Main Clinical Study Report

LEO 90100 Compared with Calcipotriol plus Betamethasone Dipropionate Ointment, LEO 90100 Vehicle and Ointment Vehicle in Subjects with Psoriasis Vulgaris

A phase 2 study comparing treatment with LEO 90100 with calcipotriol plus betamethasone ointment, LEO 90100 vehicle and ointment vehicle in subjects with psoriasis vulgaris.

A multi-centre, prospective, randomised, investigator blinded, 4-arm, parallel group, 4-week study in subjects with psoriasis vulgaris.

The clinical study report has been redacted using the following principles: Where necessary, information is anonymised to protect the privacy of study subjects and named persons associated with the trial as well as to retain commercial confidential information.

Summary data are included but data on individual study subjects, including data listings, are removed. This may result in page numbers not being consecutively numbered.

Access to anonymised data on individual study subject may be obtained upon approval of a research proposal by the Patient and Scientific Review Board.

Appendices to the clinical study report are omitted.

Further details and principles for anonymisation is available in the document LEO PHARMA PRINCIPLES FOR ANONYMISATION OF CLINICAL TRIAL DATA.

LEO Pharmaceutical Products Ltd. A/S
(LEO Pharma A/S)
Clinical Development and Safety

LEO 90100-35
10-Jun-2013

00362426
1 Report Statement

APPROVAL STATEMENT
The following persons have approved this Clinical Study Report on behalf of LEO Pharma A/S using electronic signatures:

Biostatistics and Data management

Medical Department

APPROVAL STATEMENT, INVESTIGATORS
The International Co-ordinating Investigator approves the main Clinical Study Report by manually signing the International Co-ordinating Investigator Clinical Study Report Approval Form, which is a separate document adjoined to this report.

The following person has approved this main Clinical Study Report:

International Co-ordinating Investigator
COMPLIANCE WITH GOOD CLINICAL PRACTICE
This Clinical Study Report is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3 Structure and Content of Clinical Study Reports; E6 Good Clinical Practice; E9 Statistical Principles for Clinical Trials and M4 Common Technical Document).

DISCLOSURE OF CLINICAL TRIAL RESULTS
Results from this clinical trial will be posted under the identifier NCT01536886 on www.clinicaltrials.gov which is a publicly accessible database.

2 Synopsis
The synopsis of this Clinical Study Report exists as a separately approved document.

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4 List of Abbreviations and Definition of Terms

LIST OF ABBREVIATIONS

ADR  Adverse Drug Reaction
AE   Adverse Event
BDP  Betamethasone dipropionate
BSA  Body Surface Area
eCRF Electronic Case Report Form
CRO  Contract Research Organisation
CMO  Contract Manufacturing Organisation
DK   Denmark
DME  Dimethyl Ether
FAS  Full Analysis Set
FU   Follow-up
GCP  Good Clinical Practice
GPV  Global Pharmacovigilance
HQ   Head Quarter
ICH  International Conference on Harmonisation
ICTM International Clinical Trial Manager
IEC  Independent Ethics Committee
IGA  Investigator’s Global Assessment of disease severity
IND  Investigational New Drug
IRB  Institutional Review Board
IWRS Interactive Web Response System
MedDRA Medical Dictionary for Regulatory Activities
LCRA Lead Clinical Research Associate
LOCF Last Observation Carried Forward
PASI Psoriasis Area and Severity Index
m-PASI Modified Psoriasis Area and Severity Index
PP   Per Protocol
PUVA Psoralen plus ultraviolet light A
SAE  Serious Adverse Event
SAPU Statistical Analysis Plan Update
Terms defined by ICH Guidelines are not mentioned here.

**Assessment**
A (cluster of) characteristic(s) measured and/or recorded for a subject.

**Concomitant Medication**
Any medication taken by a subject during a clinical trial apart from the trial medication.

**Enrolled Subject**
A subject for whom informed consent has been obtained and a CRF number assigned.

**Fraud**
Fabrication of data, selective and undisclosed rejection of undesired results, substitution with fictitious data, deliberately incorrect use of statistical methods for the purposes of reaching other conclusions than those warranted by the data, misinterpretation of results and conclusions, plagiarism of results or entire articles from other researchers, misrepresentation of other researchers’ results, unwarranted authorship, and misleading application for positions or funds.

**International Clinical Trial Manager (ICTM)**
The person appointed by LEO to be the main international representative responsible for all aspects of a clinical trial as outlined in Clinical Development and Safety (formerly International Clinical Development) SOPs.

**Investigator Agreement**
A contract between LEO and an investigator specifying the conditions for the co-operation in the clinical trial and the investigators’ responsibilities.
**Investigator Staff Signature Form**
A form used:

1. for the investigator to delegate trial-related tasks/duties
2. for trial site staff to sign and date to accept delegation
3. for trial site staff to document signatures and initials
4. for the investigator to authorise tasks/duties delegated.

**Investigator Trial File**
The collection of trial documents required by LEO GCP SOPs, ICH Guidelines and/or regulatory requirements to be on file at the trial site.

**LEO**
LEO (no suffix): Refers to the corporate organisation of LEO Pharma.

**Monitor**
A person appointed by LEO to carry out monitoring of a clinical trial.

**Lead Clinical Research Associate (LCRA)**
The person appointed by LEO to be the national sponsor representative responsible for all aspects of a clinical trial within a country as outlined in Clinical Development and Safety (formerly International Clinical Development) SOPs.

**Subject Identification List**
A summary list kept by the investigator in the Investigator Trial File that records the names of all subjects enrolled and the date of enrolment in the trial at that trial site, with the subject’s corresponding CRF Book Number, to allow the investigator/institution to reveal the identity of any subject, if required.

**Subject Study Card**
A card given to a subject by the trial site at the time trial medication is first dispensed to a subject, to identify that the subject is having treatment with an investigational product.

**Randomisation Code List**
A list of (sequential) numbers to each of which a treatment is allocated (assigned). Treatment
may be revealed as a code letter (e.g., A, B, …) or by directly revealing the specific treatment (investigational product).

**Response Criterion**
An assessment or a transformation of the assessment(s) described on a subject level, for which a statistical analysis is performed, i.e., a P-value or a confidence interval is stated, or for which tabulation serves as important supportive evidence of efficacy/safety.

**Subject Screening Log**
A document kept by the investigator which identifies patients/subjects who entered pre-trial screening.

Subject Screening Log is synonymous with Patient Screening Log.
5 Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The clinical study protocol and any relevant amendments to the clinical study protocol were approved by/received favourable opinion from the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs).

The appropriate regulatory authority(ies) was notified of/approved the clinical trial, as required.

A list of all IRBs consulted is given in Appendix 16.1.3.

5.2 Ethical Conduct of the Trial

The clinical trial was conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments.

The clinical trial was conducted in accordance with the principles of GCP. The study was conducted in accordance with applicable national regulatory requirements and under a US Investigational New Drug (IND).

Subjects were asked to consent that data could be recorded, collected, processed and transferred to EU and non-EU countries in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

All information containing personal data was to be handled in accordance with the general terms of the authorisation granted by the Danish Data Protection Agency to LEO Pharma A/S (as appended to the Clinical Study protocol) in accordance with the EU Data protection Directive (95/46/EC) as well as any national data protection legislation.

5.3 Subject Information and Informed Consent

All subjects received written and verbal information concerning the clinical trial. This information emphasised that participation in the trial was voluntary and that the subject could withdraw from the trial at any time and for any reason. All subjects were given an opportunity
to ask questions and were given sufficient time to consider all relevant issues before consenting.

The subject's signed and dated informed consent to participate in the clinical trial was obtained prior to any trial-related activities being carried out.

A representative subject information sheet and informed consent form is provided in Appendix 16.1.3.

All investigators signed an Investigator Agreement before the clinical trial was initiated to confirm the above.
## 6 Investigators and Trial Administrative Structure

LEO Pharma A/S was the sponsor of the clinical trial and participating LEO affiliates were authorised by the sponsor to act on behalf of the sponsor in the countries where the clinical trial was conducted.

<table>
<thead>
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The CRO was responsible for central laboratory analyses.

Contract Research Organisation (CRO): [Name], TKL Research Inc., 365 W. Passaic Street, Rochelle Park, NJ 07652, USA Tel: [Phone] ext. [Ext], e-mail: [Email]

The CRO was responsible for project management, clinical conduct, data management, interactive web response system (IWRS) for randomisation, and monitoring.

Clinical trial supply: [Name], United Kingdom. Tel: [Phone] email: [Email]

The CMO (Contract Manufacturing Organisation) was responsible for the secondary packaging, labelling and distribution of trial medication, and also the receipt, accountability, reconciliation and destruction of returned trial medication.

Global Pharmacovigilance: [Name], Global Pharmacovigilance, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark. Tel.: [Phone], email: [Email]
A list of investigators, including Curriculum Vitae and other persons whose participation materially affected the conduct of the trial is included in Appendix 16.1.4.
7 Introduction

The trial was performed as a phase 2 clinical trial of LEO 90100, a fixed combination product containing calcipotriol plus betamethasone dipropionate (BDP) in an aerosol formulation, in subjects with psoriasis vulgaris.

7.1 Psoriasis Vulgaris

Psoriasis is a multisystem disease with predominantly skin and joint manifestations affecting approximately 1 to 3% of the population (1-3). The major manifestation of psoriasis is chronic inflammation of the skin, characterised by sharply demarcated, scaling, and erythematous plaques that may be painful and often severely pruritic. The psoriatic appearance of the skin is produced by an increased rate of epidermal proliferation with impaired differentiation of keratinocytes resulting in a thickened, undulating epidermis covered by a thickened, parakeratotic stratum corneum. Dermal capillaries become tortuous and dilated and there is infiltration of both epidermis and dermis with immunologically active cells (4, 5).

The most common clinical type of psoriasis, affecting 80-90% of patients, is psoriasis vulgaris (plaque-type psoriasis) (1). Although psoriasis may occur at any site, the scalp, elbows, legs, knees, arms and trunk are commonly affected sites. The nails are involved in about 30% of patients with psoriasis and in about 20% psoriatic arthritis arises, usually many years after the initial cutaneous manifestation (6). Psoriasis is associated with multiple medical as well as psychiatric comorbidities such as the metabolic syndrome, cardiovascular disease (7-9) and depression including suicidal ideation (10-12). Studies have revealed that patients with psoriasis are emotionally and physically impaired by their disease to an extent comparable to patients with heart disease, diabetes or cancer (13-14). Psoriasis is therefore a significant problem for affected subjects in everyday life, and has a significant impact on their health-related quality of life.

Psoriasis is a chronic disease that waxes and wanes during a patient’s lifetime, with few spontaneous remissions (1). There is currently no cure for psoriasis vulgaris and treatment is targeted at reducing the signs of erythema, scaling and infiltration and associated symptoms such as pruritus, and improving patient quality of life (15). Treatments are selected based on disease severity, patient preference and response. Topical therapy is the regimen of choice for subjects with less extensive disease who comprise two thirds of all psoriasis subjects in order to reduce the risk of systemic toxicity (4). A number of topical therapies are available for
psoriasis vulgaris, including corticosteroids, vitamin D analogues, retinoids and emollients. Among these, vitamin D analogues and topical corticosteroids are the two with the greatest proven efficacy in randomised clinical trials, particularly when used in combination (16).

However, application of topical therapies can be cumbersome, messy and time-consuming, which can have a negative impact on adherence to the prescribed treatment regimen and ultimately result in poor control of the disease (17). Thus there is an ongoing need for development of topical psoriasis treatments that are, in addition to being highly efficacious, also convenient and easy to use.

### 7.2 Investigational Product

LEO 90100 is an aerosol formulation of calcipotriol 50 mcg/g and betamethasone 0.5 mg/g (as dipropionate) currently under development for the topical treatment of psoriasis vulgaris. The formulation is manufactured by dissolving DAIVOBET/DOVOBET/TACLONEX ointment in a mixture of the propellants dimethyl ether (DME) and butane, in a pressurized container with a continuous valve. The pressurized drug product is a homogeneous, white, opalescent liquid. At discharge, a quick-breaking foam is formed.

LEO 90100 has been developed with the purpose of providing additional choices to users and prescribers of the currently approved product DAIVOBET/DOVOBET/TACLONEX ointment, which contains the same active ingredients in the same concentration. The aerosol formulation is expected to be easier and less time consuming to apply, and to have favourable cosmetic properties which might improve patient adherence as compared to an ointment formulation.

DAIVOBET/DOVOBET/TACLONEX ointment has proven highly effective in the treatment of psoriasis vulgaris on trunk and limbs with an improved benefit/safety profile compared to each active component used as monotherapy. The assumption that the same constituents (calcipotriol plus BDP) combined in an aerosol delivery system would also be effective in the treatment of psoriasis vulgaris were supported by the results of an exploratory clinical trial (modified psoriasis plaque test), in which LEO 90100 showed better anti-psoriatic effect than DAIVOBET/DOVOBET/TACLONEX ointment and betamethasone dipropionate in LEO 90100 vehicle.
Further information regarding the properties, mechanism of action, safety and tolerability data of the investigational product can be found in the Clinical Study Protocol (CSP), Appendix 16.1.1.

7.3 Trial Rationale

The purpose of this trial was to compare LEO 90100 with DAIVOBET/DOVOBET/TACLONEX ointment in patients with psoriasis vulgaris. The results of this trial will allow a comparison of the risk/benefit profile of LEO 90100 and DAIVOBET/DOVOBET/TACLONEX ointment.

This trial was one of two concurrent, multicentre, randomised phase 2 trials investigating the safety and efficacy of LEO 90100 in subjects with psoriasis vulgaris. The objective of the other phase 2 trial (LEO 90100-07) was to investigate the comparative efficacy of LEO 90100 to each of its active constituents, calcipotriol and BDP, in subjects with psoriasis vulgaris on the trunk, limbs and scalp.
8 Trial Objectives

8.1 Primary Objective

The primary objective was to compare the efficacy of treatment with LEO 90100 with calcipotriol plus BDP ointment for up to 4 weeks in subjects with psoriasis vulgaris.

8.2 Secondary Objectives

Secondary objectives were:

- To compare the safety of treatment with LEO 90100 with calcipotriol plus BDP ointment for up to 4 weeks in subjects with psoriasis vulgaris.
- To compare the efficacy at week 1 of treatment with LEO 90100 with calcipotriol plus BDP ointment in subjects with psoriasis vulgaris.
9 Investigational Plan

The entire Clinical Study Protocol and any amendments are presented in Appendix 16.1.1 and the unique pages of the case report form (CRF) are presented in Appendix 16.1.2.

9.1 Overall Trial Design and Plan - Description

This was a phase 2 trial comparing treatment with LEO 90100 with calcipotriol plus BDP ointment, LEO 90100 vehicle and ointment vehicle in subjects with psoriasis vulgaris. It was designed as a multi-centre, prospective, randomised, investigator blinded, 4-arm, parallel group, 4-week trial in subjects with psoriasis vulgaris. It was planned to randomise approximately 400 subjects.

