in Study LEO80185-G23 there were no subjects with “severe” and “very severe” disease. In Study LEO80185-G21, which included subjects with “severe” and “very severe” disease, the baseline PASI was higher than the other two studies and the psoriasis covered a lower BSA than observed in LEO80185-G23.

Table 23. Summary of results of pooled data and individual studies

Response rate Controlled disease	LEO80185- G23 (%)	LEO80185-G21 (%)	MBL0202INT (%)	Pooled data (%)
Week 4	13.3	18.6	16.0	15.0
Week 8	29.0	39.9	27.2	31.1

Table 24. Pooled Data - 'Controlled disease' (IGA) at Week 4 and 8 by study, treatment group and pooled treatment group: full analysis set

	Daivobet gel	Betametha- sone gel	Calcipotriol gel	Gel vehicle	Tacalcitol
Week Controlled disease	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)
Week 4					
Controlled Disease	124 (15.0)	68 (12.1)	8 (4.6)	4 (1.8)	12 (6.5)
Non- Controlled Disease	703 (85.0)	494 (87.9)	167 (95.4)	222 (98.2)	172 (93.5)
Total	827 (100.0)	562 (100.0)	175 (100.0)	226 (100.0)	184 (100.0)
Lower 95% CL(controlled)	12.6	9.5	2.0	0.5	3.4
Upper 95% CL(controlled)	17.6	15.1	8.8	4.5	11.1
Week 8					
Controlled Disease	257 (31.1)	117 (20.8)	23 (13.1)	11 (4.9)	33 (17.9)
Non- Controlled Disease	570 (68.9)	445 (79.2)	152 (86.9)	215 (95.1)	151 (82.1)
Total	827 (100.0)	562 (100.0)	175 (100.0)	226 (100.0)	184 (100.0)
Lower 95% CL(controlled)	27.9	17.5	8.5	2.5	12.7
Upper 95% CL(controlled)	34.4	24.4	19.1	8.5	24.3

Table 25. Pooled data - Statistical analysis of 'Controlled disease' (IGA) at Week 4 and 8 by study: full analysis set

Week Study	Treatment comparison	Odds ratio ¹	95% CI	Treatment diff p-value ²	Homogeneity p-value ³
Week 4					

Week Study	Treatment comparison	Odds ratio ¹	95% CI	Treatment diff p-value ²	Homogeneity p-value ³
LEO80185-G23	Daivobet gel - Betamethasone gel	1.05	0.71 to 1.54	0.82	0.65
	Daivobet gel - Calcipotriol gel	2.95	1.15 to 7.60	0.019	0.43
	Daivobet gel - Gel vehicle	8.44	1.92 to 37.08	0.001	0.96
MBL0202INT	Daivobet gel - Betamethasone gel	2.02	0.84 to 4.82	0.11	0.39
	Daivobet gel - Calcipotriol gel	5.98	1.53 to 23.34	0.006	0.92
	Daivobet gel - Gel vehicle	10.83	1.04 to 112.73	0.027	1.00
LEO80185-G21	Daivobet gel - Tacalcitol	3.51	1.71 to 7.17	0.001	0.21
	Daivobet gel - Gel vehicle	32.90	3.42 to 316.23	0.001	0.99
Week 8					
LEO80185-G23	Daivobet gel - Betamethasone gel	1.50	1.11 to 2.02	0.008	0.56
	Daivobet gel - Calcipotriol gel	2.78	1.46 to 5.31	0.002	0.94
	Daivobet gel - Gel vehicle	7.51	3.00 to 18.80	<0.001	0.98
MBL0202INT	Daivobet gel - Betamethasone gel	2.40	1.11 to 5.20	0.027	0.88
	Daivobet gel - Calcipotriol gel	2.89	1.31 to 6.38	0.006	0.29
	Daivobet gel - Gel vehicle			<0.001	
LEO80185-G21	Daivobet gel - Tacalcitol	3.42	2.05 to 5.70	<0.001	0.99

Week Study	Treatment comparison	Odds ratio ¹	95% CI	Treatment diff p-value ²	Homogeneity p-value ³
	Daivobet gel - Gel vehicle	13.90	4.99 to 38.72	<0.001	0.88

1) Odds of controlled disease in Daivobet® gel group relative to comparison group.

2) Adjusted for centre effect by Cochran-Mantel-Haenszel test.

3) Breslow-Day test for homogeneity across centres.

Study LE080185-G21 recruited subjects with more severe psoriasis (mild disease was excluded). The definition of 'controlled disease' was different for those with 'moderate' disease or worse at baseline (defined as 'clear' or 'minimal'/'almost clear') compared with those with 'mild' disease at baseline (who had to achieve 'clear'). This may have accounted for the higher response rate in study LE080185-G21.

No analysis of the pooled data is provided in the report.

Psoriasis Area and Severity Index (PASI)

Table 26. Pooled data – Percentage change in PASI from Baseline to Week 4 and 8: full analysis set

Week Study	Treatment comparison	Odds ratio ¹	95% CI	Treatment diff p-value ²
Week 4				
LE080185-G23	Daivobet gel - Betamethasone gel	-3.93	-7.64 to -0.23	0.038
	Daivobet gel - Calcipotriol gel	-16.27	-22.73 to -9.30	<0.001
	Daivobet gel - Gel vehicle	-28.91	-35.36 to -22.45	<0.001
MBL0202INT	Daivobet gel - Betamethasone gel	-8.71	-16.09 to -1.33	0.21
	Daivobet gel - Calcipotriol gel	-15.82	-23.28 to -8.36	<0.001
	Daivobet gel - Gel vehicle	-31.33	-40.92 to -21.74	<0.001
LE080185-G21	Daivobet gel - Tacalcitol	-15.45	-20.85 to -10.06	<0.001
	Daivobet gel - Gel vehicle	-39.60	-46.21 to -32.99	<0.001
Week 8				
LE080185-G23	Daivobet gel - Betamethasone gel	-7.62	-12.10 to -3.14	<0.001

Week Study	Treatment comparison	Odds ratio ¹	95% CI	Treatment diff p-value ²
	Daivobet gel - Calcipotriol gel	-14.86	-22.67 to -7.05	<0.001
	Daivobet gel - Gel vehicle	-34.24	-42.03 to -26.44	<0.001
MBL0202INT	Daivobet gel - Betamethasone gel	-7.18	-15.23 to 0.86	0.080
	Daivobet gel - Calcipotriol gel	-14.65	-22.78 to -6.52	<0.001
	Daivobet gel - Gel vehicle	-44.06	-54.52 to -33.61	<0.001
LEO80185-G21	Daivobet gel - Tacalcitol	-14.94	-21.38 to -8.49	<0.001
	Daivobet gel - Gel vehicle	-38.97	-46.86 to -31.08	<0.001

1) ANOVA, adjusted for the effect of centre and baseline IGA

Mild/moderate analysis set

Table 27. Pooled data – Subjects achieving ‘controlled disease’ at week 4 and 8 by study and pooled data

Response rate Controlled disease	LEO80185-G23 (%)	LEO80185-G21 (%)	MBL0202INT (%)	Pooled data (%)
Week 4	13.3	20.8	20.6	15.0
Week 8	29.0	41.5	31.7	31.1

Table 28. Pooled data - ‘Controlled disease’ (IGA) at Week 4 and 8 by study, treatment group and pooled treatment group: mild/moderate analysis set

	Daivobet gel	Betamethasone gel	Calcipotriol gel	Gel vehicle	Tacalcitol gel
Week Controlled disease	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)	Number of subjects (%)
Week 4					
Controlled Disease	117 (15.9)	67 (12.2)	8 (4.9)	4 (2.1)	10 (8.4)
Non-Controlled	621	480	155	190	109

	Daivobet gel	Betamethasone gel	Calcipotriol gel	Gel vehicle	Tacalcitol
Disease	(84.1)	(87.8)	(95.1)	(97.9)	(91.6)
Total	738 (100.0)	547 (100.0)	175 (100.0)	194 (100.0)	119 (100.0)
Lower 95% CL(controlled)	13.3	9.6	2.1	0.6	4.1
Upper 95% CL(controlled)	18.7	15.3	9.4	5.2	14.9
Week 8					
Controlled Disease	234 (31.7)	116 (21.2)	23 (14.1)	11 (5.7)	25 (21.0)
Non-Controlled Disease	504 (68.3)	431 (78.8)	140 (85.9)	183 (94.3)	94 (79.0)
Total	738 (100.0)	547 (100.0)	163 (100.0)	194 (100.0)	119 (100.0)
Lower 95% CL(controlled)	28.4	17.9	9.2	2.9	14.1
Upper 95% CL(controlled)	35.2	24.9	20.4	9.9	29.4

Table 29. Pooled data - Statistical analysis of 'Controlled disease' (IGA) at Week 4 and 8 by study: mild/moderate analysis set

Week Study	Treatment comparison	Odds ratio ¹	95% CI	Treatment diff p-value ²	Homogeneity p-value ³
Week 4					
LEO80185-G23	Daivobet gel - Betamethasone gel	1.05	0.71 to 1.54	0.82	0.65
	Daivobet gel - Calcipotriol gel	2.95	1.15 to 7.60	0.019	0.43
	Daivobet gel - Gel vehicle	8.44	1.92 to 37.08	0.001	0.96
MBL0202INT	Daivobet gel - Betamethasone gel	2.52	1.01 to 6.29	0.039	0.16
	Daivobet gel -	6.67	1.71 to	0.003	0.89

Week Study	Treatment comparison	Odds ratio ¹	95% CI	Treatment diff p-value ²	Homogeneity p-value ³
	Calcipotriol gel		26.03		
	Daivobet gel - Gel vehicle	21.50	1.29 to 358.02	0.012	1.00
LEO80185-G21	Daivobet gel - Tacalcitol	3.34	1.44 to 7.75	0.003	0.17
	Daivobet gel - Gel vehicle	67.80	3.63 to 1266.51	<0.001	1.00
Week 8					
LEO80185-G23	Daivobet gel - Betamethasone gel	1.50	1.11 to 2.02	0.008	0.56
	Daivobet gel - Calcipotriol gel	2.78	1.46 to 5.31	0.002	0.94
	Daivobet gel - Gel vehicle	7.51	3.00 to 18.80	<0.001	0.98
MBL0202INT	Daivobet gel - Betamethasone gel	2.61	1.11 to 6.17	0.030	0.92
	Daivobet gel - Calcipotriol gel	2.85	1.25 to 6.47	0.009	0.27
	Daivobet gel - Gel vehicle			<0.001	
LEO80185-G21	Daivobet gel - Tacalcitol	3.25	1.73 to 6.10	<0.001	1.00
	Daivobet gel - Gel vehicle	10.18	3.65 to 28.42	<0.001	0.72

1) Odds of controlled disease in Daivobet® gel group relative to comparison group.

2) Adjusted for centre effect by Cochran-Mantel-Haenszel test.

3) Breslow-Day test for homogeneity across centres.

Table 30. Meta-analysis of 'Controlled disease' (IGA) at Week 4 and 8: mild/moderate analysis set

Week Treatment comparison	Odds ratio ¹	95% CI	Treatment difference p- value ²	Homogeneity p- value ³
Week 4				
Daivobet gel - Betamethasone gel	1.22	0.86 to 1.73	0.28	0.51
Daivobet gel - Calcipotriol gel	3.90	1.79 to 8.46	0.001	0.53
Daivobet gel - Gel vehicle	15.22	4.62 to 50.13	0.001	1.00
Week 8				
Daivobet gel - Betamethasone gel	1.60	1.21 to 2.12	0.001	0.83
Daivobet gel - Calcipotriol gel	2.81	1.69 to 4.66	0.001	0.83
Daivobet gel - Gel vehicle	10.30	5.22 to 20.34	0.001	1.00

1) Odds of controlled disease in Daivobet gel group relative to comparison group.

2) Adjusted for study and centre effect by Cochran-Mantel-Haenszel test.

3) Breslow-Day test for homogeneity across centres.

Treatment comparison at Week 4: the analysis of the pooled treatment groups found that Daivobet gel was not statistically significantly superior to betamethasone gel (OR = 1.22, p=0.28). Daivobet gel was statistically significantly better than calcipotriol gel and gel vehicle.

Further, the meta-analysis of 'controlled disease' at week 4 did not show superiority of Daivobet gel using the Hochberg adjustment for multiple primary endpoints since the largest p-value amongst the three pairwise comparisons (versus betamethasone gel, calcipotriol gel, and gel vehicle) was 0.28, which is larger than 0.05.

Treatment comparison at Week 8: the analysis of the pooled treatment found that Daivobet gel was statistically significantly superior to betamethasone gel, calcipotriol gel and gel vehicle.

Further, the meta-analysis of 'controlled disease' at week 8 showed superiority of Daivobet gel using the Hochberg adjustment for multiple primary endpoints since the largest p-value amongst the three pairwise comparisons (versus betamethasone gel, calcipotriol gel, and gel vehicle) was 0.001, which is smaller than 0.025.