Subjects with psoriasis vulgaris on the trunk and/or limbs of at least mild severity according to the Investigators global assessment of disease severity (IGA) were enrolled. Eligible subjects were randomised to receive up to 4 weeks treatment once daily with either:

- LEO 90100
- LEO 90100 vehicle
- Calcipotriol plus BDP ointment
- Ointment vehicle

Randomisation to treatment groups was in a 3:1:3:1 ratio. The randomisation of subjects was stratified according to baseline disease severity (mild: at least moderate) as determined by the IGA.

The overall trial design is shown in Figure 1.
Figure 1: Trial design for LEO 90100-35

9.1.1 Individual Phases

The trial consisted of a washout/screening period (up to 4 weeks), a 4-week treatment period and, if required, a 2-week safety follow-up period.

Washout/Screening phase

Prior to attending any trial procedure, a signed informed consent had to be obtained from the subject.

Prior to randomisation, the subjects entered a washout phase (if required) where anti-psoriatic treatment and other relevant medication/treatments had to be discontinued as defined by the exclusion criteria (see Section 9.3.2). Depending on prior use of disallowed treatments, the
washout/screening phase could last for up to 4 weeks prior to the first administration of investigational products.

**Treatment phase**
The treatment phase lasted for up to 4 weeks. There were 4 visits: Visit 1 (week 0, baseline), Visit 2 (week 1), Visit 3 (week 2) and Visit 4 (week 4). Visits 2-4 were to be performed within ±2 days of the scheduled time relative to visit 1; if the visit was performed outside of the visit window, the (sub)investigator was to record the reason in the subject’s medical record. The investigational product was applied once daily to psoriasis lesions on the trunk and limbs. Subjects classified as clear at Visit 2 or 3 were allowed to stop using treatment at the (sub)investigator’s discretion. If their psoriasis reappeared subjects were to reinitiate the treatment without consulting the (sub)investigator. All subjects had last visit at Visit 4 even if their psoriasis cleared before.

**Follow-up phase**
The treatment phase was followed by a follow-up (FU) phase if there was an ongoing adverse event at the last on treatment visit, which was classified as possible or probably related to the study medication or not assessable in relation to the trial medication. This phase lasted for 14 ±2 days relative to the last on-treatment visit and was concluded by a follow-up visit/contact. The follow-up visit/contact could have been conducted earlier if final outcome of the event had been determined. The follow-up visit/contact was made either as a telephone call or as a regular visit, according to the investigator’s discretion.

### 9.2 Discussion of Trial Design, Including the Choice of Control Groups

The trial was designed as a 4-arm (LEO 90100, LEO 90100 vehicle, Calcipotriol plus BDP ointment and ointment vehicle), randomised and investigator-blinded trial, as full double-blinding was not possible because of the difference in formulation. For each active treatment arm a corresponding vehicle control was also included, in order to blind the subjects on either treatment as to whether they received active or vehicle as well securing the blinding of the assessing dermatologist. Further, vehicle control enhances interpretation of safety data. Randomisation was used to minimise selection bias ensuring a similar mix of subjects in each group.

**Subjects**
The inclusion/exclusion criteria were designed to select a population that is representative for
the target population; i.e., subjects of all disease severities (‘mild’ to ‘severe’ according to the IGA) amenable to topical therapy, appropriate for the comparison of the 2 treatments.

**Duration and dosing regimen**

The treatment duration of 4 weeks was considered appropriate to obtain sufficient data on the efficacy and safety of the evaluated investigational products. Treatment duration of 4 weeks has been shown to be safe and effective in several studies of DAIVOBET/DOVOBET/TACLONEX ointment (18-21). A once daily treatment regimen was chosen as this is considered more convenient for the subject and has shown to be effective in previous studies. It decreases drug exposure and time spent on application and is thus expected to enhance subject compliance.

**Endpoints**

The IGA was chosen as the primary efficacy assessment. The IGA is a static skin scoring system, consisting of a five point scale from clear to severe.

The primary endpoint was subjects with ‘controlled disease’ according to the IGA. ‘Controlled disease’ is defined as clear or almost clear for subjects with at least moderate disease at baseline and clear for subjects with mild disease at baseline. The percentage of subjects who achieve ‘controlled disease’ is regarded as the best evidence of efficacy (22). Comparison of the percentage of subjects with ‘controlled disease’ between the treatment arms reflects the difference in the effect of the treatments.

In order to facilitate standardisation of assessments and to minimise inter-rater variability, the IGA scale includes a detailed description of the morphological characteristics for each severity category, thus assisting the investigator in evaluation.

The Psoriasis Area and Severity Index (PASI) is a well established assessment that has been used in all previous studies of psoriasis conducted by LEO. The PASI was included to enable comparison of results across several studies and also to assess the development of response to treatment over time. This trial used a modified PASI excluding head (m-PASI) as a secondary response criterion.

To assess treatment satisfaction evaluation of the Treatment Satisfaction Questionnaire of Medication (TSQM) version II was included in the study. The TSQM is a validated questionnaire developed to permit comparisons of patient treatment satisfaction across medication
types and patient conditions (23-24). The questionnaire includes 4 domains: effectiveness, side effects, convenience and global satisfaction.

Because of the potential effect of the vitamin D analogue containing investigational products on calcium metabolism and homeostasis, safety analysis of parameters of calcium metabolism was made following sampling of venous blood and urine collected at Day 0 and Day 28 (or the last on-treatment visit as applicable).

Local safety was evaluated by scoring of application site skin reactions.

**Concomitant treatments**

During the course of the trial, subjects were not allowed to use any concomitant treatments that have a possible effect on the psoriasis on the trunk and/or limbs. This included various systemic treatments (e.g. systemic corticosteroids, retinoids, methotrexate, ciclosporin and other immunosuppressants and biological therapies). Topical treatments which could have a systemic effect on the psoriasis lesions on trunk and limbs if used to treat psoriasis or other skin conditions (e.g. eczema) in other locations were also not allowed (i.e. vitamin D analogues and class 1-5 corticosteroids on the scalp, face and skinfolds).

Treatment options for psoriasis or other dermatological disorders on the scalp, face and skinfolds were therefore limited to the immunomodulators such as tacrolimus or pimecrolimus or class 6 & 7 corticosteroids. This restriction on concomitant topical therapies on other body regions was to assert a level of control over the concomitant medication related effects observed during the trial and to allow use of the trial medication up to the maximum recommended level.

A stable concomitant treatment regimen (no start or change of dosage during the study) with drugs that have a potential effect on psoriasis (e.g., beta blockers, anti-malarials, ACE inhibitors and lithium) was allowed during the trial. Although these drugs have a potential effect on psoriasis, they are not known to cause fluctuations in the disease severity and therefore should not affect the subject’s response to trial medication.

Prior to randomisation, a washout period was to be completed if the patient was being treated, or had recently been treated with anti-psoriatic treatments or other relevant medication that could influence the outcome of the trial.
9.3 Selection of Trial Population

Approximately 400 subjects with psoriasis vulgaris on the trunk and/or limbs of at least mild severity according to the IGA were planned to be enrolled in the trial and randomised in a 3:1:3:1 ratio: 150 subjects in the LEO 90100 group, 50 in the LEO 90100 vehicle group, 150 in the calcipotriol plus BDP ointment group and 50 in the ointment vehicle group.

Subjects were evaluated for trial eligibility according to the following inclusion (Section 9.3.1) and exclusion (Section 9.3.2) criteria:

9.3.1 Inclusion Criteria

1. Signed and dated informed consent obtained prior to any trial related activities (including washout period).
2. Age 18 years or above
3. Either sex
4. Any race or ethnicity
5. All skin types
6. Attending a hospital outpatient clinic or the private practice of a board certified dermatologist.
7. A clinical diagnosis of psoriasis vulgaris of at least 6 months duration involving the trunk and/or limbs amenable to treatment with a maximum of 90 g of study medication per week.
8. Psoriasis vulgaris on the trunk and/or limbs (excluding psoriasis on the genitals and skin folds) involving 2-30% of the Body Surface Area (BSA).
9. An Investigator’s Global Assessment of disease severity (IGA) of at least mild on trunk and/or limbs at Day 0 (Visit 1).
10. An m-PASI score of at least 2 on the trunk and/or limbs at Day 0 (Visit 1).
11. Females of childbearing potential must have a negative pregnancy test at Day 0 (Visit 1).
12. Females of childbearing potential must agree to use a highly effective method of birth control during the study. A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year), such as implants, injectables, combined oral contraceptives, some intra-uterine devices, sexual abstinence or vasectomy.

The subjects must have used the contraceptive method continuously for at least 1 month prior to the pregnancy test, and must continue using the contracep-
A female is defined as not of child-bearing potential if she is postmenopausal (12 months with no menses without an alternative medical cause), or surgically sterile (tubal ligation/section, hysterectomy or bilateral ovariectomy).

13. Able to communicate with the investigator and understand and comply with the requirements of the study.

### 9.3.2 Exclusion Criteria

1. Systemic treatment with biological therapies, whether marketed or not, with a possible effect on psoriasis vulgaris within the following time periods prior to randomisation:
   - etanercept – within 4 weeks prior to randomisation
   - adalimumab, alefacept, infliximab – within 8 weeks prior to randomisation
   - ustekinumab – within 16 weeks prior to randomisation
   - other products – 4 weeks/5 half-lives (whichever is longer)

2. Systemic treatment with all other therapies with a possible effect on psoriasis vulgaris (e.g., corticosteroids, retinoids, methotrexate, ciclosporin and other immunosuppressants) within 4 weeks prior to randomisation.

3. Subjects who have received treatment with any non-marketed drug substance (i.e. a drug which has not yet been made available for clinical use following registration) within the 4-week period prior to randomisation or longer, if the class of substance required a longer treatment free period as defined in exclusion criterion 1 for biological treatments.

4. PUVA therapy within 4 weeks prior to randomisation.

5. UVB therapy within 2 weeks prior to randomisation.

6. Topical anti-psoriatic treatment on the trunk and limbs (except for emollients) within 2 weeks prior to randomisation.

7. Topical treatment on the face and skin folds with class 1-5 corticosteroids or vitamin D analogues within 2 weeks prior to randomisation.

8. Topical treatment on the scalp with class 1-5 corticosteroids, vitamin D analogues or prescription shampoos within 2 weeks prior to randomisation.

9. Planned excessive exposure of area(s) to be treated with study medication to either natural or artificial sunlight (including tanning booths, sun lamps etc.) during the study.
10. Planned initiation of, or changes to, concomitant medication that could affect psoriasis vulgaris (e.g. beta blockers, antimalarial drugs, lithium, ACE inhibitors) during the study.

11. Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis.

12. Subjects with any of the following conditions present on the treatment area: viral (e.g. herpes or varicella) lesions of the skin, fungal and bacterial skin infections, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, ulcers and wounds.

13. Other inflammatory skin disorders (e.g. seborrhoeic dermatitis or contact dermatitis) on the treatment area that may confound the evaluation of psoriasis vulgaris.

14. Known or suspected disorders of calcium metabolism associated with hypercalcaemia.

15. Known or suspected severe renal insufficiency or severe hepatic disorders.

16. Known or suspected hypersensitivity to component(s) of the investigational products.

17. Current participation in any other interventional clinical study.

18. Previously randomised in this study.

19. Females who are pregnant, wishing to become pregnant during the study or are breast-feeding.

9.3.3 Removal of Subjects from Therapy or Assessment

Subjects could have been withdrawn for any of the following reasons:

1. *Unacceptable treatment efficacy*: the investigator was free to withdraw the subject at any time for medical reasons.

2. *Unacceptable adverse events*: any adverse event that the investigator or the subject considered unacceptable.

3. *Exclusion criteria*: any exclusion criteria which emerged/became apparent during the subject’s participation in the clinical trial.

4. *Voluntary withdrawal*: subject was free to withdraw from the clinical trial at any time and for any reason.

5. *Other reasons*: other reasons than stated above which required the subject to (be) withdraw(n) were to be specified.

Subjects who were discovered, after enrolment/randomisation, not to have fulfilled all in-/exclusion criteria at time of enrolment, were withdrawn from treatment unless the investigator, based on clinical and ethical evaluation, found withdrawal inappropriate. The final
efficacy assessment (at the correct scheduled time) should, however, have been attempted to be completed for all subjects. Such deviation(s) from the (Consolidated) Clinical Study Protocol had to be reported to LEO (and IEC/IRB, as appropriate) and recorded in the Clinical Study Report.

Subjects who withdrew from treatment for any other reasons should likewise, as a minimum, have been asked to complete the final efficacy assessment (at the correct scheduled time).

Reason(s) for withdrawal were recorded in the eCRF.

Subjects withdrawn were not be substituted.

9.4 Treatments

9.4.1 Treatments Administered

Subjects were randomised to receive one of the following treatments:

- LEO 90100
- LEO 90100 vehicle
- Calcipotriol plus BDP ointment
- Ointment vehicle

At Day 0 (Visit 1) subjects were given a treatment instruction sheet and verbal instruction about how to apply trial medication. The first application of the trial medication was made under the supervision and instruction of the trial staff. The study medication was to be applied once daily to psoriasis lesions on the trunk, arms, and legs for up to 4 weeks. Subjects were instructed not to apply the trial medication on psoriasis on the scalp, face, genitals, or skin folds. Skin folds included the axillae, the inguinal folds, the intergluteal folds, and the inframammary folds. There was no specific requirement with regard to the time of day for application.

Subjects classified as clear on the trunk and limbs and/or scalp at any of Visits 2 or 3 were allowed to stop the treatment on the cleared area at the (sub)investigator’s discretion. Subjects were not allowed to discontinue treatment themselves between visits, but were only allowed to stop using the treatment on the advice of the (sub)investigator at a scheduled visit. If their psoriasis reappeared the subject was asked to reinitiate the treatment without consulting the (sub)investigator.
9.4.2 Identity of Investigational Product(s)

LEO 90100 and the LEO 90100 vehicle were provided in aluminium cans of 30 g. Calcipotriol plus BDP ointment and the ointment vehicle were provided in tubes of 30 g. Details of the investigational products are given in Table 1 to Table 4 below.

Table 1: Identity of LEO 90100

<table>
<thead>
<tr>
<th>Finished product (Brand) name (if available)/name investigational product:</th>
<th>LEO 90100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation:</td>
<td>Aerosol, foam</td>
</tr>
<tr>
<td>Active ingredient name/strength:</td>
<td>Calcipotriol (as hydrate) 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate)</td>
</tr>
<tr>
<td>Excipients:</td>
<td>Paraffin, white soft</td>
</tr>
<tr>
<td></td>
<td>Paraffin, liquid</td>
</tr>
<tr>
<td></td>
<td>PPG-15 stearylether</td>
</tr>
<tr>
<td></td>
<td>All-rac-alpha-tocopherol</td>
</tr>
<tr>
<td></td>
<td>Dimethyl ether</td>
</tr>
<tr>
<td></td>
<td>Butane</td>
</tr>
</tbody>
</table>

Manufacturer’s name of bulk medication (IMP):

| LEO Pharma, 285 Cashel Road, Dublin 12, Ireland |

Manufacturer’s name of IMP in primary packaging:

| Germany |

Certifier’s name of IMP in primary packaging:

| LEO Pharma, 55 Industrieparken, 2750 Ballerup, Denmark |

Manufacturer’s name of secondary packaging and labelling:

| United Kingdom |

Certifier’s name of secondary packaging and labelling:

| United Kingdom |

Lot number(s)/expiry date(s):

| 113727401 / Jul-2013 |
### Table 2: Identity of LEO 90100 vehicle

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<thead>
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<th>Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finished product (Brand) name (if available)/name investigational product</td>
<td>LEO 90100 vehicle</td>
</tr>
<tr>
<td>Formulation</td>
<td>Aerosol. foam</td>
</tr>
<tr>
<td>Active ingredient name/strength</td>
<td>NA</td>
</tr>
<tr>
<td>Excipients</td>
<td>Paraffin, white soft</td>
</tr>
<tr>
<td></td>
<td>Paraffin, liquid</td>
</tr>
<tr>
<td></td>
<td>PPG-15 stearylether</td>
</tr>
<tr>
<td></td>
<td>All-rac-alpha-tocopherol</td>
</tr>
<tr>
<td></td>
<td>Dimethyl ether</td>
</tr>
<tr>
<td></td>
<td>Butane</td>
</tr>
<tr>
<td>Manufacturer’s name of bulk medication (IMP):</td>
<td>LEO Pharma, 285 Cashel Road, Dublin 12, Ireland</td>
</tr>
<tr>
<td>Manufacturer’s name of IMP in primary packaging</td>
<td>[Redacted] Germany</td>
</tr>
<tr>
<td>Certifier’s name of IMP in primary packaging</td>
<td>LEO Pharma, 55 Industriparken, 2750 Ballerup, Denmark</td>
</tr>
<tr>
<td>Manufacturer’s name of secondary packaging and labelling</td>
<td>[Redacted] United Kingdom</td>
</tr>
<tr>
<td>Certifier’s name of secondary packaging and labelling</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Lot number(s)/expiry date(s)</td>
<td>113727301 / Jul-2013</td>
</tr>
</tbody>
</table>
Table 3: Identity of Calcipotriol plus BDP ointment

<table>
<thead>
<tr>
<th>Finished product (Brand) name (if available)/name investigational product:</th>
<th>Taclonex® ointment, 30 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation:</td>
<td>Ointment</td>
</tr>
<tr>
<td>Active ingredient name/strength:</td>
<td>Calcipotriol (as hydrate) 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate)</td>
</tr>
<tr>
<td>Excipients:</td>
<td>Paraffin, white soft Paraffin, liquid PPG-15 stearylether All-rac-alpha-tocopherol</td>
</tr>
<tr>
<td>Manufacturer’s name bulk medication (IMP):</td>
<td>LEO Pharma, 285 Cashel Road, Dublin 12, Ireland</td>
</tr>
<tr>
<td>Manufacturer’s name of IMP in primary packaging</td>
<td>LEO Pharma, 285 Cashel Road, Dublin 12, Ireland</td>
</tr>
<tr>
<td>Certifier’s name of IMP in primary packaging</td>
<td>LEO Pharma, 55 Industrparken, 2750 Ballerup, Denmark</td>
</tr>
<tr>
<td>Manufacturer’s name of secondary packaging and labelling</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Certifier’s name of secondary packaging and labelling</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Lot number(s)/expiry date(s):</td>
<td>120887101 / Jul-2013</td>
</tr>
</tbody>
</table>
Table 4: Identity of Ointment vehicle

<table>
<thead>
<tr>
<th>Finished product (Brand) name (if available)/name investigational product:</th>
<th>Ointment vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation:</td>
<td>Ointment</td>
</tr>
<tr>
<td>Active ingredient name/strength:</td>
<td>NA</td>
</tr>
<tr>
<td>Excipients:</td>
<td>Paraffin, white soft Paraffin, liquid PPG-15 stearylether All-rac-alpha-tocopherol</td>
</tr>
<tr>
<td>Manufacturer’s name bulk medication (IMP):</td>
<td>LEO Pharma, 285 Cashel Road, Dublin 12, Ireland</td>
</tr>
<tr>
<td>Manufacturer’s name of IMP in primary packaging</td>
<td>LEO Pharma, 285 Cashel Road, Dublin 12, Ireland</td>
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<tr>
<td>Certifier’s name of IMP in primary packaging</td>
<td>LEO Pharma, 55 Industriparken, 2750 Ballerup, Denmark</td>
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<td>Manufacturer’s name of secondary packaging and labelling</td>
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<td>Certifier’s name of secondary packaging and labelling</td>
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<tr>
<td>Lot number(s)/expiry date(s):</td>
<td>120687101 / Jul-2013</td>
</tr>
</tbody>
</table>

For details on labelling and storage of the investigational products, see Sections 10.6.1 and 10.6.2 of the clinical study protocol (Appendix 16.1.1).

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects who were found to comply with all the protocol’s inclusion and exclusion criteria were randomised to one of the trial treatments at Visit 1 (Day 0). Treatment assignment was via a central IWRS in accordance with a pre-planned computer generated randomisation schedule in a 3:1:3:1 ratio. A subject was to be assigned the next (ascending) randomisation code number available. Two separate randomisation code lists were used, one for subjects with mild disease and one for subject with at least moderate disease according to the IGA for trunks and limbs at baseline.
9.4.4 Selection of Doses in the Trial

The maximum weekly dose for LEO 90100 was selected based on the recommended maximum weekly dose for DAIVOBET/DOVOBET/TACTIONEX ointment, which is 100 g. Since 30 g is currently the only available pack size of LEO 90100, the maximum weekly dose was set to 90 g (3 × 30 g) for practical reasons.

9.4.5 Selection and Timing of Dose for each Subject

Described in Section 9.4.1.

9.4.6 Blinding

This was an investigator-blind trial. As two of the treatments were in an aerosol foam formulation and two were in an ointment formulation, the subject knew if s/he was receiving an aerosol foam or an ointment. However, the subject would not know if s/he has received active treatment or placebo. Further, the trial medication was handed out to the subjects by a designated person so the investigator would not know which investigational product the subject has received.

The packaging and labelling of the investigational products contained no evidence of their identity. There was a slight weight difference between the can and the tube; however none other than individuals handling trial medication had the possibility of weighing the two against each other. No effects of the investigational products were expected which would reveal the identity of the individual treatment allocations. Consequently, it was expected that the (sub)investigators would remain unaware of the individual treatment assignment during the conduct of the clinical trial.

Emergency un-blinding of individual subject treatment could be made via the IWRS to obtain information regarding an individual subject’s treatment assignment. An emergency un-blinding request could be made by the (sub)investigators, other health care professional, or authorised LEO personnel.

The clinical trial was un-blinded when a final validated database had been produced, the statistical analysis specified in the protocol had been reviewed in relation to the blinded data actually obtained and the Statistical Analysis Plan Update (SAPU) had been approved.
9.4.7 Prior and Concomitant Therapy

Prior to the Study Treatment Phase
The washout phase was up to 4 weeks (28 days). Subjects who had been treated with medications requiring more than 4 weeks washout were not eligible for the trial. However, a subject could be eligible if s/he has had a treatment free period prior to entering the trial (i.e. having signed Informed Consent), e.g. if a subject had been off infliximab 6 weeks prior to entering the trial, the subject might still have been eligible for the trial after 2 weeks washout.

Treatments requiring washout
Systemic treatment with biological therapies, whether marketed or not, with a potential effect on psoriasis vulgaris (e.g. alefacept, etanercept, infliximab, adalimumab and ustekinumab, see exclusion criterion 1)*

- Systemic treatments with all other therapies with a potential effect on psoriasis vulgaris (e.g. corticosteroids, retinoids, methotrexate, ciclosporin and other immunosuppressants) (4 weeks)
- PUVA therapy (4 weeks)
- UVB therapy (2 weeks)
- Topical anti-psoriatic treatment on the trunk and/or limbs (2 weeks)**
- Topical treatment with class 1-5*** corticosteroids and vitamin D analogues on the face, skin folds and scalp (2 weeks)
- Use of prescription shampoos on the scalp (2 weeks)
- Use of non-marketed drug substances (see exclusion criterion 3)

*) Note: duration of the washout phase should not exceed 28 days

**) Note: use of emollients was allowed on treatment areas during this 2-week period

***) Please see Appendix III of the study protocol (Appendix 16.1.1) for Potency Classification of Topical Corticosteroids

During the Study Treatment Phase
Concomitant medication for conditions other than psoriasis vulgaris (with no potential effect on psoriasis vulgaris) could be continued throughout the trial without any change in dosage
whenever possible. Use of concomitant treatment was recorded in the subject’s medical record and the eCRF (treatment/drug name, dose, indication and dates of start and stop).

Use of non-marketed/other investigational products was not permitted during the trial.

Changes in doses (including starting) of drugs that, while not specifically indicated for treatment of the indication being studied, are known to have an effect (positive or negative) on the indication, were not permitted. This included, but was not limited to beta-blockers, antimalarial drugs, lithium and ACE inhibitors.

Inhaled steroids, bath oils and moisturising soaps were allowed during the trial.

Except for some topical treatments on the face, skin folds and scalp (see below), use of any drug except the investigational product for the treatment of psoriasis vulgaris was not allowed.

Accordingly, only the following concomitant topical anti-psoriatic treatments were permitted during the trial:

**Face, Skin Folds and Scalp**
All topical medications were allowed except class 1 to 5 corticosteroids, vitamin D analogues and prescription shampoos for the scalp.

- Unlimited use of emollients was allowed.

### 9.4.8 Treatment Compliance

At all on-treatment visits, the subject was asked if s/he had used the medication as prescribed. If this was not the case, the degree and nature of non-compliance was specified.

Subjects classified as clear at any of Visits 2 or 3 could stop the treatment at the (sub)investigator’s discretion. They were to remain in the trial and attend all visits up to and including week 4 (Visit 4). Although classified as clear, the subjects still had study medication dispensed at each visit and were to restart treatment if required, based on their own judgement. More than one discontinuation/restart cycle was allowed. Subjects were not allowed to discontinue treatment themselves between visits, but were only allowed to stop using the treatment on the advice of the (sub)investigator at a scheduled visit.
At the end of trial, the investigational products returned to the CMO were reconciled with the Individual Drug Accountability Forms. All returned cans were weighed by the CMO to determine the amount of the investigational product used.

Following packaging, and prior to supply of the investigational product, 10 cans were weighed and the average used as a basis to calculate the amount of trial medication used per treatment phase visit interval for each subject.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The schedule of trial assessments for all trial visits is presented in Table 5.
Table 5: Schedule of trial assessments

<table>
<thead>
<tr>
<th>Visit window / Day</th>
<th>Screening</th>
<th>1&lt;sup&gt;)&lt;/sup&gt;</th>
<th>2&lt;sup&gt;)&lt;/sup&gt;</th>
<th>3&lt;sup&gt;)&lt;/sup&gt;</th>
<th>4&lt;sup&gt;)&lt;/sup&gt;</th>
<th>FU&lt;sup&gt;7)&lt;/sup&gt;, if required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to -28</td>
<td>0</td>
<td>7 ±2 Day</td>
<td>14 ±2 Day</td>
<td>28 ±2 Day</td>
<td>+14 ±2 Day</td>
<td>2 weeks after last visit</td>
</tr>
</tbody>
</table>

| Informed consent  | X         |              |              |              |              |                             |
| Subject demographics | X        |              |              |              |              |                             |
| In-/exclusion criteria | X  | X           |              |              |              |                             |
| Pregnancy test<sup>1)</sup> |              |              |              |              |              |                             |
| Relevant medical history | X        |              |              |              |              |                             |
| Concurrent diagnoses | X        |              |              |              |              |                             |
| Concomitant medication | X  | X            | X            | X            | X            | X                           |
| Vital signs<sup>2)</sup> |              | X            |              |              |              |                             |
| Physical examination<sup>3)</sup> | X          |              |              |              |              |                             |
| Randomisation     | X         |              |              |              |              |                             |
| Adverse Event(s)  | X         | X            | X            | X            | X            | X                           |
| Laboratory – biochemistry, urinalysis<sup>4)</sup> |              | X            |              |              |              |                             |
| Laboratory – 25-hydroxy vitamin D | X |              |              |              |              |                             |
| Investigator’s assessment of BSA involvement | X  | X            | X            | X            | X            |                             |
| Investigator’s global assessment of disease severity (IGA) | X  | X            | X            | X            | X            |                             |
| Investigator’s assessment of extent and severity of clinical signs (m-PASI) | X  | X            | X            | X            | X            |                             |
| Local safety and tolerability |              | X            | X            | X            |              |                             |
| Patient’s global assessment of disease severity | X  | X            | X            | X            | X            |                             |
Subject’s assessment of itching by use of VAS

Subject’s assessment of treatment satisfaction by use of TSQM

Dispensing of trial medication

Compliance check

Return of trial medication

End of trial Form 

3) Physical examination was to as minimum include height and weight.

4) Biochemistry and urinalysis included serum calcium, serum albumin, urine calcium and urine creatinine.

5) For subjects prematurely withdrawn from treatment all trial procedures scheduled for Visit 4 was to be completed.

6) If no washout was needed the subject could enter Visit 1 directly. Subjects entering Visit 1 without washout needed to have all trial procedures done applicable for screening visit.

7) The treatment phase was followed by a FU phase if there was an on-going adverse event at the last on-treatment visit, which was classified as possible or probably related to the study medication or not assessable in relation to the study medication.

9.5.1.1 Subject Eligibility

Subject’s eligibility for the clinical trial was to be checked according to the inclusion and exclusion criteria at visits specified in the schedule (Table 5).

Demographic data

Demographic data comprised of date of birth, sex, ethnic origin and race. The subjects were asked to self-reported their ethnicity (Hispanic or Latino, not Hispanic or Latino) and race
(American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other).

Skin type
In addition, the skin type of the subjects was recorded according to the classification in Table 6.

Table 6: Fitzpatrick Skin Type

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

Duration of psoriasis
The duration of psoriasis vulgaris was recorded, to the nearest whole year.

Medical history/concurrent diagnoses/concomitant medication
Relevant medical history, all concurrent diagnoses and all concomitant medication were recorded, including previous use of biologics available in the US, immunosuppressant, corticosteroids, retinoids, Vitamin D analogues, calcineurin inhibitors and coal tar. Approximate date and route of administration were to be recorded. Other locations for psoriasis were recorded, i.e. skin folds, face, scalp, nails and genitals.