Percentage change in PASI from baseline to week 4 and 8

Table 31. Pooled data – Percentage change in PASI at week 4 and 8

Response rate Percentage change in PASI	LEO80185- G23 (%)	LEO80185- G21 (%)	MBL0202INT (%)	Pooled data (%)
Week 4	-47.4	-54.9	-51.8	-50.1
Week 8	-56.7	-56.2	-60.1	-57.5

Table 32. Pooled data – Statistical analysis of treatment comparisons – percentage change in PASI from baseline to week 4 and 8

Week Study	Treatment comparison	Odds ratio ¹	95% CI	Treatment diff p-value ²
Week 4				
LEO80185- G23	Daivobet gel - Betamethasone gel	-3.93	-7.64 to -0.23	0.038
	Daivobet gel - Calcipotriol gel	-16.27	-22.73 to -9.30	<0.001
	Daivobet gel - Gel vehicle	-28.91	-35.36 to - 22.45	<0.001
MBL0202INT	Daivobet gel - Betamethasone gel	-9.70	-17.98 to -1.41	0.22
	Daivobet gel - Calcipotriol gel	-16.79	-25.05 to -8.54	<0.001
	Daivobet gel - Gel vehicle	-31.11	-41.52 to - 20.69	<0.001
LEO80185- G21	Daivobet gel - Tacalcitol	-16.49	-23.16 to -9.83	<0.001
	Daivobet gel - Gel vehicle	-39.14	-47.15 to - 31.13	<0.001
Week 8				
LEO80185- G23	Daivobet gel - Betamethasone gel	-7.62	-12.10 to -3.14	<0.001
	Daivobet gel - Calcipotriol gel	-14.86	-22.67 to -7.05	<0.001

Week Study	Treatment comparison	Odds ratio ¹	95% CI	Treatment diff p-value ²
	Daivobet gel - Gel vehicle	-34.24	-42.03 to -26.44	<0.001
MBL0202INT	Daivobet gel - Betamethasone gel	-7.17	-16.16 to 1.83	0.12
	Daivobet gel - Calcipotriol gel	-16.56	-25.53 to -7.60	<0.001
	Daivobet gel - Gel vehicle	-45.86	-57.16 to -34.55	<0.001
LEO80185-G21	Daivobet gel - Tacalcitol	-15.41	-23.37 to -7.45	<0.001
	Daivobet gel - Gel vehicle	-35.44	-45.01 to -25.87	<0.001

1) Odds of controlled disease in Daivobet gel group relative to comparison group.

2) Adjusted for study and centre effect by Cochran-Mantel-Haenszel test.

Table 33. Pooled data - Meta-analysis of percentage change in PASI from baseline to Week 4 and 8: mild/moderate analysis set

Week / Percentage change in PASI	Daivobet gel	Betamethasone gel	Calcipotriol gel	Gel vehicle	Tacalcitol
Week 4					
Least square mean ¹	-50.1	-44.9	-33.6	-18.0	-36.0
95% CI ¹	-52.6 to -47.7	-47.9 to -42.0	-38.3 to -28.8	-22.2 to -13.7	-42.3 to -29.6
Mean	-48.3	-42.5	-32.2	-16.5	-36.1
SD	30.1	29.9	25.8	33.0	29.3
Median	-50.0	-42.3	-32.7	-14.8	-40.0
Minimum	-100.0	-100.0	-93.8	-98.1	-91.1
Maximum	118.8	62.0	59.3	172.7	28.6

Week / Percentage change in PASI	Daivobet gel	Betamethasone gel	Calcipotriol gel	Gel vehicle	Tacalcitol gel
Number	738	547	163	194	119
Difference ²		-5.22	-16.59	-32.20	-14.20
95% CI		-8.50 to -1.93	-21.59 to -11.60	-36.78 to -27.62	-20.89 to -7.50
P value		0.002	<0.001	<0.001	<0.001
Week 8					
Least square mean ¹	-57.5	-50.0	-42.4	-20.7	-41.7
95% CI ¹	-60.4 to -54.6	-53.5 to -46.5	-48.0 to -36.7	-25.8 to -15.7	-49.2 to -34.1
Mean	-56.3	-49.0	-42.4	-18.9	-38.2
SD	33.1	35.7	33.2	42.0	36.1
Median	-63.8	-53.8	-44.8	-16.7	-38.5
Minimum	-100	-100.0	-100.0	-100.0	-94.1
Maximum	73.2	82.8	59.3	172.7	46.7
Number	738	547	163	194	119
Difference ²		-7.52	-15.17	-36.77	-15.85
95% CI		-11.42 to -3.62	-21.10 to -9.23	-42.21 to -31.33	-23.80 to -7.90
P value		<0.001	<0.001	<0.001	<0.001

Treatment comparison at Week 4: the analysis of the pooled treatment groups found that Daivobet gel was statistically significantly more effective than betamethasone gel (difference -5.22, p=0.002) and calcipotriol gel (difference -16.59, p<0.001) and gel vehicle (difference -32.20, p<0.001).

Further, the meta-analysis of 'controlled disease' at week 4 showed superiority of Daivobet gel using the Hochberg adjustment for multiple primary endpoints since the largest p-value amongst the three pair wise comparisons (versus betamethasone gel, calcipotriol gel, and gel vehicle) was 0.002, which is larger than 0.05.

Treatment comparison at Week 8: the analysis of the pooled treatment found that Daivobet gel was statistically significantly more effective than betamethasone gel (difference -7.52, $p < 0.001$), calcipotriol gel and gel vehicle (difference -36.77, $p < 0.001$).

Further, the meta-analysis of 'controlled disease' at week 8 showed superiority of Daivobet gel using the Hochberg adjustment for multiple primary endpoints since the largest p-value amongst the three pair wise comparisons (versus betamethasone gel, calcipotriol gel, and gel vehicle) was < 0.001 , which is smaller than 0.05.

6.1.4. Evaluator's conclusions on clinical efficacy for extension of indication to include psoriasis of the body

No study was conducted in which there was a direct comparison between Daivobet ointment and Daivobet gel. This is surprising as the company development plan stated that the Daivobet gel was developed as a formulation expected to have similar efficacy and safety but greater patient acceptability. This has not been tested. One of the supportive studies (PLQ001) does compare gel with ointment but no direct analysis of results is given.

Instead the company provided studies in which the primary efficacy outcome was the percentage of patients with 'controlled disease' ('clear' or 'almost clear'):

- one comparative study against the individual components (in the gel vehicle) which found superiority to betamethasone alone only at 8 weeks (not at 4 weeks). It was superior to calcipotriol and gel vehicle at both 4 and 8 weeks
- one comparative study against tacalcitol (which is not approved for sale in Australia) and the gel vehicle which found that the combination was superior to the tacalcitol and gel vehicle at both 4 and 8 weeks
- one supportive study which also found that Daivobet gel was superior to calcipotriol gel and the gel vehicle at 4 and 8 weeks but was only superior to betamethasone at 8 weeks
- one supportive study which suggests similar effectiveness (absolute change in TCS) between Daivobet gel and ointment

Efficacy beyond 8 weeks was not tested. Only approx 30% of all patients achieved 'clear' disease at 8 weeks and so it is disappointing that a longer term trial was not conducted as there is likely to be pressure to continue treatment beyond 8 weeks if some improvement is achieved but not clearing of all lesions. The results are consistent in the studies presented.

The studies presented are not strictly in compliance with the approved guideline. Only one primary efficacy parameter was included in each study. Secondary outcomes did include other scoring systems. No long term study is presented (required in guideline).

It is risky and difficult to compare results across different trials but comparing the results presented in this submission versus that presented in the original ointment submission the impression is that the gel formulation is slightly less effective than the ointment formulation.

7. Clinical safety

7.1. Studies providing evaluable safety data

Comment: The Summary of Clinical Safety presents data on the 'safety analysis set' comprising only the 3 comparative studies (LEO80185-G23, LEO80185-G21 and MBL0202INT). The PD study (LEO80185-G24) and the other efficacy study PLQ-001 is included only in some sections of the summary but not in all the tabulations of AEs. Where possible the data from the additional studies is taken from the individual study reports in addition to the data presented by the applicant in the summary.

The following studies provided evaluable safety data:

Comparative efficacy studies

In the comparative efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by means of non-leading questioning of the subjects and by recording changes not reported by the subjects but observed by the investigator.
- AEs of particular interest, including cutaneous events, were assessed in studies MBL0202INT and LEO80185-G21 as lesional/perilesional AE or distant from the treated lesions. A lesional/perilesional AE was defined as an AE located less than or equal to 2 cm from the lesional border of areas treated with the investigational product. Study LEO80185-G23 did not record cutaneous AEs in the same manner as the other two studies (although this was planned in the protocol) but it was recorded whether AEs were 'in the treatment area' or not. The AEs recorded 'in the treatment area' in Study LEO80185-G23 have been pooled together with the lesional/perilesional AEs in Study MBL0202INT and LEO80185-G21. This is a conservative approach as any non-cutaneous AEs and AEs distant from the treated lesions but in the treatment area would be included.
- Laboratory tests were only conducted in the comparative Studies LEO80185-G23 and PLQ-001. No clinical laboratory evaluations were performed in Studies LEO80185-G21 or MBL0202INT. Study LEO80185-G23 included measurement of serum calcium, albumin, ALP, and phosphate, plasma PTH, and urinary calcium, phosphate and creatinine from a spot test. Albumin corrected serum calcium, and urinary calcium:creatinine and phosphate:creatinine ratios were calculated.

Pivotal studies that assessed safety as a primary outcome

No pivotal studies assessed safety as a primary outcome.

Dose-response and non-pivotal efficacy studies

Not applicable. Studies included in the safety analysis set included all comparative efficacy studies.

Other studies evaluable for safety only

Not applicable.

Clinical pharmacology studies

Study LEO80185-G24 provides safety data on the effect of Daivobet gel on the HPA axis and calcium metabolism.

7.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

7.3. Patient exposure

Table 34. Exposure to Daivobet and comparators in clinical studies

Study type/ Indication	Controlled studies					Un- contr olled studie s	Tota l Daiv obet gel
	Daivobet gel	Gel vehicle	Betametha- sone gel	Calcipo- triol gel	Tacalcitol ointment		
Clinical pharmacology LEO80185-G24						43	43
Pivotal: LEO80185-G23	482	95	479	96			482
LEO80185-G21	182	91	0	0	184		182
Other MBL0202INT	160	40	83	79			160
PLQ-001*	24						24
TOTAL	848	226	562	175	184	43	891

* in study PLQ-001 each patient served as own control for comparison with calcipotriol cream and ointment

Table 35. Duration of exposure to Daivobet gel in clinical studies: Duration of exposure to study treatment in 'controlled non-scalp studies': safety analysis set

Length of drug exposure	Daivobet gel (n=824)	Betametha-sone gel (n=562)	Calcipotriol gel (n=175)	Gel vehicle (n=226)	Tacalcitol (n=184)
Exposure <4 weeks. No (%)	43 (5.2)	47 (8.4)	15 (8.6)	30 (13.3)	11 (6.0)
Exposure ≥4 weeks. No (%)	781 (94.8)	515 (91.6)	160 (91.4)	196 (86.7)	173 (94.0)
Exposure ≥8 weeks. No (%)	615 (74.6)	400 (71.2)	123 (70.3)	143 (63.3)	123 (66.8)
Mean exposure (weeks)	7.7	7.4	7.4	7.0	7.6
Number of exposed subjects	824	562	175	226	184

Length of drug exposure	Daivobet gel (n=824)	Betametha-sone gel (n=562)	Calcipotriol gel (n=175)	Gel vehicle (n=226)	Tacalcitol (n=184)
Subject-treatment-weeks	6323	4176	1290	1581	1391

For study-G24: the 43 subjects in the study had a mean duration of exposure of 7.5 weeks (SD 1.1; range 4.3 to 8.3 weeks).

In Study PLQ-001 – 24 subjects were treated with 18 applications over 3 weeks.

In each of the ‘controlled non-scalp studies’, subjects were instructed to treat all psoriasis vulgaris lesions on the trunk and/or arms and/or legs (genitals and skin folds were excluded) with a maximum of 100 g of topical gel per week. The amount of study drug used in the ‘controlled non-scalp studies’ was calculated by subtracting the weight of the used bottles from the mean weight of full bottles. An average weekly amount of study drug used was calculated by dividing the total amount of study drug used by the number of days of exposure then multiplying by 7 and is shown in Table below.

Table 36. Average weekly amount of study drug used for the ‘controlled non-scalp studies’: safety analysis set

Average study drug used ¹ (g/week)	Daivobet gel (n=824)	Betametha-sone gel (n=562)	Calcipotriol gel (n=175)	Gel vehicle (n=226)	Tacalcitol (n=184)
Mean	29.0	27.4	29.8	28.3	33.2
SD	23.2	22.1	22.2	23.3	23.2
Median	22.6	21.1	25.5	19.6	27.3
Minimum	0	0	0	0	0
Maximum	102	91	94	92	95
Number ²	706	454	146	171	150

1) Calculated by subtracting the weight of the used bottles from the mean normal weight of full bottles. Negative weights have been set to zero.

2) Only subjects who returned all dispensed bottles provide data.

The mean amount of Daivobet gel used was 29.0 g/week with approximately 46 % of subjects using <20 g/week and 73% using <40 g/week.

In Study LE080185-G24 the average weekly amount of Daivobet gel used was 52 g (range 7.6 to 93 g).