Vital Signs
Heart rate and blood pressure were measured after the subject had been resting in a supine position for five minutes.

Physical Examination
A routine medical examination was made which as minimum included weight and height. Any
findings either prevented eligibility for the trial or were documented as concurrent diagnoses as appropriate.

9.5.1.2 Efficacy Assessment

9.5.1.2.1 Investigator Assessments

Definition of the body areas to be assessed
The treatment areas to be assessed were the trunk and limbs.

The trunk and limbs included the arms (including hands), trunk (including neck) and the legs (including buttocks and feet).

The scalp, face, skin folds and genitals were not to be treated with the Investigational Product or assessed as part of the efficacy analysis.

The (sub)investigator made the following clinical assessments. Ideally, all assessments for a subject were to be made by the same (sub)investigator.

Investigator’s global assessment of disease severity (IGA)
At all treatment phase visits (Visits 1 to 4), the (sub)investigator made a global assessment of the disease severity of the psoriasis on the trunk and limbs by use of the 5-point scale shown in Table 7. This assessment represented the average lesion severity on the trunk and limbs. The assessment was based on the condition of the disease at the time of evaluation, and not in relation to the condition at a previous visit.
## Table 7: Investigator’s Global Assessment of Disease Severity – 5-point Scale

<table>
<thead>
<tr>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear</td>
<td>Plaque thickening = no elevation or thickening of normal skin</td>
</tr>
<tr>
<td></td>
<td>Scaling = no evidence of scaling</td>
</tr>
<tr>
<td></td>
<td>Erythema = none (no residual red coloration but post-inflammatory</td>
</tr>
<tr>
<td></td>
<td>hyperpigmentation may be present)</td>
</tr>
<tr>
<td>Almost</td>
<td>Plaque thickening = none or possible thickening but difficult to ascertain</td>
</tr>
<tr>
<td>clear</td>
<td>whether there is a slight elevation above normal skin level</td>
</tr>
<tr>
<td></td>
<td>Scaling = none or residual surface dryness and scaling</td>
</tr>
<tr>
<td></td>
<td>Erythema = light pink coloration</td>
</tr>
<tr>
<td>Mild</td>
<td>Plaque thickening = slight but definite elevation</td>
</tr>
<tr>
<td></td>
<td>Scaling = fine scales partially or mostly covering lesions</td>
</tr>
<tr>
<td></td>
<td>Erythema = light red coloration</td>
</tr>
<tr>
<td>Moderate</td>
<td>Plaque thickening = moderate elevation with rounded or sloped edges</td>
</tr>
<tr>
<td></td>
<td>Scaling = most lesions at least partially covered</td>
</tr>
<tr>
<td></td>
<td>Erythema = definite red coloration</td>
</tr>
<tr>
<td>Severe</td>
<td>Plaque thickening = marked or very marked elevation typically with hard</td>
</tr>
<tr>
<td></td>
<td>or sharp edges</td>
</tr>
<tr>
<td></td>
<td>Scaling = non-tenacious or thick tenacious scale, covering most or all of</td>
</tr>
<tr>
<td></td>
<td>the lesions</td>
</tr>
<tr>
<td></td>
<td>Erythema = very bright red coloration; extreme red coloration; deep red</td>
</tr>
<tr>
<td></td>
<td>coloration</td>
</tr>
</tbody>
</table>

**Note:** At Day 0 (Visit 1) the disease severity must have been graded as at least mild in order to meet the inclusion criteria. Subjects classified as having at least ‘moderate’ disease at baseline who achieved ‘clear’ or ‘almost clear’ disease severity were considered to have ‘controlled disease’. Subjects classified at baseline as having ‘mild’ disease had to achieve ‘clear’ to be considered to have ‘controlled disease’.

**Investigator’s assessment of the extent and severity of clinical signs (redness, thickness, scaliness)**

At all treatment phase visits (Visits 1 to 4), the (sub)investigator made assessments of the extent and severity of clinical signs of the subject’s psoriasis using a modified PASI scoring system (excluding head), in terms of three clinical signs: redness, thickness and scaliness.
The extent of psoriatic involvement was recorded for each of the three areas arms, trunk and legs using the following scale:

0 = no involvement  
1 = <10%  
2 = 10 - 29%  
3 = 30 - 49%  
4 = 50 - 69%  
5 = 70 - 89%  
6 = 90 - 100%

The severity of the psoriatic lesions in each of the three areas was recorded for each of the signs of redness, thickness and scaliness. For each clinical sign, a single score, reflecting the average severity of all psoriatic lesions on given body region, was determined according to the scale in Table 8:

**Table 8: Severity score for redness, thickness and scaliness**

<table>
<thead>
<tr>
<th>Redness</th>
<th>0 = none (no erythema)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 = mild (faint erythema, pink to very light red)</td>
</tr>
<tr>
<td></td>
<td>2 = moderate (definite light red erythema)</td>
</tr>
<tr>
<td></td>
<td>3 = severe (dark red erythema)</td>
</tr>
<tr>
<td></td>
<td>4 = very severe (very dark red erythema)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thickness</th>
<th>0 = none (no plaque elevation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 = mild (slight, barely perceptible elevation)</td>
</tr>
<tr>
<td></td>
<td>2 = moderate (definite elevation but not thick)</td>
</tr>
<tr>
<td></td>
<td>3 = severe (definite elevation, thick plaque with sharp edge)</td>
</tr>
<tr>
<td></td>
<td>4 = very severe (very thick plaque with sharp edge)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scaliness</th>
<th>0 = none (no scaling)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 = mild (sparse, fine-scale lesions, only partially covered)</td>
</tr>
<tr>
<td></td>
<td>2 = moderate (coarser scales, most of lesions covered)</td>
</tr>
<tr>
<td></td>
<td>3 = severe (entire lesion covered with coarse scales)</td>
</tr>
<tr>
<td></td>
<td>4 = very severe (very thick coarse scales, possibly fissured)</td>
</tr>
</tbody>
</table>

**Investigator’s assessment of the body surface area involvement of psoriasis vulgaris**

At all treatment phase visits (1 to 4) the (sub)investigator assessed the extent of the subject’s psoriatic involvement on the trunk and limbs. The total psoriatic involvement on the trunk and limbs (excluding skin folds and genitals) was recorded as a percentage of the total BSA,
estimating that the surface of the subject’s full, flat palm (including the five digits) correlates to approximately 1% of the total BSA. The purpose of this was to obtain an estimate of the area on the trunk and limbs to be treated with study medication.

9.5.1.2.2 Subject Assessments

The subject’s assessments had to be made prior to the investigator’s assessments.

Patient’s global assessment of disease severity
This assessment was made at all treatment phase visits (1 to 4), based on the condition of the disease at the time of the evaluation and not in relation to the condition at a previous visit, using the scale in Table 9. The (sub)investigator explained the categories of the scale to the subject and the subject told the (sub)investigator which category to mark.

Table 9: Patient’s Global Assessment of Disease Severity – 5-point Scale

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Severity of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear</td>
<td>No psoriasis symptoms at all</td>
</tr>
<tr>
<td>Very mild</td>
<td>Very slight psoriasis symptoms, does not interfere with daily life</td>
</tr>
<tr>
<td>Mild</td>
<td>Slight psoriasis symptoms, interferes with daily life only occasionally</td>
</tr>
<tr>
<td>Moderate</td>
<td>Definite psoriasis symptoms, interferes with daily life frequently</td>
</tr>
<tr>
<td>Severe</td>
<td>Intense psoriasis symptoms, interferes or restricts daily life very frequently</td>
</tr>
</tbody>
</table>

Subjects classifying themselves as being ‘clear’ or having ‘very mild’ disease were considered to have ‘controlled disease’.

Subject’s assessment of itching by use of a Visual Analogue Scale
This assessment was made by the subject at all treatment phase visits (1 to 4). The visual analogue scale (VAS) was used to assess itch using a horizontal line. The line represented the range of itch severity, from 0 (no itch at all) at one end to 10 (worst itch you can imagine) at the other. The subject was asked to put a single vertical line across the horizontal line at the spot he/she felt best reflected the severity of itch during the past 24 hours.

Subject’s assessment of treatment satisfaction by use of TSQM
The subject’s assessment of treatment satisfaction was performed at Visit 4 by means of the Treatment Satisfaction Questionnaire of Medication (TSQM) version II which is a validated
questionnaire developed to permit comparisons of patient treatment satisfaction across medication types and patient conditions. The questionnaire had to be completed by the subject while at the investigator site.

9.5.1.3 Safety Assessments

9.5.1.3.1 Local Safety and Tolerability

Local safety and tolerability comprised of signs assessed by the (sub)investigator and symptoms reported by the subject.

At Visits 2-4 the (sub)investigator assessed application site reactions for the following signs: erythema, dryness, erosion and oedema. For each sign a skin reaction score was recorded by use of a 4-point scale: 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense).

At Visits 2-4 the subject report application site reactions for the following symptoms: burning and pain. The (sub)investigator explained the scores/categories of the scale to the subject and the subject was to tell the (sub)investigator which scores/category to mark. For each symptom a skin reaction score was recorded by use of a 4-point scale: 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense).

9.5.1.3.2 Laboratory Analysis

Samples for analysis of the parameters listed below were taken as scheduled (Table 5) or on withdrawal from or early completion of the treatment phase of the clinical trial. A urine pregnancy test was performed at the trial site at Day 0 (Visit 1), prior to randomisation, in female subjects of child-bearing potential. The test kits were provided by the Central Laboratory. All other laboratory analysis was performed centrally.

A sample of venous blood and a spot urine sample were taken at Day 0 (Visit 1/Baseline) and at Day 28 (Visit 4). If at the last on treatment visit the albumin-corrected serum calcium was above the reference range or if any other laboratory parameter result was abnormal and judged as clinically significant, a follow-up visit was required for further sampling. The Central Laboratory provided the materials and instructions necessary for the collections and transport of the samples.

Parameters analysed in blood and urine samples are given in Table 10.
Table 10: Serum biochemistry and urinalysis

<table>
<thead>
<tr>
<th>Serum Biochemistry</th>
<th>Urinalysis (spot urine sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium*a</td>
<td>Visit 1 and 4 Calcium*b</td>
</tr>
<tr>
<td>Albumin*a</td>
<td>Visit 1 and 4 Creatinine*b</td>
</tr>
<tr>
<td>25-hydroxy vitamin D</td>
<td>Visit 1</td>
</tr>
</tbody>
</table>

*aAlbumin-corrected serum calcium was calculated in mmol/l using the formula:
serum calcium (total) in mmol/l + (0.02 × [40-serum albumin in g/l])

*bCalcium:creatinine ratio was calculated.

Review of laboratory results

If any of the laboratory results were abnormal and judged as clinically significant, the (sub)investigator was to follow-up with the subject as clinically appropriate (this may involve requesting repeat samples). Likewise, if the albumin-corrected serum calcium result was above the reference range at the last on-treatment visit, a follow-up visit was to be performed for repeat sampling. Clinically significant laboratory values were to be regarded as an AE.

9.5.1.3.3 Adverse Events

An adverse event (AE) is defined as:

‘Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal investigational product.’ (ICH Harmonized Tripartite Guideline for Good Clinical Practice, E6 (R1)).

A serious adverse event (SAE) is any untoward medical occurrence that

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect
• other medically important conditions*)

*) Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are allergic broncospasm, blood dyscrasias, and convulsions.

Global Pharmacovigilance is responsible for the assessment of headquarter expectedness according to LEO procedures. The relevant reference document for this clinical trial was Investigator’s Brochure (LEO 90100), edition 2 and subsequent updates, and the Company Core Safety Information, CCSI_Daivobet_02 (Daivobet ointment) as agreed between the Head of International Clinical Development and the Medical Director, Global Pharmacovigilance.

At all visits, the subject was asked a non-leading question by the investigator: “How have you felt since I saw you last?” No specific symptoms were asked for.

If there were no AEs to record, no further questions were asked and “NO” was stated. In case there were one or more AEs to record, then “YES” was stated and the investigator recorded the event term, intensity, duration, suspected causal relationship to the investigational product and outcome.

The investigator also observed the subject for any changes not reported by the subject, and recorded these changes.

Only medically qualified personnel assessed AEs.

**Reporting of Adverse Events**

Events reported by the subject, or observed by the (sub)investigator, that fell into any of the above definitions were to be recorded on the AE page of the CRF and described in the following manner:

The nature of the event was described in precise, English medical terminology (i.e., not necessarily the exact words used by the subject). Whenever possible, a specific diagnosis was to be stated (e.g., allergic contact dermatitis).
For cutaneous adverse events the **location** had to be part of the adverse event description and described using the following terminology:

- *lesional/perilesional* ($\leq 2$ cm from the border of lesion(s) treated with investigational product) or
- *distant* (>2 cm from the lesion border)

The **intensity** of the event was described in terms of mild, moderate or severe according to the investigator’s clinical judgement.

- **Mild**: The AE does not interfere in a significant manner with the subject’s normal functioning level and requires no medical intervention.
- **Moderate**: The AE interferes with the subject’s normal functioning level and may or may not require medical intervention.
- **Severe**: The AE produces significant impairment of the subject’s functioning or requires medical intervention.

The **duration** of the event was reported as the start date and stop date of the event.

The **causal relation** of the event to the use of the investigational product was described in terms of probable, possible, not related or not assessable according to the following:

**Probably related**
Follows a reasonable temporal sequence from administration of the investigational product

- Could not be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject
- Follows a known pattern of response to the investigational product
- Disappears or decreases on cessation or reduction in dose of the investigational product
- Reappears or worsens upon re-challenge.

**Possibly related**
Follows a reasonable temporal sequence from administration of the investigational product

- Could also be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject
• Follows a known pattern of response to the investigational product.

Not related:
Does not follow a reasonable temporal sequence from administration of the investigational product

• Is better explained by other factor like the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject

• Does not follow a known pattern of response to the investigational product.

Not assessable:
The AE cannot be judged otherwise because the information is insufficient or contradictory. A final assessment (i.e. probably, possibly or not related) is to be made as more information becomes available, at the latest when the subject has completed the trial.

The outcome of the event was classified and handled as follows:

• Recovered/resolved: The event has stopped. The stop date of the event was to be recorded.

• Recovering/resolving: The subject is clearly recovering from an event. The event is, however, not yet completely resolved. Follow-up on the event was required until final outcome has been established.

• Not recovered/not resolved: Event is still ongoing. Follow-up on the event was required until final outcome has been established.

• Recovered with sequelae: The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke. The stop date of the event was to be recorded.

• Fatal: The subject has died as a consequence of the event. Date of death was recorded as stop date for the adverse event.

• Unknown: Unknown to investigator, e.g., subject lost to follow-up.
Once a subject had completed the trial, the investigator was to follow-up for outcome on all non-serious AEs classified as possibly/probably related to the investigational product or not assessable until last follow-up visit or until final outcome was determined, whichever came first.