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Comparative studies

Table 37. Adverse events occurring in $\geq 1\%$ of subjects in the Daivobet gel, betamethasone gel, calcipotriol gel or gel vehicle group by Med- DRA primary system organ class and preferred term for the 'controlled non-scalp studies': safety analysis set

System Organ Class Preferred Term ¹	Daivobet gel (n=824) No (%)	Betametha- sone gel (n=562) No (%)	Calcipotriol gel (n=175) No (%)	Gel vehicle (n=226) No (%)	Tacalcitol (n=184) No (%)
Infections and infestations					
Nasopharyngitis	44 (5.3)	21 (3.7)	10 (5.7)	6 (2.7)	6 (3.3)
Upper respiratory tract infection	30 (3.6)	11 (2.0)	4 (2.3)	4 (1.8)	10 (5.4)
Influenza	11 (1.3)	6 (1.1)	1 (0.6)	4 (1.8)	2 (1.1)
Sinusitis	11 (1.3)	4 (0.7)	2 (1.1)	2 (0.9)	1 (0.5)
Bronchitis	9 (1.1)	2 (0.4)	1 (0.6)	1 (0.4)	1 (0.5)
Nervous system disorders					
Headache	13 (1.6)	7 (1.2)	0 (0.0)	3 (1.3)	2 (1.1)
Burning sensation.	2 (0.2)	0 (0.0)	0 (0.0)	5 (2.2)	2 (1.1)
Sciatica	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders					
Oropharyngeal pain	4 (0.5)	1 (0.2)	3 (1.7)	3 (1.3)	0 (0.0)
Gastrointestinal disorders					
Diarrhoea	4 (0.5)	2 (0.4)	1 (0.6)	5 (2.2)	3 (1.6)
Skin and subcutaneous tissue disorders					
Pruritus	13 (1.6)	3 (0.5)	6 (3.4)	16 (7.1)	13 (7.1)
Psoriasis	3 (0.4)	6 (1.1)	3 (1.7)	3 (1.3)	3 (1.6)
Erythema	2 (0.2)	1 (0.2)	2 (1.1)	0 (0.0)	1 (0.5)
Skin burning sensation	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.9)	1 (0.5)
General disorders and administration site conditions					

System Organ Class Preferred Term ¹	Daivobet gel (n=824) No (%)	Betamethasone gel (n=562) No (%)	Calcipotriol gel (n=175) No (%)	Gel vehicle (n=226) No (%)	Tacalcitol (n=184) No (%)
Pain	4 (0.5)	2 (0.4)	2 (1.1)	0 (0.0)	0 (0.0)
Application site pain	3 (0.4)	1 (0.2)	0 (0.0)	3 (1.3)	2 (1.1)
Investigations					
Blood parathyroid hormone increased	13 (1.6)	9 (1.6)	0 (0.0)	1 (0.4)	0 (0.0)

1) Classification according to MedDRA version 14.1.

7.4.1.2. Other studies

The adverse events for Study LE080185-G24 are shown in the table below.

Table 38. Study LE08085-G24 Adverse events by MedDRA primary system organ class and preferred term: safety analysis set

Daivobet gel (n=43)		
System Organ Class Preferred Term ¹	Number of subjects	%
ENDOCRINE DISORDERS		
Adrenal suppression	3	7.0
GASTROINTESTINAL DISORDERS		
Abdominal pain	1	2.3
Diarrhoea	1	2.3
Gastroesophageal reflux disease	1	2.3
INFECTIONS AND INFESTATIONS		
Gastroenteritis viral	1	2.3
Helicobacter infection	1	2.3
Impetigo	1	2.3
Tooth infection	1	2.3
Upper respiratory tract infection	1	2.3

Daivobet gel (n=43)		
System Organ Class Preferred Term ¹	Number of subjects	%
INVESTIGATIONS		
Myelocyte count	1	2.3
METABOLISM AND NUTRITION DISORDERS		
Hypocalcaemia	1	2.3
MUSCULOSKELETAL DISORDERS AND CONNECTIVE TISSUE		
Back pain	1	2.3
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Hyperhidrosis	1	2.3
VASCULAR DISORDERS		
Hypertension	2	4.7
Total number of adverse events ²	17	
Total number of subjects	13	30.2

1) Classification according to MedDRA version 14.1.

2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

7.4.2. Treatment-related adverse events (adverse drug reactions)

7.4.2.1. Comparative studies

Table 39. Adverse drug reactions occurring in $\geq 1\%$ of subjects in the Daivobet gel, betamethasone gel, calcipotriol gel or gel vehicle group by MedDRA primary system organ class and preferred term for the 'controlled non-scalp studies': safety analysis set

System Organ Class Preferred Term ¹	Daivobet gel (n=824) No (%)	Betameth- asone gel (n=562) No (%)	Calcipotriol gel (n=175) No (%)	Gel vehicle (n=226) No (%)	Tacalcitol (n=184) No (%)
Nervous system disorders					
Burning sensation	2 (0.2)	0 (0.0)	0 (0.0)	5 (2.2)	2 (1.1)

System Organ Class Preferred Term ¹	Daivobet gel (n=824) No (%)	Betamethasone gel (n=562) No (%)	Calcipotriol gel (n=175) No (%)	Gel vehicle (n=226) No (%)	Tacalcitol (n=184) No (%)
Skin and subcutaneous tissue disorders					
Pruritus	12 (1.5)	2 (0.4)	5 (2.9)	15 (6.6)	11 (6.0)
Erythema	1 (0.1)	0 (0.0)	2 (1.1)	0 (0.0)	1 (0.5)
Skin burning sensation	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.9)	1 (0.5)
General disorders and administration site conditions					
Application site pain	3 (0.4)	1 (0.2)	0 (0)	0 (1.3)	2 (1.1)
Pain	2 (0.2)	1 (0.2)	2 (1.1)	0 (0.0)	0 (0.0)
Investigations					
Blood parathyroid hormone increased	7 (0.9)	6 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)

1) Classification according to MedDRA version 14.1.

7.4.2.2. Other studies

Table 40. Relationship of adverse events to trial medication by MedDRA primary system organ class and preferred term: safety analysis set

System Organ Class Preferred Term ¹	Daivobet gel (n=43)	
	No of subjects	%
ENDOCRINE DISORDERS		
Adrenal suppression	3	7.0
INFECTION AND INFESTATIONS		
Tooth infection	1	2.3
INVESTIGATIONS		
Myelocyte count	1	2.3
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Hyperhidrosis	1	2.3

System Organ Class Preferred Term ¹	Daivobet gel (n=43)	
	No of subjects	%
Total number of adverse events ²	6	
Total number of subjects	6	14.0

1) Classification according to MedDRA version 14.1.

2) Different adverse drug reactions within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

7.4.3. Deaths and other serious adverse events

There were no deaths in either the comparative efficacy studies or the PD study.

7.4.3.1. Comparative studies

Two SAE occurred in the Daivobet group - hypertension and cerebral infarction. Both were considered unrelated to study medication by the investigator.

7.4.3.2. Other studies

In Study LEO 80185-G24 there was one SAE. This was the presence of myelocytes in the peripheral blood film. This occurred 2 months after starting therapy (Day 56). The investigator considered this to be of mild intensity. The patient was not withdrawn from the study. At follow up 2 weeks later the haematology was repeated and was negative for myelocytes and the event was reported as resolved. The investigator considered the event to be possibly related to the study medication.

7.4.4. Discontinuation due to adverse events

7.4.4.1. Comparative studies

In the Daivobet gel group, the only AEs that led to withdrawal of more than one subject were psoriasis and application site pain (reported by 2 subjects each).

7.4.4.2. Other studies

In Study LEO 80185-G24 four subjects receiving Daivobet gel withdrew due to AEs, one with hypertension (transient hypertensive state post Cortrosyn injection [ACTH challenge test]) of mild intensity which resolved on the same day and three who were withdrawn as required by the protocol due to signs of adrenal suppression.

7.5. Laboratory tests

No clinical laboratory evaluations were performed in Studies LEO80185-G21, MBL0202INT or PLQ-001. Limited laboratory tests were performed in Studies LEO80185-G23 and LEO80185-G24.

7.5.1. Liver function

No data provided.

7.5.2. Kidney function

No data provided.

7.5.3. Other clinical chemistry

7.5.3.1. Comparative studies

Study LE080185-G23 included measurement of serum calcium, albumin, ALP and phosphate, plasma PTH; and urinary calcium, phosphate and creatinine from a spot test. Albumin corrected serum calcium, and urinary calcium:creatinine and phosphate creatinine ratios were calculated.

7.5.3.1.1. Albumin corrected serum calcium

Mean albumin corrected serum calcium was similar across the treatment groups at all visits and mean changes from baseline were small (range -0.019 to -0.006 mmol/L across the groups and visits). The majority of subjects in all treatment groups had albumin corrected serum calcium values within the normal reference range at baseline and did not record a shift at Weeks 4 and 8 or the end of treatment. For the minority of subjects that recorded a shift, the pattern of shifts from low to normal values and normal to low values was similar across the treatment groups. Only one subject in the betamethasone gel group shifted from a normal value to a high value at Week 4 only. One subject in the betamethasone and one in the gel vehicle group had an albumin corrected serum calcium above the normal reference range (2.15 to 2.55 mmol/L) at baseline but had normal values at all the other measured timepoints.

7.5.3.1.2. Urinary calcium:creatinine ratio

Urinary calcium:creatinine ratio was similar across all treatment groups at all visits and mean changes from baseline were small (range -0.31 to 0.07 mmol/g across groups and visits). The majority of subjects in all treatment groups had urinary calcium:creatinine ratio values within the normal reference range (0.300 to 6.100 mmol/g in males and 0.225 to 8.200 mmol/g in females) at baseline and did not record a shift at Week 4 and 8 or the end of treatment. For the minority of subjects that recorded a shift, the pattern of shifts was largely similar across the treatment groups.

7.5.3.1.3. Parathyroid hormone

Blood parathyroid hormone increase was reported as a common AE in study LE080185-G23. Plasma PTH was similar across the treatment groups at all visits and mean changes from baseline were generally small (range -0.760 to -0.194 pmol/L across groups and visits). The majority of subjects in all treatment groups had plasma PTH values within the normal reference range (1.48 to 7.63 pmol/L) at baseline and did not record a shift at Weeks 4 and 8 or the end of treatment. For the minority of subjects that recorded a shift, the pattern of shifts was largely similar across the treatment groups. Based on the numbers of subjects who had baseline and end of treatment values, 35 subjects (approx 8%) in the Daivobet gel group shifted from normal to high values of PTH and 44 (approx 10%) shifted from high to normal values. In the betamethasone gel, calcipotriol gel and gel vehicle groups the corresponding numbers shifting from normal to high PTH values were 25, 5 and 5 subjects (approx 6% each) and from high to normal values were 40, 10 and 7 subjects (approx 10%, 12% and 9%) respectively. Approximately 20% of subjects across all treatment groups reported a high value at baseline and a similar number in all groups shifted from high to normal values after treatment.

7.5.3.2. Other studies

Study LE080185-G24 evaluated the effect of once daily use of Daivobet gel on HPA axis and calcium metabolism. Calcium metabolism evaluation was performed at baseline and after 4 and 8 weeks of treatment (Day 28 and 56). The evaluation included measurement of serum calcium, albumin, phosphate, alkaline phosphatase (ALP), plasma PTH level and calculation of the albumin-corrected serum calcium concentration. Also 24 hour urine was collected and urinary volume, calcium, phosphate, hydroxyproline, sodium and creatinine excretion were measured and the calcium:creatinine, phosphate:creatinine, hydroxyproline:creatinine and sodium:creatinine ratios were calculated.

7.5.3.2.1. *Albumin corrected serum calcium*

The mean change in albumin corrected serum calcium from baseline to end of treatment (LOCF) was 0.03 mmol/L (95% CI -0.01 to 0.07). Most subjects had values within the normal reference range at baseline and did not record a shift at Days 28 or 56. No subject had albumin-corrected serum calcium values above the normal reference range (2.15 to 2.55 mmol/L) at any visit. The number of subjects with a shift from normal to low was similar to the numbers who shifted from low to normal.

7.5.3.2.2. *24 hour urinary calcium*

The mean change in 24 hour urinary calcium from baseline to end of treatment (LOCF) was -0.4 mmol/24 hr (90% CI -1.2 to 0.3). Most subjects had values within the normal reference range (2.5 to 7.5 mmol/24 hr) at baseline and did not record a shift at Day 28 or 56.

There were 2 subjects with possible clinically significant increases in 24 hour urinary calcium excretion. One subject had a low value of 1.82 mmol at baseline which increased to 9.61 mmol at Day 28. This subject used an average weekly amount of 87.6 g of gel and the total amount used from baseline to Day 28 was 362.81 g. This subject showed signs of adrenal suppression and was withdrawn at Day 28 as per protocol. The other subject had values within the reference range at baseline and Day 28 but above at Day 56 (9.66 mmol). Between Days 28 and 56 the subject used an average amount of 73.5 g of gel and the total amount used was 325.88 g. This subject had an adequate response to the ACTH challenge test.

7.5.3.2.3. *Urinary calcium:creatinine ratio*

The mean change in urinary calcium:creatinine ratio from baseline to end of treatment was -0.42 mmol/g (95% CI -0.88 to 0.04). Most subjects had urinary calcium:creatinine ratio within the normal reference range (0.300 to 6.100 mmol/g in males and 0.225 to 8.200 mmol/g in females) at baseline and did not record a shift at Day 28 or 56. Only one subject shifted from a normal to a high value. Three subjects shifted to lower categories during treatment: two from high to normal values and one from a normal to a low value.

7.5.3.2.4. *Parathyroid hormone*

The mean changes from baseline in plasma PTH were small, -0.18 (95% CI -0.72 to 0.37) at 28 days and -0.13 (95% CI -0.91 to 0.65) at Day 56. Most subjects had plasma PTH values within the normal reference range (1.48 to 7.63 pmol/L) at baseline and did not record a shift at Day 28 and 56. At Day 28, two subjects shifted from normal to low values (none of these had increased albumin corrected serum calcium values), and the number of subjects who shifted from normal to high values was the same. Three subjects shifted from high to normal values. At Day 56, one subject shifted from a normal value to a high value and two shifted from a high value to a normal value.

7.5.4. **Haematology**

No data provided.

7.5.5. **Vital signs**

7.5.5.1. *Comparative studies*

Vital signs were not recorded in the comparative clinical trials.