### 9.5.1.3.4 Other Events to be Reported

**Pregnancy**

Pregnancy, which occurred during a clinical trial with an investigational product, was to be reported to LEO within 24 hours of first knowledge using the Pregnancy Follow-up Form supplied by LEO. All pregnancies were to be followed-up until delivery or termination.

**Overdose**

Any overdose defined as any higher dose than prescribed for the individual subject was to be reported on the AE form of the eCRF book. AEs originating in the overdose were to be documented on a separate line.

**Aggravation of Condition**

Any clinically significant aggravation/exacerbation/worsening of the initially treated condition compared to baseline, judged by an overall medical assessment, was to be reported as an AE.

### 9.5.1.3.5 Serious Adverse Events

**Reporting of Serious Adverse Events**

Any SAE, related or unrelated to the investigational product or any trial procedure after signature of the Informed Consent Form was to be reported to TKL Research and LEO on the (paper) Serious Adverse Event Form – Clinical Trial within 24 hours.

Note: Planned hospitalisation or planned prolonged of hospitalisation do not fulfil the criteria for being an SAE. The elective nature of the event must be clearly documented in the subject’s medical record.

SAEs were to be reported on the adverse event form of the eCRF book. Additionally reports were to be made using the paper Serious Adverse Event Form – Clinical Trial, supplied by LEO. Apart from the assessment of the intensity, causal relationship to the investigational
product(s) and/or trial procedures, the action taken and the outcome to date, this report had to contain a comprehensive narrative description of the course of the event.

The completed Serious Adverse Event Form – Clinical Trial was to be faxed or scanned and emailed to both LEO and TKL Research as specified in the protocol (Appendix 16.1.1).

All other relevant reports of diagnostic procedures, hospital records, autopsy reports etc. were to be included, as applicable or upon request from TKL Research or LEO Pharma Global Pharmacovigilance.

The IRB(s)/IEC(s), regulatory authorities and concerned investigators were to be notified of SAEs according to current regulation and local requirements.

All Suspected, Unexpected Serious Adverse Reactions (SUSARs) are subject to expedited reporting to regulatory authorities. Global Pharmacovigilance was to unblind such cases prior to reporting. Investigators remained blinded.

SAEs were to be followed indefinitely until a final outcome had been established i.e., the follow-up may have continued beyond the end of the clinical trial.

9.5.2 Appropriateness of Measurements

The efficacy measures used in this trial (the IGA, m-PASI) are standard in clinical trials of psoriasis. The 5-point scale used for the IGA was developed in consultation with the FDA. The TSQM is a validated patient reporting instrument measuring treatment satisfaction. A visual analogue scale (VAS) is a commonly used method to quantify itch. All safety measures used in this trial are also standard.

9.5.3 Primary Efficacy Variable(s)

The primary response criterion was subjects with ‘controlled disease’ (‘clear’ or ‘almost clear’ for subjects with at least moderate disease at baseline, ‘clear’ for subjects with mild disease at baseline) according to the IGA on the trunk and limbs at week 4.

9.5.4 Secondary Response Criteria

- Subjects with ‘controlled disease’ according to the IGA on the trunk and limbs at week 1.
- m-PASI at week 1
• m-PASI at week 4
• Subjects with PASI 50 (at least 50% reduction in m-PASI from baseline) at week 4
• Subjects with PASI 75 (at least 75% reduction in m-PASI from baseline) at week 4
• Subjects with ‘controlled disease’ (clear or very mild) according to the patient’s global assessment of disease severity at week 4
• The change in itch as assessed by the Visual Analogue Scale from baseline to each subsequent visit
• TSQM at end of treatment

The PASI used in this trial was modified (m-PASI) to exclude assessment of head (scalp, face), as study treatment was not allowed to be used on these body regions. m-PASI was calculated using the formula given below based on the investigator’s assessment of the extent and severity of the disease locally (trunk, arms, legs):

\[
\text{Arms } 0.2 \ (R + T + S)E = X \\
\text{Trunk } 0.3 \ (R + T + S)E = Y \\
\text{Legs } 0.4 \ (R + T + S)E = Z
\]

where: R = score for redness; T = score for thickness; S = score for scaliness; E = score for extent

The sum of X + Y + Z gives the total m-PASI, which can range from 0 to 64.8.

The evaluation of safety was based on the following parameters:

• Any reported adverse event.
• Any reported adverse drug reaction.
• Change in albumin-corrected serum calcium from baseline to week 4
• Change in urine calcium:creatinine ratio from baseline to week 4
• Reason for withdrawal from the study
• Investigator's assessment of the BSA involvement of psoriasis vulgaris
• Change in vital signs (blood pressure, heart rate) from baseline to week 4

Local safety and tolerability parameters
9.5.5 Drug Concentration Measurements

Not applicable.

9.6 Data Quality Assurance

LEO has implemented a system of quality assurance, including all the elements described in this report. Within this system company Standard Operating Procedures (SOPs) are implemented to ensure that clinical studies are conducted in compliance with regulatory requirements and Good Clinical Practice. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

Trial sites, facilities, laboratories and all data (including sources) and documentation were available for GCP audit by LEO or inspection by competent authorities.

For this trial, one site audit was conducted. No critical findings were identified. The audit certificate(s) are provided in Appendix 16.1.8.

Data Handling

LEO, as sponsor of this trial, is responsible to the authorities for assuring the proper conduct of the trial with regard to protocol adherence and validity of the data recorded on the eCRFs. Monitors were assigned to serve as the principal link between (sub)investigators and LEO and to advise the investigators on the collection and maintenance of accurate, complete, legible, well organised, and easily retrievable data for the trial. In addition, they were to explain to the investigators any aspect of the (conduct of the) trial, including interpretation of the protocol, the purpose of collection of the specified data and reporting responsibilities.

In this trial data were collected by means of Remote Data Capture. The investigator, or staff authorised by the investigator, were to enter subject data into an eCRF designed by LEO. A uniquely numbered eCRF was used for each subject enrolled. Data recorded in the eCRF were accessible to site staff through a secure internet connection immediately after entry of data had taken place.

The eCRFs were to be maintained in an up-to-date condition at all times by the investigator. The investigator, or sub-investigator(s) authorised by the investigator, were to electronically sign all sections of eCRFs used. This signature information (incl. date of signature) was kept in an audit trail and could not be altered. Only medically qualified (sub)investigators were to
sign data on clinical assessments/safety. Any correction(s) to data in the eCRF, made by the investigator or authorised site staff, after original entry, were documented in the audit trail. Changes to data already approved, required the re-signature of investigator or authorised staff. The person making the change and the date, time and reason for the change were identified in the audit trail.

Subject data were to be entered into the eCRF by authorised site staff in a timely manner. Data were to be entered by site staff and systematic data validation was performed through the discrepancy management system within the data collection software. Queries for discrepant data were generated either automatically by the system upon entry or generated manually by the monitor or the trial data manager. All queries, whether generated by the system or by a user, would be in an electronic format. This systematic validation was made to ensure that a clean and consistent database was provided prior to the statistical analysis being performed.

Data were and are handled in accordance with the general terms and conditions of the authorisation granted by the Danish Data Protection Agency to LEO Pharma A/S, as required, according to the Danish Personal Act and any national legislation implementing the Data Protection Directive (95/46/EC).

LEO HQ is considered data responsible for all international clinical trials sponsored by LEO.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

The statistical analysis was planned in the clinical study protocol (Appendix 16.1.1) and further detailed in the SAPU dated 28-Nov-2012 (Appendix 16.1.9).

All subjects enrolled in the trial (i.e. for whom signed informed consent has been obtained and a CRF number assigned) were accounted for. All randomised subjects were included in the full analysis set (intention-to-treat 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.
A 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 (i.e. inclusion criteria 7, 8 and 9 see section 9.3.1). Further exclusion of subjects or subject data were decided upon after the blind review of the data, reviewing all the remaining in- and exclusion criteria, but focusing on concomitant medication that may affect psoriasis and also considering compliance/adherence.

The decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets were documented in the SAPU before breaking the blind.

9.7.1.1 Reasons for Leaving the Study

The reasons for leaving the study were presented for all randomised subjects, by last visit attended and by treatment group.

9.7.1.2 Baseline Characteristics

Descriptive statistics of demographics, disease-related and other baseline characteristics were presented for all randomised subjects and by treatment group. Presentations of age, sex, ethnicity, race and baseline IGA by treatment were also given by centre.

Categorical data were summarised using the number and percentage of subjects in each category and treatment group. Continuous data were summarised using the mean, median, standard deviation (SD), minimum and maximum values.

9.7.1.3 Analysis of Efficacy

The statistical analysis of efficacy was based on the defined response criteria.

9.7.1.4 Primary Response Criterion

The primary response criterion was analysed for the full analysis set and for the per protocol analysis set. The analysis for the full analysis set was regarded as primary while the analysis for per protocol analysis set was supportive.

The primary endpoint was Subjects with ‘controlled disease’ according to the IGA at week 4.
The number and proportion of subjects who achieved ‘Controlled disease’ according to the IGA at week 4 was tabulated for each treatment group and also presented for each centre by treatment group.

In clinical terms the hypothesis was as follows: LEO 90100 is superior to calcipotriol plus BDP ointment with respect to the proportion of subjects with ‘controlled disease’ according to the IGA.

The odds ratio of ‘Controlled disease’ at week 4 for LEO 90100 relative to Calcipotriol plus BDP ointment was tested equal to one using the Cochran-Mantel-Haenszel test adjusting for (pooled) centre. A 95% confidence interval was calculated. Prior to this an analysis of the effect of baseline IGA (stratum) on the odds as well as (pooled) centre effects was to be attempted. The Breslow-Day test for homogeneity of the odds ratio across (pooled) centres was performed at a 10% level; if significant, a sensitivity analysis was to be performed to identify possible extreme centres, omitting centres with the smallest and highest odds ratios respectively.

The proportion of subjects who achieved ‘controlled disease’ at week 4 was tabulated by treatment group and by centre. The number and proportion of subjects who achieved ‘Controlled disease’ according to the IGA at all visits were tabulated for each treatment group.

The number and proportion of subjects in each of the 5 categories (‘Clear’ to ‘Severe’) were tabulated for each of the treatments pooling all centres together. These tabulations were intended for descriptive purposes only and no statistical analyses of these data were undertaken.

9.7.1.5 Secondary Response Criteria

The secondary response criteria were analysed for the full analysis set.

The secondary endpoint Subjects with ‘controlled disease’ according to the IGA at week 1 was analysed as the primary endpoint.

m-PASI
The m-PASI at each visit was summarised for each treatment group.
For m-PASI at week 1 and week 4 respectively, the LEO 90100 and Calcipotriol plus BDP ointment groups were compared using ANOVA including (pooled) centre, treatment and baseline m-PASI in the model. The adjusted difference between LEO 90100 and Calcipotriol plus BDP ointment and the corresponding p-value as well as a 95% confidence interval was calculated for each week.

Also, for each week, a percentage change based on the adjusted mean value and population mean of baseline m-PASI was calculated for either treatment as well as the corresponding adjusted difference. Ninety-five percent confidence intervals were calculated similarly.

The number and proportion of subjects who achieved at least 50% as well at least 75% reduction in m-PASI from baseline (PASI 50 and PASI 75) were tabulated at each visit for each treatment group.

Each of the endpoints were analysed as the primary endpoint, except that no sensitivity analysis was carried out if the Breslow-Day test was significant; also the effect of baseline PASI 50 or PASI 75 was not analysed.

**Patient’s global assessment of disease severity**
The number and proportion of subjects in each of the five categories (‘Clear’ to ‘Severe’) were tabulated at each visit for each treatment group.

The number and proportion of subjects who achieved ‘Controlled disease’ according to the subject’s global assessment of disease severity at week 4 were tabulated for each treatment.

The analysis was done in the same way as for PASI 50.

**Patient’s assessment of itching by use of visual analogue scale**
The change in the visual analogue scale from baseline to each visit was summarised for each treatment group.

For the change in the visual analogue scale from baseline to week 1, week 2, and week 4, respectively, the LEO 90100 and calcipotriol plus BDP ointment groups were compared using ANCOVA including (pooled) centre, treatment, week and baseline visual analogue scale score in the model. The adjusted difference LEO 90100 – calcipotriol plus BDP ointment, the corresponding p-value as well as a 95% confidence interval were calculated for each week.
Treatment Satisfaction Questionnaire for Medication
The scores for the four dimensions of TSQM were in essence ordered categorical data. The LEO 90100 and calcipotriol plus BDP ointment groups were compared using either a t-test or a Wilcoxon test for each dimension.

9.7.1.6 Analysis of Safety
The analysis of safety was based on the safety analysis set.

9.7.1.6.1 Adverse Events
Any AEs were coded during the course of the trial and were in accordance with the current version of the MedDRA dictionary. The AEs were presented by Preferred Terms and Primary System Organ Class.

All AEs recorded during the course of the trial were included in the subject data listings. An event was considered emergent with the trial treatment if started after the first application or if started before the first application (applicable if subject had a wash-out) and worsened in intensity after. The tabulations described in the following only included the AEs that were emergent with trial treatment.

The number of subjects experiencing each type of AE (according to MedDRA Preferred Terms within Primary System Organ Class) was tabulated by treatment group regardless of the number of times each AE was reported by each subject. The percentage of subjects with AEs was compared between treatment groups by a chi-square test or Fisher’s exact test.

The intensity for each type of AE (according to the Preferred Term) was tabulated by treatment group. Where there were several recordings of intensity for a given type of AE (according to the Preferred Term), intensity was taken as the most severe recording for that AE.

The causal relationship to trial medication for each type of AE (according to the coding system) was tabulated by treatment group. Where there were several recordings of causal relationship to trial medication for a given type of AE (according to the coding system), causal relationship was taken as the worst recording from the last report of that AE, since that is when the investigator was in possession of most information and so best able to judge causal relationship.
Adverse drug reactions were defined as AEs for which the investigator had not described the causal relationship to trial medication as ‘not related’. The number of subjects experiencing each type of ADR (according to the Preferred Term) was tabulated regardless of the number of times each ADR was reported by each subject. The percentage of subjects with ADRs was compared between treatment groups by a chi-square test or Fisher’s exact test.

Serious adverse events were tabulated separately, and a narrative for each will be given.

9.7.1.6.2 Laboratory Safety Examinations

The change in albumin-corrected serum calcium and the change in urinary calcium:creatinine ratio from baseline to week 4 were summarised for each treatment group.

The albumin-corrected serum calcium and the urinary calcium:creatinine ratio were to be classified as ‘low’, ‘normal’ or ‘high’, depending on whether the values were below, within or above the reference range, respectively. Shift tables were produced showing the categories at baseline against those at week 4.