7.5.5.2. *Other studies*

Vital signs – blood pressure and heart rate were collected at screening and after 4 and 8 weeks of treatment in Study LE080185-G24. The changes from baseline to end of study were small and there were no changes of clinical significance.

7.5.6. Lesional and perilesional adverse events

7.5.6.1. Comparative studies

Table 41. Lesional/perilesional adverse events on the body occurring in $\geq 1\%$ of subjects in the Daivobet gel, betamethasone gel, calcipotriol gel or gel vehicle group by MedDRA primary system organ class and preferred term for the 'controlled non-scalp studies': safety analysis set

System Organ Class Preferred Term ¹	Daivobet gel (n=824) No (%)	Betamethasone gel (n=562) No (%)	Calcipotriol gel (n=175) No (%)	Gel vehicle (n=226) No (%)	Tacalcitol (n=184) No (%)
Nervous system disorders					
Burning sensation	2 (0.2)	0 (0.0)	0 (0.0)	4 (1.8)	2 (1.1)
Skin and subcutaneous tissue disorders					
Pruritus	9 (1.1)	2 (0.4)	4 (2.3)	15 (6.6)	12 (6.5)
Psoriasis	3 (0.4)	3 (0.5)	1 (0.6)	3 (1.3)	1 (0.5)
Erythema	1 (0.1)	1 (0.2)	2 (1.1)	0 (0.0)	1 (0.5)
Skin burning sensation	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.9)	1 (0.5)
General disorders and administration site conditions					
Application site pain	3(0.4)	1 (0.2)	0 (0.0)	3 (1.3)	2 (1.1)
Pain	2 (0.2)	1 (0.2)	2 (1.1)	0 (0.0)	0 (0.0)

1) Classification according to MedDRA version 13.0.

7.5.6.2. Other studies

Table 42. Lesional/perilesional adverse events by MedDRA primary system organ class and preferred term: safety analysis set

Daivobet gel (n=43)		
System Organ Class Preferred Term ¹	Number of subjects	%
INFECTIONS AND INFESTATIONS		
Impetigo	1	2.3
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Hyperhidrosis	1	2.3
Total number of adverse events ²	2	

Daivobet gel (n=43)		
System Organ Class Preferred Term ¹	Number of subjects	%
Total number of subjects	2	4.7

1) Classification according to MedDRA version 14.1.

2) Different adverse events within the same preferred term and system organ class and involving the same subject have been counted as one. A single subject could appear in multiple classes.

7.5.7. Adverse events related to corticosteroid use and calcipotriol absorption

The following types of AEs were which were related to the two components of the Daivobet gel were reviewed in the studies:

- events potentially related to corticosteroid use: skin atrophy, skin striae, telangiectasia, tachyphylaxis or rebound (including lesional/perilesional or treatment related psoriasis), skin hypopigmentation, hypertrichosis, suppression of the HPA axis, pustular psoriasis, and lesional/perilesional or treatment related skin infections (folliculitis, rash pustular, herpes simplex, furuncle), hypertension, diabetes mellitus, increased blood glucose.
- events potentially related to calcipotriol absorption: hypercalcaemia, blood calcium increased, urine calcium increased.

7.5.7.1. Comparative studies

Events potentially related to corticosteroid use included the following:

- There were no AEs of suppression of the HPA axis, skin atrophy, skin striae, telangiectasia, skin hypopigmentation, hypertrichosis, or pustular psoriasis considered clinically significant in any treatment group.
- There were no AEs of tachyphylaxis or rebound.
- Lesional/perilesional or treatment related psoriasis was reported for 3 (0.4%) subjects in the Daivobet gel group, 4 (0.7%) in the betamethasone gel group, 1 (0.6%) in the calcipotriol gel group, 3 (1.3%) in the gel vehicle group and 1 (0.5%) in the tacalcitol ointment group.
- Lesional/perilesional or treatment related infections of any type were reported for 5 (0.6%) subjects in the Daivobet gel group, 2 (0.4%) in the betamethasone gel group, 1 (0.6%) in the calcipotriol gel group, none in the gel vehicle group and 1 (0.5%) in the tacalcitol ointment group. These were:
 - Folliculitis reported for 4 (0.5%) subjects in the Daivobet gel group, one of whom experienced three separate episodes. In the betamethasone gel group, 1 (0.2%) had folliculitis.
 - Cellulitis reported for 1 (0.1%) subject in the Daivobet gel group, and 1 (0.2%) in the betamethasone gel group.
 - Candidiasis reported for 1 subject (0.6%) in the calcipotriol gel group and tinea pedis and body tinea each reported for 1 subject (0.5%) in the tacalcitol ointment group.
- Diabetes mellitus/Type 2 diabetes mellitus were reported for 5 (0.6%) subjects in the Daivobet gel group and 2 (0.4%) in the betamethasone gel group. Additionally, 1 subject (0.2%) in the betamethasone gel group had hyperglycaemia. There were no other AEs of diabetes mellitus/Type 2 diabetes mellitus, hyperglycaemia or blood glucose increased considered clinically significant.

The incidence of each of these events was low and similar across the treatment groups but it should be noted that the duration of treatment was only 8 weeks.

There were no adverse events potentially related to calcipotriol absorption identified in the studies.

7.5.7.2. Other studies

7.5.7.2.1. Study LEO80185-G24

There were seven cases of AEs potentially related to corticosteroid use – three cases of adrenal suppression (7.0% of subjects), two infections (4.7% of subjects) ie one case of lesional/perilesional impetigo and one tooth infection that was considered an ADR, and two cases of hypertension (4.7% of cases).

There were no AEs reported that were potentially related to calcipotriol absorption.

7.5.8. Withdrawal and rebound

Possible withdrawal and rebound effects were examined in Study LEO80185-G21. Of the 398 subjects who completed the treatment phase, a total of 103 had controlled disease and entered the 8 week observation phase (67 Daivobet gel, 31 tacalcitol and 5 gel vehicle). No subjects experienced a rebound of their psoriasis.

7.6. Post-marketing experience

A summary of safety information relating to Daivobet gel indicated for use on non-scalp areas received by the applicant from world-wide sources in the period August 1st 2008 to July 31st 2011 was included in the Summary of Clinical Safety. The company also included three periodic safety update reports (PSURs) covering the periods 1 Feb 2010 to 31 Jul 2010, 1 Aug 2010 to 31 Jan 2011 and 1 Feb 2011 to 31 July 2011.

There is marked inconsistency between the serious AEs reported in the 6 monthly PSURs and those reported in the consolidated document as follows:

Distribution by seriousness	1 Feb 2010 to 31 Jul 2010	31 Jul 2010, 1 Aug 2010	1 Feb 2011 to 31 July 2011	1 Aug 2008 - 31 July 2011
Serious	6	7	5	1
Non-serious	58	74	77	13

No explanation for this discrepancy is provided.