The Vitamin D level was to be classified as ‘low’, ‘normal’ or ‘high’, depending on whether the value was below, within or above the reference range, respectively, at Visit 1.

For both laboratory safety parameters shift tables based on clinically significant values were to be produced as above.

9.7.1.6.3 Vital Signs

The change in vital signs (blood pressure, heart rate) from baseline to week 4 were summarised as mean, SD, median, minimum and maximum values for each treatment group.

9.7.1.7 Evaluation of Other Observations

BSA was summarised by treatment group and visit.

The weight of study medication used was calculated by subtracting the weight of the used dispensed tubes and cans from the mean weight of a set of full tubes and cans. For the cans a correction factor (0.41) was used to correct for the propellant gasses. The weight of study medication used was summarised by treatment group for each visit interval and for the total
treatment period using the mean, SD, median, minimum and maximum values for the safety analysis set.

Compliance with treatment instructions was summarised for each treatment group for all randomised subjects. The percentage of missed applications for each visit interval (Visit 1 to Visit 2, Visit 2 to Visit 3 and Visit 3 to Visit 4) was calculated as follows: the number of applications of study medication missed for a particular visit interval was divided by the total number of days for the visit interval and multiplied by 100 to give a percentage.

The percentage of missed applications for the total treatment period was calculated as follows: the total number of applications of study medication missed between Visit 1 and the last on-treatment visit was divided by the total number of days between Visit 1 and the last on-treatment visit and multiplied by 100 to give a percentage.

The percentage of missed applications was allocated to one of the following categories: \( \leq 10\% \), \( >10\% \) to \( \leq 20\% \), \( >20\% \) to \( \leq 30\% \), \( >30\% \) to \( \leq 40\% \), \( >40\% \) to \( \leq 50\% \), \( >50\% \).

The six assessments of local safety and tolerability were to be summarised for each treatment group as categorical data at all visits for the safety analysis set. Due to the inconsistency of reporting local safety and tolerability (see Section 9.8) these assessments were summarised by centre for each treatment group as described in the SAPU.

9.7.1.8 General Principles

All significance tests were two-sided and all confidence intervals are presented with 95% degree of confidence. In the analyses where pooled centre was adjusted for, the validity of the statistical tests would depend on there being a sufficient number of subjects recruited in each treatment group at each centre. If a centre randomised fewer than 16 subjects, it was to be pooled with the next smallest centre to form a pooled centre of 16 or more randomised subjects. However, in order to facilitate aggregation of results from this trial and the concurrent phase 2 trial comparing LEO 90100 to its individual components (LEO 90100-07), it was decided to pool centres common to both trials based on their geographical location, rather than on the number of subjects randomised in a particular trial. Details of centre pooling were documented in the SAPU before breaking the randomisation code.

An observed cases approach was used for tabulations of data by visit (i.e. involving only those subjects who attended each specific visit).
For IGA, m-PASI and Patient’s Global Assessment of severity data an additional week 4 visit and an additional week 1 visit were tabulated using the last observation carried forward (LOCF) approach. The week 4 (LOCF) value for a particular efficacy measure was defined as the last value recorded for that efficacy measure. The week 1 (LOCF) value for a particular efficacy measure was defined as the value recorded at baseline for that efficacy measure.

Drop-outs and missing values were accounted for by the analysis of last observation values and by the definition of trial analysis sets prior to unblinding. The definition of methods to handle drop-outs and missing values may be refined, before breaking the randomisation code, by updating this aspect in the SAPU during the blind review of data actually obtained.

All the analyses specified in the protocol were reviewed in relation to the blinded data actually obtained and the SAPU was finalised before breaking the randomisation code. (NB: This does not apply to two subjects whose treatment code was broken during the trial in connection with the reporting of a SUSAR; described in Section 11.1.1.).

### 9.7.2 Determination of Sample Size

With 67% of subjects achieving ‘controlled disease’ with LEO 90100 and 50% for calcipotriol plus BDP ointment, 143 subjects in both treatment groups would be needed to obtain 80% power at a 5% significance level comparing the two groups using Fisher’s exact test. This number was rounded to 150 to account for drop-out.

Subjects were to be randomised to the treatment groups in a 3:1:3:1 ratio. Withdrawn subjects were not to be replaced.

With 150 subjects in LEO 90100 and calcipotriol plus BDP groups the sample size of the vehicle groups was fixed at 50. No power calculation for comparison to the vehicle groups has been carried out, because no comparison was planned to performed, as the vehicle groups only served a blinding purpose. This gives 400 subjects in all.

Each centre was to recruit a minimum of 8 subjects. Due to the disproportionate allocation ratio, centres could be pooled when comparing the LEO 90100 group to the calcipotriol plus BDP group. No centres were to recruit more than 56 subjects (approximately 14% of the total sample size).

The sample size calculations were carried out using the Proc Power in SAS®, version 9.2.
9.8 Changes in the Conduct of the Trial or Planned Analyses

There were no protocol amendments but there was one important change to the protocol planned analyses of local safety and tolerability due to the inconsistency in reporting of local safety and tolerability data across centres (described below). This change was made prior to breaking the blind and was documented in the SAPU (Appendix 16.1.9).

During the trial, the sponsor observed through medical monitoring of the clinical database some trends within data collected for the Local Safety and Tolerability (large inter-site variability) which indicated the possibility that guidance on how to conduct this assessment might have not optimally communicated to all study sites. This assessment was described in the Clinical Study Protocol only briefly, and further detailed guidance was given in the Guide to Clinical Assessments (Appendix 16.1.1).

On 20-Jul-2012, the sponsor sent a letter to all investigators to highlight the importance of conducting this assessment as described in the Guide to Clinical Assessments. For local safety and tolerability assessments conducted until this time, data discrepancies were issued in the eCRFs asking the investigators to clarify how the assessments had been conducted. Issued data discrepancies were answered by the investigators, confirming inconsistency in how the assessments had been performed and reported across centres. According to the Guide, the investigator was to assess the perilesional area (but not the lesions itself) for erythema, dryness, oedema and erosion. Furthermore, the subject was to assess the lesional/perilesional area for burning and pain. Any score of mild to severe for any sign/symptom was to be reported as an AE marked as lesional/perilesional. From investigators’ responses to discrepancies it appeared that some investigators reported also erythema, dryness, oedema and erosion in the lesional area, and scores of mild to severe for the signs/symptoms were not consistently reported as AEs.

Therefore, local safety and tolerability assessments were only presented by centre and treatment group and no overall summary by treatment group is presented.
10 Trial Population

10.1 Disposition of Subjects

A total of 427 subjects from 35 centres in the USA were enrolled into the trial (i.e. informed consent form signed and CRF number assigned). The first subject’s first visit was on 10-May-2012 and the last subject’s last visit was on 19-Sep-2012, hence the duration of the trial was 19 weeks (Table 49, End of Text [EoT]). Figure 12 (EoT) summarises subject recruitment over time.

Of the enrolled subjects, 376 were randomised in the trial (Table 50, EoT); 141 subjects to LEO 90100, 135 to Calcipotriol plus BDP ointment, 49 to LEO 90100 vehicle and 51 to Ointment vehicle. (NB: The number of randomised subjects was slightly lower than the number specified in the protocol (376 versus 400) due a limited supply of trial medication).

Table 11 summarises the reasons for withdrawals. Overall, the withdrawal rate was low with a total of 18 subjects (4.8%) withdrawing from the trial. The lowest rate of withdrawals was in the LEO 90100 group where 5 subjects (3.5%) withdrew compared with 8 (5.9%) in the Calcipotriol plus BDP ointment group. The most common reason for withdrawal was ‘Lost to follow-up’. There was 1 withdrawal (0.7%) due to an unacceptable adverse event (heart rate increased) reported in the Calcipotriol plus BDP ointment group, and 1 withdrawal (2.0%) due to unacceptable treatment efficacy reported in the Ointment vehicle group.

The reasons for withdrawal are summarised by last on-treatment visit for which data were recorded in Table 51 (EoT).
Table 11: Reasons for withdrawal: randomised subjects

<table>
<thead>
<tr>
<th>Reason for withdrawal</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Withdrawals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unacceptable treatment efficacy</td>
<td>1</td>
<td>0.3</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Unacceptable adverse event</td>
<td>1</td>
<td>0.3</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Voluntary (and no other reason)</td>
<td>5</td>
<td>1.3</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>8</td>
<td>2.1</td>
<td>3</td>
<td>2.1</td>
<td>4</td>
</tr>
<tr>
<td>Other reason(s)¹</td>
<td>3</td>
<td>0.8</td>
<td>2</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>Total number of withdrawn subjects</td>
<td>18</td>
<td>4.8</td>
<td>5</td>
<td>3.5</td>
<td>8</td>
</tr>
<tr>
<td>Completers²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>358</td>
<td>95.2</td>
<td>136</td>
<td>96.5</td>
<td>127</td>
</tr>
</tbody>
</table>

1) Other reasons included: one withdrawal of consent to start methotrexate again, one was unable to complete visits 2 and 3 and one missed visit 2
2) Withdrawal: subject who had a reason for discontinuance other than attended last visit. Completer: subject not defined as a withdrawal.
Visit attendance by treatment group is summarised in Figure 2.

**Figure 2: Visit attendance by treatment: randomised subjects**

LEO 90100

<table>
<thead>
<tr>
<th>Visit</th>
<th>Number of subjects</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (day 0)</td>
<td>141</td>
<td>0 Lost to follow up, 0 Other reasons(s), 0 Voluntary (and no other reason)</td>
</tr>
<tr>
<td>2 (week 1)</td>
<td>138</td>
<td>2 not attending, 0 Lost to follow up, 0 Voluntary (and no other reason), 0 Unacceptable adverse event</td>
</tr>
<tr>
<td>3 (week 2)</td>
<td>138</td>
<td>2 not attending, 3 Lost to follow up, 0 Unacceptable treatment efficacy</td>
</tr>
<tr>
<td>4 (week 4)</td>
<td>138</td>
<td>2 Other reasons, 0 Voluntary (and no other reason)</td>
</tr>
</tbody>
</table>
Figure 2: Visit attendance by treatment: randomised subjects (cont.)

Calcipotriol plus BDP ointment

<table>
<thead>
<tr>
<th>Visit</th>
<th>Number of subjects</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
</table>
| 1 (day 0) | 135                | 2 Lost to follow up  
1 Other reasons(s)  
0 Voluntary (and no other reason) |
| 2 (week 1) | 132                | 0 not attending  
1 Lost to follow-up  
1 Voluntary (and no other reason)  
1 Unacceptable adverse event |
| 3 (week 2) | 129                | 0 not attending  
1 Lost to follow-up  
0 Unacceptable treatment efficacy |
| 4 (week 4) | 128                | 0 Other reasons  
1 Voluntary (and no other reason) |
Figure 2: Visit attendance by treatment: randomised subjects (cont.)

**LEO 90100 vehicle**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Number of subjects</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 (day 0)</td>
<td>49</td>
<td>0 Lost to follow up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 Other reasons(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 Voluntary (and no other reason)</td>
</tr>
<tr>
<td></td>
<td>0 not attending</td>
<td></td>
</tr>
<tr>
<td></td>
<td>visit 2 and 3</td>
<td></td>
</tr>
<tr>
<td>Visit 2 (week 1)</td>
<td>49</td>
<td>0 not attending</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 Lost to follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Voluntary (and no other reason)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 Unacceptable adverse event</td>
</tr>
<tr>
<td>Visit 3 (week 2)</td>
<td>48</td>
<td>0 not attending</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Lost to follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 Unacceptable treatment efficacy</td>
</tr>
<tr>
<td>Visit 4 (week 4)</td>
<td>47</td>
<td>0 Other reasons</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 Voluntary (and no other reason)</td>
</tr>
</tbody>
</table>
Figure 2: Visit attendance by treatment: randomised subjects (cont.)

Ointment vehicle

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Primary reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>0 Lost to follow up 0 Other reason(s) 1 Voluntary (and no other reason)</td>
</tr>
<tr>
<td>50</td>
<td>0 not attending 0 Lost to follow-up 1 Voluntary (and no other reason) 0 Unacceptable adverse event</td>
</tr>
<tr>
<td>49</td>
<td>0 not attending 0 Lost to follow-up 1 Unacceptable treatment efficacy</td>
</tr>
<tr>
<td>48</td>
<td>0 Other reasons 0 Voluntary (and no other reason)</td>
</tr>
</tbody>
</table>

See Appendix 16.2.1 for individual subject data on subjects discontinued from treatment (Listing 1) and Appendix 16.2.4 for actual study period (Listing 3). A subject index is available in Appendix 16.1.7 (Listing 1) and individual data on the randomisation and treatment number is shown in Listing 2.

10.2 Protocol Deviations

Table 12 summarises the important protocol deviations.
## Table 12: Protocol deviations

<table>
<thead>
<tr>
<th>Deviation</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment of a subject who did not satisfy all Inclusion/Exclusion criteria</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td>Exclusionary medication taken or exclusionary procedure performed</td>
<td>4 (1.1%)</td>
<td>1 (0.7%)</td>
<td>1 (0.7%)</td>
<td>2 (4.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Informed consent improperly administered</td>
<td>9 (2.4%)</td>
<td>2 (1.4%)</td>
<td>2 (1.5%)</td>
<td>2 (4.1%)</td>
<td>3 (5.9%)</td>
</tr>
<tr>
<td>Randomization, dispensing or dosing error</td>
<td>1 (0.3%)</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.3%)</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16 (4.3%)</strong></td>
<td><strong>5 (3.5%)</strong></td>
<td><strong>3 (2.2%)</strong></td>
<td><strong>4 (8.2%)</strong></td>
<td><strong>4 (7.8%)</strong></td>
</tr>
</tbody>
</table>
Deviations from inclusion and exclusion criteria:

- Subject CRF [redacted] was randomised prior to completing the required washout period after participating in a previous clinical trial (exclusion criterion 3).

Procedure Compliance Deviations:

- A total of 9 subjects either signed the wrong (obsolete) version of the ICF or the ICF for the trial LEO 90100-7, another on-going US phase 2 trial with LEO 90100. When the mistake was discovered informed consent was documented using the correct form. The deviations were reported to the IRB.

- Subjects CRF [redacted], CRF [redacted], CRF [redacted], and CRF [redacted] took disallowed medication during the trial.

- Subject CRF [redacted] received wrong trial medication kit at Visit 1. The subject was randomised to LEO 90100 but received a kit with Calcipotriol plus BDP ointment.

- Subject CRF [redacted] used trial medication for 28 extra days between Visits 3 and 4.

Section 11.1 gives more details of the protocol deviations that excluded subjects and visit data from the per protocol analysis set.

All protocol deviations are listed by subject in Appendix 16.2.2.
11 Efficacy Evaluation

11.1 Data Sets Analysed

11.1.1 Full Analysis Set

A total of 427 subjects were enrolled, i.e. informed consent form signed and CRF number assigned. Among these 51 did not meet inclusion and/or exclusion criteria. Therefore, a total of 376 subjects were randomised.

All 376 randomised subjects were included in the full analysis set (FAS).

Note: Subject CRF experienced two SAEs, first recorded as SUSARs (i.e., Suspected, Unexpected Serious Adverse Reactions), and was consequently unblinded, see section 12.3.3. In the process subject CRF was unblinded by mistake, but in both cases information about actual treatment was sent to LEO GPV only, investigators remained blinded. Subject CRF was reblinded when the mistake was discovered. Both subjects were included in the full analysis set.

11.1.2 Safety Analysis Set

The safety analysis set consisted of those subjects who received any treatment with trial medication and for whom the presence or confirmed absence of AEs was available. Subject returned all units of trial medication unopened and was thus excluded from the safety analysis set. Therefore the safety analysis set included 375 subjects.

11.1.3 Per Protocol Analysis Set

The per protocol (PP) analysis set was defined by excluding subjects from the FAS who did not apply any trial medication, who did not provide efficacy data after start of treatment and who did not meet the disease defining inclusion criteria (i.e. inclusion criteria 7, 8, and 9) described in the protocol. Sixteen subjects were excluded from the PP analysis for the reasons stated above. In addition, there was one subject (CRF) who received a wrong trial medication kit at Visit 1. The subject was randomised to LEO 90100 but received a kit with Calcipotriol plus BDP ointment. This subject was thus excluded from the PP analysis set, as defined in the SAPU. The per protocol (PP) analysis set thus comprised 359 subjects.
In addition, 2 subjects that started disallowed medication during the trial and 21 subjects that violated visit 4 visit window of ±5 days were excluded from particular visits. For details on individual subject level, see SAPU in Appendix 16.1.9.

See Appendix 16.2.3 Listing 1 for individual data on subjects and observations excluded from the analysis sets and Listing 2 for analysis sets.

The number of subjects included in the trial analysis sets is summarised by treatment in Figure 3. All decisions on the inclusion or exclusion of subjects from analyses were made while the data were still blinded.
Figure 3: Trial analysis sets by treatment: randomised subjects

LEO 90100

Randomised subjects
= Full analysis set
0 No post baseline efficacy data
0 Inclusion/Exclusion criteria violated
0 No treatment with trial drug
4 More than 25% applications missed
1 Wrong trial medication

Calcipotriol plus BDP ointment

Randomised subjects
= Full analysis set
3 No post baseline efficacy data
0 Inclusion/Exclusion criteria violated
1 No treatment with trial drug
3 More than 25% applications missed
0 Wrong trial medication
Figure 3: Trial analysis sets by treatment: randomised subjects (cont.)

LEO 90100 vehicle

Randomised subjects
= Full analysis set
0 No post baseline efficacy data
2 Inclusion/Exclusion criteria violated
0 No treatment with trial drug
1 More than 25% applications missed
0 Wrong trial medication

Safety analysis set

Per protocol analysis set

Ointment vehicle

Randomised subjects
= Full analysis set
1 No post baseline efficacy data
1 Inclusion/Exclusion criteria violated
0 No treatment with trial drug
0 More than 25% applications missed
0 Wrong trial medication

Safety analysis set

Per protocol analysis set
11.2 Demographic and other Baseline Characteristics

11.2.1 Demographic Data

The mean age of the randomised subjects was 50.4 years (median 51.0; range 21-88) (Table 13) and 62.2% were men (Table 14). Most subjects were white (87.5%; Table 15) and self-reported non-Hispanic/Latino ethnicity (80.9%; Table 16). Most subjects recorded skin types II (26.1%), III (38.3%) or IV (21.3%), (Table 17). The distributions of age, sex, race, ethnicity, and skin type were similar among the groups.

Table 13: Age: randomised subjects

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>50.4</td>
<td>50.9</td>
<td>50.6</td>
<td>45.8</td>
<td>52.6</td>
</tr>
<tr>
<td>SD</td>
<td>12.9</td>
<td>12.9</td>
<td>13.1</td>
<td>13.7</td>
<td>11.1</td>
</tr>
<tr>
<td>Median</td>
<td>51.0</td>
<td>51.0</td>
<td>52.0</td>
<td>46.0</td>
<td>55.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>Maximum</td>
<td>88</td>
<td>84</td>
<td>88</td>
<td>72</td>
<td>73</td>
</tr>
<tr>
<td>Number</td>
<td>376</td>
<td>141</td>
<td>135</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 13: Age: randomised subjects
Table 14: Sex: randomised subjects

<table>
<thead>
<tr>
<th>Sex</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
<td>Number of subjects %</td>
</tr>
<tr>
<td>Male</td>
<td>234 62.2</td>
<td>87 61.7</td>
<td>87 64.4</td>
<td>30 61.2</td>
<td>30 58.8</td>
</tr>
<tr>
<td>Female</td>
<td>142 37.8</td>
<td>54 38.3</td>
<td>48 35.6</td>
<td>19 38.8</td>
<td>21 41.2</td>
</tr>
<tr>
<td>Total</td>
<td>376 100.0</td>
<td>141 100.0</td>
<td>135 100.0</td>
<td>49 100.0</td>
<td>51 100.0</td>
</tr>
</tbody>
</table>
Table 15: Race: randomised subjects

<table>
<thead>
<tr>
<th>Race</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>329 (87.5%)</td>
<td>122 (86.5%)</td>
<td>118 (87.4%)</td>
<td>45 (91.8%)</td>
<td>44 (86.3%)</td>
</tr>
<tr>
<td>Black or african american</td>
<td>24 (6.4%)</td>
<td>12 (8.5%)</td>
<td>4 (3.0%)</td>
<td>3 (6.1%)</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (2.7%)</td>
<td>2 (1.4%)</td>
<td>6 (4.4%)</td>
<td>0 (0.0%)</td>
<td>2 (3.9%)</td>
</tr>
<tr>
<td>American indian or alaska native</td>
<td>4 (1.1%)</td>
<td>2 (1.4%)</td>
<td>1 (0.7%)</td>
<td>1 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Native hawaiian or other pacific</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>islander</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (2.1%)</td>
<td>3 (2.1%)</td>
<td>5 (3.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>376 (100.0%)</td>
<td>141 (100.0%)</td>
<td>135 (100.0%)</td>
<td>49 (100.0%)</td>
<td>51 (100.0%)</td>
</tr>
</tbody>
</table>
Table 16: Ethnicity: randomised subjects

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Not hispanic or latino</td>
<td>304</td>
<td>110</td>
<td>107</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>80.9</td>
<td>78.0</td>
<td>79.3</td>
<td>83.7</td>
<td>90.2</td>
</tr>
<tr>
<td>Hispanic or latino</td>
<td>72</td>
<td>31</td>
<td>28</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>19.1</td>
<td>22.0</td>
<td>20.7</td>
<td>16.3</td>
<td>9.8</td>
</tr>
<tr>
<td>Total</td>
<td>376</td>
<td>141</td>
<td>135</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>
### Table 17: Skin type: randomised subjects

<table>
<thead>
<tr>
<th>Fitzpatrick Skin Type</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>TYPE I = White:</td>
<td>13</td>
<td>3.5</td>
<td>6</td>
<td>4.3</td>
<td>6</td>
</tr>
<tr>
<td>Always burns easily;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>never tans</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE II = White:</td>
<td>98</td>
<td>26.1</td>
<td>37</td>
<td>26.2</td>
<td>32</td>
</tr>
<tr>
<td>Always burns easily;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tans minimally</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE III = White:</td>
<td>144</td>
<td>38.3</td>
<td>44</td>
<td>31.2</td>
<td>61</td>
</tr>
<tr>
<td>Burns moderately;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tans gradually (light</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>brown)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE IV = White:</td>
<td>80</td>
<td>21.3</td>
<td>33</td>
<td>23.4</td>
<td>26</td>
</tr>
<tr>
<td>Burns minimally;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>always tans well</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(moderate brown)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE V = Brown:</td>
<td>28</td>
<td>7.4</td>
<td>16</td>
<td>11.3</td>
<td>6</td>
</tr>
<tr>
<td>Rarely burns; tans</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>profusely (dark brown)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYPE VI = Black:</td>
<td>13</td>
<td>3.5</td>
<td>5</td>
<td>3.5</td>
<td>4</td>
</tr>
<tr>
<td>Never burns; deeply</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11.2.2 Disease-related baseline data

The key disease-related baseline data are summarised in Table 18 to Table 23. A table summarising levels of 25-hydroxy vitamin D at baseline is given in Table 53 (EoT).

The disease severity (according to the IGA) at baseline is presented in Table 18, m-PASI at baseline in Table 19, and BSA involvement at baseline in Table 20. The majority of subjects were assessed as having ‘moderate disease’ according to the IGA at baseline (292 subjects; 77.7%). The distribution of the IGA at baseline was similar among the treatment groups. The mean score for m-PASI was 6.81 and similar in all treatment groups. The investigator’s assessment of clinical signs which are used for calculating the m-PASI score is given in Table 52 (EoT).

As per the protocol, all subjects had psoriasis vulgaris involving 2-30% of the BSA. Overall the mean BSA involvement was 7.5% (median 5.0; range 2-30%) and the extent of psoriasis was similar among the four groups.
### Table 18: Disease severity (IGA) at baseline: randomised subjects

<table>
<thead>
<tr>
<th>IGA at baseline</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Mild</td>
<td>63</td>
<td>16.8</td>
<td>22</td>
<td>15.6</td>
<td>22</td>
</tr>
<tr>
<td>Moderate</td>
<td>292</td>
<td>77.7</td>
<td>112</td>
<td>79.4</td>
<td>106</td>
</tr>
<tr>
<td>Severe</td>
<td>21</td>
<td>5.6</td>
<td>7</td>
<td>5.0</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
</tr>
</tbody>
</table>

### Table 19: m-PASI at baseline: randomised subjects

<table>
<thead>
<tr>
<th>m-PASI at baseline</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>6.81</td>
<td>7.04</td>
<td>6.69</td>
<td>6.69</td>
<td>6.59</td>
</tr>
<tr>
<td>SD</td>
<td>3.73</td>
<td>4.17</td>
<td>3.34</td>
<td>4.02</td>
<td>3.12</td>
</tr>
<tr>
<td>Median</td>
<td>5.85</td>
<td>5.70</td>
<td>6.00</td>
<td>6.00</td>
<td>5.60</td>
</tr>
<tr>
<td>Minimum</td>
<td>2.0</td>
<td>2.1</td>
<td>2.1</td>
<td>2.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Maximum</td>
<td>22.6</td>
<td>22.2</td>
<td>22.6</td>
<td>22.1</td>
<td>17.5</td>
</tr>
</tbody>
</table>
Table 20: BSA involvement of Psoriasis Vulgaris at baseline: randomised subjects

<table>
<thead>
<tr>
<th>BSA at baseline</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7.5</td>
<td>7.7</td>
<td>7.4</td>
<td>7.5</td>
<td>6.9</td>
</tr>
<tr>
<td>SD</td>
<td>6.6</td>
<td>6.9</td>
<td>6.3</td>
<td>7.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Median</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Maximum</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Number</td>
<td>376</td>
<td>141</td>
<td>135</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>
As per the protocol all randomised subjects had psoriasis vulgaris with a duration of at least 6 months. The mean duration was 16.1 years (median 12.7; range 1-52) and comparable across all treatment groups (Table 21). The most common locations of psoriasis vulgaris apart from the trunk and limbs were the scalp (35.1%), the nails (21.3%), and the face (17.6%) (Table 22). The majority of subjects had previously received treatment for their psoriasis (79.5%), the most common being topical corticosteroids (56.9%) (Table 23). The distribution of previous psoriasis treatment was similar among all treatment groups.

The measurements of 25-hydroxy vitamin D levels at baseline revealed that approximately 90% of subjects had levels below the normal reference range of 75.0-250.0 nmol/L Table 53 (EoT).

As shown in Table 54 (EoT) all treatment groups were balanced for weight, height and BMI at baseline.

**Table 21: Duration of Psoriasis Vulgaris: randomised subjects**

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>16.1</td>
<td>16.1</td>
<td>16.3</td>
<td>15.1</td>
<td>16.8</td>
</tr>
<tr>
<td>SD</td>
<td>12.7</td>
<td>12.5</td>
<td>12.5</td>
<td>13.5</td>
<td>13.1</td>
</tr>
<tr>
<td>Median</td>
<td>12.0</td>
<td>13.0</td>
<td>12.0</td>
<td>10.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Maximum</td>
<td>52</td>
<td>51</td>
<td>52</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>Number</td>
<td>376</td>
<td>141</td>
<td>135</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>
Table 22: Other current location of Psoriasis Vulgaris: randomised subjects

<table>
<thead>
<tr>
<th>Location of psoriasis</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=376)</td>
<td>(n=141)</td>
<td>(n=135)</td>
<td>(n=49)</td>
<td>(n=51)</td>
</tr>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td><strong>Psoriasis vulgaris of the scalp</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>132</td>
<td>35.1</td>
<td>55</td>
<td>39.0</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>244</td>
<td>64.9</td>
<td>86</td>
<td>61.0</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>244</td>
<td>64.9</td>
<td>86</td>
<td>61.0</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>314</td>
<td>83.5</td>
<td>117</td>
<td>83.0</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
</tr>
<tr>
<td><strong>Psoriasis vulgaris of the skin folds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>62</td>
<td>16.5</td>
<td>24</td>
<td>17.0</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>314</td>
<td>83.5</td>
<td>117</td>
<td>83.0</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>314</td>
<td>83.5</td>
<td>117</td>
<td>83.0</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
</tr>
<tr>
<td><strong>Psoriasis vulgaris of the face</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>66</td>
<td>17.6</td>
<td>25</td>
<td>17.7</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>310</td>
<td>82.4</td>
<td>116</td>
<td>82.3</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>310</td>
<td>82.4</td>
<td>116</td>
<td>82.3</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
</tr>
</tbody>
</table>
Table 22: Other current location of Psoriasis Vulgaris: randomised subjects (Continued...)