However, review of all the adverse events reported does not highlight any significant new events or trends to increasing frequency.

7.7. Evaluator's overall conclusions on clinical safety

Safety in the clinical trials and post marketing data has not indicated any new or significant safety issues beyond the risk of HPA axis suppression. This (worst case scenario) was found in approximately 7% (3/43) in a small trial, but only assessed following 4-8 weeks of therapy. No long term study was conducted and so if the product is approved there should be very clear indication of risk and statement that safety beyond 8 weeks has not been studied.

The company claim that a long term study is not required as the long term safety is "well known" from the Daivobet ointment submission.

The wording of the Precautions section of the proposed PI is different from that in the Daivobet ointment PI which appears to be more strongly worded.

The results for safety were consistent in the clinical studies and appear to be consistent with that previously presented in the ointment submissions.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of Daivobet gel in the proposed usage are:

- Product is statistically significantly superior to betamethasone alone in improving symptoms of psoriasis after 8 weeks of therapy and superior to calcipotriol alone in the gel vehicle after 4 and 8 weeks. Daivobet gel was not superior to betamethasone alone in the gel vehicle at 4 weeks.
- The results are consistent in the studies provided.

8.2. First round assessment of risks

The risks of Daivobet gel in the proposed usage are:

- Studies conducted are very short – only 8 weeks. No study longer than 8 weeks was provided despite EU guideline requiring at least one long term study of 12 months
- Studies conducted in very homogeneous population – predominantly white populations from US, Canada and northern Europe (Germany, Ireland, Sweden, UK and France)
- Studies conducted mostly over the Northern winters – in patients selected to be avoiding sunlight. Unsure of relevance and applicability to Australian conditions but the same comments appear to have been made about the previous ointment dossier
- HPA suppression seen in 7% of patients after 8 weeks – consistent with previous studies on the ointment formulation
- Pivotal studies only included patients with mild –moderate disease. This is not included in the proposed indication

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of Daivobet gel, given the proposed usage, is favourable.

9. First round recommendation regarding authorisation

Based on the clinical data presented in the submission approval is recommended.

10. Clinical questions

The sponsor was requested to address the following questions:

1. Please explain why the [proposed] indication say, “Body Psoriasis: Daivobet gel should be applied to the affected areas of skin once daily for up to 8 weeks or until cleared”, when no data beyond 8 weeks of treatment were submitted?

2. How do the doses applied in studies LEO80185-G24 and MBL0404FR relate to those proposed in the draft PI?
3. In Study LEO80185-G23, please clarify the pre-determined sequence of statistical testing and the sequence of testing. It is noted that there was no difference at Week 4 for the first test in the sequence, betamethasone gel. Statistical significance has been reported for secondary endpoints.
4. No detailed formulation details are provided in the application form or other parts of the clinical module of the submission. Please confirm that the formulation is unchanged from that currently approved and the formulation was the same in all clinical trials in the submission.

11. Second round evaluation of clinical data submitted in response to questions

11.1. Evaluation of sponsor responses to clinical questions

Question 1 Dosage and administration instructions

Sponsor response was to agree to amend the Dosage and Administration section to: remove the treatment beyond eight weeks. The wording would be: "Body Psoriasis: Daivobet gel should be applied to the affected skin once daily until cleared for up to 8 weeks."

The wording suggested by company is clumsy and may be misinterpreted to imply treatment until cleared (which may be longer than eight weeks) and remains cleared for eight weeks.

It is suggested that more accurate wording which reflects what was done in the clinical trials would be: "Body Psoriasis: Daivobet should be applied once daily for up to eight weeks."

Question 2. Studies presented and Product Information

Study MBL040FR was not included as part of this evaluation (it had been submitted in a previous submission and is not available to the evaluator) and LEO80815-G24 was a supporting (other) study. The company response cannot be verified for study MBL040FR but is correct for study LEO80815-G24.

The company response stated:

"The studies LEO80185-G24 and MBL0404FR included subjects with psoriasis vulgaris involving 15-30% of the body surface area. The weekly amount of medication supplied was 100 g and 110 g in LEO-G24 and MBL0404FR respectively. The mean weekly amounts applied were 52.27 g (range 7.64 to 92.95 g) in study LEO80185-G24 (gel) and 62.5 g (range 29.7 to 105.8 g) in study MBL0404FR (gel and ointment). The maximum dosages applied in these studies were at the level of the maximum proposed dose. Overall, in these studies there were no reports of hypercalcaemia and no correlation between amount of drug used and the ACTH stimulated serum cortisol levels."

The dose proposed in the PI is consistent with that seen in the clinical trials – "When using calcipotriol containing products, the maximum daily dose should not exceed 15 grams and the maximum weekly dose should not exceed 100 grams. The total body surface area treated with calcipotriol should not exceed 30%."

Question 3 Statistical testing in LEO80815-G23

The sponsor's response states that there was no pre-determined sequence of testing. The reason for this was to avoid prioritisation of the two endpoints. The sponsor states that the Hochberg procedure allows this, because the p values are calculated for each of the co-primary

endpoints and only the actual values determines the conclusions, as described by the method. The explanation given in the Statistical Analysis Plan Update states:

“For each comparison the Hochberg correction for the p-values for the two endpoints means that the largest of the two p-values must be <5% for both to be statistically significant. If the largest p-value is ≥5% then the corresponding hypothesis cannot be rejected. If the smaller p-value is <2.5%, then it is statistically significant and the corresponding hypothesis is rejected, otherwise it cannot be rejected. This means that both p-values must be <5% for LE080125 [Daivobet] to be superior to that comparator at both week 4 and week 8. If LE080185 is superior to all three comparators at weeks 4 and 8, then superiority can be claimed for both endpoints. If statistical significance is obtained at week 8 for all three comparators, then superiority of LE080185 can be claimed at week 8. The conclusion is similar for week 4.”

The company conducted the statistical analysis in line with the statistical plan. They acknowledge that this method does not control strongly the type 1 error. However, they state that the method of evaluating p-values set out in the submission, which was the intended application of the Hochberg method for adjusting for multiplicity controls the type 1 error strongly. This appears an adequate response.

Question 4 Formulation of Daivobet 50/500 gel in clinical trials

The sponsor has confirmed that the formulation is unchanged from the current approved and the formulation was the same in all the clinical trials in the submission.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

No new clinical information was submitted in response to questions. Accordingly, the risks of Daivobet gel are unchanged from those identified in Section 8.1.

12.2. Second round assessment of risks

No new clinical information was submitted in response to questions. Accordingly, the risks of Daivobet are unchanged from those identified in Section 8.2.

12.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Daivobet, given the proposed usage, is favourable.

13. Second round recommendation regarding authorisation

Based on the clinical data presented in the submission approval is recommended.

The proposed indication should be changed to be the same as that approved in Europe. The indication should be:

“Topical treatment of scalp psoriasis in adults. Topical treatment of mild to moderate ‘non-scalp’ plaque psoriasis in adults.”

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