<table>
<thead>
<tr>
<th>Location of psoriasis</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Psoriasis vulgaris of the nails</td>
<td>Yes</td>
<td>80</td>
<td>21.3</td>
<td>32</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>296</td>
<td>78.7</td>
<td>109</td>
<td>77.3</td>
</tr>
<tr>
<td>Total</td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
</tr>
</tbody>
</table>

Psoriasis vulgaris of the genitals

<table>
<thead>
<tr>
<th>Location of psoriasis</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Psoriasis vulgaris of the genitals</td>
<td>Yes</td>
<td>40</td>
<td>10.6</td>
<td>18</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>336</td>
<td>89.4</td>
<td>123</td>
<td>87.2</td>
</tr>
<tr>
<td>Total</td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
</tr>
</tbody>
</table>
Table 23: Previous treatment of Psoriasis Vulgaris: randomised subjects

<table>
<thead>
<tr>
<th>Previous Treatment</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Biologics</td>
<td>31</td>
<td>8.2</td>
<td>13</td>
<td>9.2</td>
<td>11</td>
</tr>
<tr>
<td>Coal tar</td>
<td>50</td>
<td>13.3</td>
<td>19</td>
<td>13.5</td>
<td>19</td>
</tr>
<tr>
<td>Medicated shampoos</td>
<td>29</td>
<td>7.7</td>
<td>8</td>
<td>5.7</td>
<td>12</td>
</tr>
<tr>
<td>Photo therapy</td>
<td>26</td>
<td>6.9</td>
<td>10</td>
<td>7.1</td>
<td>9</td>
</tr>
<tr>
<td>Systemic treatment (excl. biologics)</td>
<td>40</td>
<td>10.6</td>
<td>11</td>
<td>7.8</td>
<td>19</td>
</tr>
<tr>
<td>Topical calcineurin inhibitors</td>
<td>6</td>
<td>1.6</td>
<td>2</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>214</td>
<td>56.9</td>
<td>85</td>
<td>60.3</td>
<td>78</td>
</tr>
<tr>
<td>Topical vitamin D analogues, plain and combinations with corticostes</td>
<td>94</td>
<td>25.0</td>
<td>42</td>
<td>29.8</td>
<td>26</td>
</tr>
<tr>
<td>Other</td>
<td>33</td>
<td>8.8</td>
<td>15</td>
<td>10.6</td>
<td>10</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>299</td>
<td>79.5</td>
<td>120</td>
<td>85.1</td>
<td>104</td>
</tr>
</tbody>
</table>
11.2.3 Concurrent diagnosis and use of concomitant medication

Relevant medical history and concurrent diagnoses at baseline by MedDRA primary SOC are summarised in Table 55 (EoT). The most common relevant medical history and concurrent diagnoses were surgical and medical procedures, immune system disorders, and musculoskeletal and connective tissue disorders. The distribution of concurrent diagnoses at baseline was considered similar across the four treatment groups.

Concomitant medication at baseline is summarised in Table 56 (EoT). The most common concomitant medications at baseline were for the cardiovascular system, the alimentary tract and metabolism, and the nervous system. There were no major differences between the treatment groups.

See Appendix 16.2.4 (Listings 1 to 10) for individual subject demographic, disease-related and other baseline data. See Appendix 16.2.6 for individual subject data on IGA (Listing 1) and the investigator’s assessment of extent and severity of clinical signs (Listing 2).

11.3 Measurement of Treatment Compliance

Compliance with treatment instructions for the prescribed trial medication is shown in Table 24 for the FAS.

Overall the compliance during the trial was considered high, with 130 subjects (92.2%) in the LEO 90100 group, 122 subjects (92.4%) in the Calcipotriol plus BDP group, 45 subjects (91.8%) in the LEO 90100 vehicle group, and 45 subjects (90.0%) in the Ointment vehicle group indicating that they either applied the medication as instructed or missed 10% or less of the applications. Similar results were seen for the PP analysis set.

Compliance with treatment instructions is presented by visit in Table 57 (EoT). In general the number of subjects who were fully compliant with treatment instructions was similar throughout the trial in all treatment groups. See Appendix 16.2.5 for individual subject data on drug accountability and compliance.
Table 24: Adherence to treatment instructions over the total study period: full analysis set

<table>
<thead>
<tr>
<th>Percentage missed applications</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>102</td>
<td>72.3</td>
<td>99</td>
<td>75.0</td>
<td>39</td>
<td>79.6</td>
<td>40</td>
<td>80.0</td>
</tr>
<tr>
<td>Yes: &lt;= 10% applications missed</td>
<td>28</td>
<td>19.9</td>
<td>23</td>
<td>17.4</td>
<td>6</td>
<td>12.2</td>
<td>5</td>
<td>10.0</td>
</tr>
<tr>
<td>&gt;10% and &lt;=20% applications missed</td>
<td>6</td>
<td>4.3</td>
<td>6</td>
<td>4.5</td>
<td>3</td>
<td>6.1</td>
<td>4</td>
<td>8.0</td>
</tr>
<tr>
<td>&gt;20% and &lt;=30% applications missed</td>
<td>3</td>
<td>2.1</td>
<td>3</td>
<td>2.3</td>
<td>1</td>
<td>2.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;30% and &lt;=40% applications missed</td>
<td>1</td>
<td>0.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>&gt;40% and &lt;=50% applications missed</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.8</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;50% applications missed</td>
<td>1</td>
<td>0.7</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>141</strong></td>
<td><strong>100.0</strong></td>
<td><strong>132</strong></td>
<td><strong>100.0</strong></td>
<td><strong>49</strong></td>
<td><strong>100.0</strong></td>
<td><strong>50</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
11.4 Efficacy Results and Tabulation of Individual Subject Data

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Endpoint - ‘Controlled Disease’ according to the Investigator’s Global Assessment of Disease Severity at Week 4

The percentage of subjects with ‘Controlled disease’ (‘clear’ or ‘almost clear’ for subjects with at least moderate disease at baseline, ‘clear’ for subjects with mild disease as baseline) according to the IGA on the trunk and limbs at week 4 (LOCF) is shown in Table 25 for the FAS and in Table 26 for the PP analysis set.

For the FAS, the proportion of subjects who achieved ‘controlled disease’ at week 4 was 54.6% in the LEO 90100 group compared to 43.0% in the Calcipotriol plus BDP ointment group, 6.1% in the LEO 90100 vehicle group, and 7.8% in the Ointment vehicle group. LEO 90100 was statistically significantly more effective than Calcipotriol plus BDP ointment (odds ratio [OR] 1.7; 95% CI 1.1 to 2.8; p=0.025). Similar results were seen when adjusting for baseline IGA, Table 58 (EoT).

Centre specific OR for the FAS is graphically presented in Figure 4 and tabulated in Table 59 (EoT). Results for the primary endpoint are presented by pooled centre in Table 56 (EoT).
Table 25: Analysis of Percentage of subjects with “Controlled disease” (IGA) at week 4 (LOCF): full analysis set

<table>
<thead>
<tr>
<th>Controlled Disease at week 4</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Disease</td>
<td>77</td>
<td>58</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Non-controlled Disease</td>
<td>64</td>
<td>77</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>141</td>
<td>135</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>

Statistical analysis

- Difference (%) 11.6
- 95% CI -0.1 to 23.4
- Odds ratio\(^1\) 1.7
- 95% CI 1.1 to 2.8
- CMH test p-value\(^2\) 0.025
- Breslow-Day test p-value\(^3\) 0.023

1) Cochran-Mantel-Haenszel odds ratio for Controlled disease (LEO90100 relative to Cal B/D Ointment) 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
Table 26: Analysis of Percentage of subjects with “Controlled disease” (IGA) at week 4: PP analysis set

<table>
<thead>
<tr>
<th>Controlled Disease at week 4</th>
<th>LEO 90100 (n=125)</th>
<th>Cal B/D Ointment (n=116)</th>
<th>LEO 90100 Vehicle (n=43)</th>
<th>Ointment Vehicle (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Disease</td>
<td>70</td>
<td>56</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Non-controlled Disease</td>
<td>55</td>
<td>60</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
<td>116</td>
<td>43</td>
<td>44</td>
</tr>
</tbody>
</table>

Statistical analysis

<table>
<thead>
<tr>
<th>Difference (%)</th>
<th>7.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td>-4.9 to 20.3</td>
</tr>
<tr>
<td>Odds ratio¹</td>
<td>1.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.9 to 2.4</td>
</tr>
<tr>
<td>CMH test p-value²</td>
<td>0.14</td>
</tr>
<tr>
<td>Breslow-Day test p-value³</td>
<td>0.033</td>
</tr>
</tbody>
</table>

¹) Cochran-Mantel-Haenszel odds ratio for Controlled disease (LEO90100 relative to Cal B/D Ointment) 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
The results for the PP analysis set were similar and supported the results for the FAS. Compared to FAS, approximately same proportion of subjects achieved ‘controlled disease’ with LEO 90100 (56.0%) but somewhat higher proportion (about 5% more) achieved ‘controlled disease’ with Calcipotriol plus BDP ointment. The comparison between LEO 90100 and Calcipotriol plus BDP ointment was not statistically significant (OR 1.5; 95% CI 0.9 to 2.4; p=0.14).

The Breslow-Day test to investigate the consistency of the response across pooled centres was significant at the 10% level, indicating a significant treatment-by-centre effect. Three pooled centres were identified with extreme values of odds ratio: (OR=0), (OR=0) and (both having an OR of infinity). The sensitivity analysis of the primary response criterion excluding these pooled centres was undertaken as described in the protocol. Adjusting for zeroes by adding \( \frac{1}{2} \) in each cell for these three centres gave the following ORs: : 0.06, : 14.73 and : 33.0. Omitting the centres and then gave a Breslow-Day test with a P-value of 0.26 and a common OR of 1.71 with a P-value of 0.04 for the OR being equal to one (analysis not shown).
This result is corroborated by the analysis shown in Table 58, where the effect of the IGA at baseline as well as the centres are taken into account to describe the effects on the odds ratios other than the treatments. In this analysis the difference between centres is not significant (P=0.19), the effect of baseline IGA is significant (P<0.001) and the OR for LEO 90100 to Ointment is 1.8 with a P-value of 0.02.

Results for the primary endpoint are presented by pooled centre in Table 60 (EoT).

The percentage of subjects with ‘controlled disease’ according to the IGA at weeks 1, 2, and 4 is shown in Figure 5 and Table 27. In both groups receiving active treatment, the proportion of subjects with ‘controlled disease’ increased as the trial progressed; from 3.6% at week 1 to 55.1% at week 4 in the LEO 90100 group and from 6.1% to 45.7% in the Calcipotriol plus BDP ointment group. Between week 1 and week 2 the increase was considerably larger in the LEO 90100 group compared to the Calcipotriol plus BDP ointment group while the increase was similar between week 2 and week 4. No major changes were seen in the vehicle groups.

Figure 5: Percentage of subjects with “Controlled disease” (IGA) at weeks 1, 2, and 4: full analysis set
The percentage of subjects in each IGA category is shown in Table 61 (EoT).

11.4.1.2 ‘Controlled Disease’ according to the Investigator’s Global Assessment of Disease Severity at Week 1

The percentage of subjects with ‘controlled disease’ according to the IGA on the trunk and limbs at week 1 is shown in Table 28. Overall the proportion of subjects who achieved ‘controlled disease’ at week 1 was low in all treatment groups; 3.6% in the LEO 90100 group, 6.1% in the Calcipotriol plus BDP ointment group, 2.0% in the LEO 90100 vehicle group, and 4.0% in the Ointment vehicle group. The comparison between LEO 90100 and Calcipotriol plus BDP ointment was not statistically significant.
### Table 28: Analysis of Percentage of subjects with “Controlled disease” (IGA) at week 1: full analysis set

<table>
<thead>
<tr>
<th></th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controlled Disease at week 1</strong></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Controlled Disease</td>
<td>5</td>
<td>3.6</td>
<td>8</td>
<td>6.1</td>
</tr>
<tr>
<td>Non-controlled Disease</td>
<td>133</td>
<td>96.4</td>
<td>124</td>
<td>93.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>138</td>
<td>100.0</td>
<td>132</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Statistical analysis**

- Difference (%): -2.4
- 95% CI: -7.6 to 2.7
- Odds ratio\(^1\): 0.5
- 95% CI: 0.2 to 1.7
- CMH test p-value\(^2\): 0.29
- Breslow-Day test p-value\(^3\): 0.53

---

1. Cochran-Mantel-Haenszel odds ratio for Controlled disease (LEO90100 relative to Cal B/D Ointment) 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
11.4.1.3 m-PASI

In addition to IGA, m-PASI at week 1 and week 4, and PASI 75 and PASI 50 at week 4 were included as efficacy response criteria.

The mean m-PASI at baseline and at weeks 1, 2, and 4 is graphically presented in Figure 6 and the results of the statistical analysis at week 4 and week 1 are presented in Table 29 and Table 30 respectively. A summary of m-PASI at baseline and change from baseline to subsequent visits is shown in Table 62 (EoT).

There was a statistically significant difference in mean m-PASI score between LEO 90100 and Calcipotriol plus BDP ointment both at week 4 (mean difference -0.6; 95% CI -1.1 to -0.2; p=0.005) and at week 1 (mean difference -0.7; 95% CI -1.1 to -0.3; p=0.001).

Figure 6: Mean m-PASI at baseline and at weeks 1, 2 and 4: full analysis set
Table 29: Analysis of Mean m-PASI at week 4 adjusted for baseline (LOCF): full analysis set

<table>
<thead>
<tr>
<th>Mean PASI score</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>Ointment Vehicle (n=49)</th>
<th>LEO 90100 Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.04</td>
<td>6.69</td>
<td>6.69</td>
<td>6.59</td>
</tr>
<tr>
<td>Week 4</td>
<td>1.99</td>
<td>2.45</td>
<td>4.39</td>
<td>4.43</td>
</tr>
<tr>
<td>Week 4 Adjusted mean^2</td>
<td>1.82</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical analysis
Difference^1,^2: -0.6
95% CI: -1.1 to -0.2
P-value^3: 0.005

1) LEO90100 minus Cal B/D Ointment
2) Adjusted for the effect of pooled centre and baseline disease severity
3) T-test for adjusted difference

Table 30: Analysis of Mean m-PASI at week 1 adjusted for baseline (LOCF): full analysis set

<table>
<thead>
<tr>
<th>Mean PASI score</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>Ointment Vehicle (n=49)</th>
<th>LEO 90100 Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.04</td>
<td>6.69</td>
<td>6.69</td>
<td>6.59</td>
</tr>
<tr>
<td>Week 1</td>
<td>4.05</td>
<td>4.57</td>
<td>5.27</td>
<td>4.73</td>
</tr>
<tr>
<td>Week 1 Adjusted mean^2</td>
<td>3.95</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical analysis
Difference^1,^2: -0.7
95% CI: -1.1 to -0.3
P-value^3: 0.001

1) LEO90100 minus Cal B/D Ointment
2) Adjusted for the effect of pooled centre and baseline disease severity
3) T-test for adjusted difference

Adjusted for baseline, the mean m-PASI at week 4 was 1.82 in the LEO 90100 group and 2.46 in the Calcipotriol plus BDP group. This corresponds to a mean percentage reduction in m-PASI at week 4 of 74.18% in the LEO 90100 group and 63.23% in the Calcipotriol plus BDP ointment group, compared to approximately 35.32 and 31.35% reduction in the vehicle groups (Table 31). The onset of action of LEO 90100 was more rapid with an adjusted mean...
m-PASI after 1 week of 3.95% compared to 4.64 in the Calcipotriol plus BDP Ointment group. This corresponds to a mean percentage change of 43.36% in the LEO 90100 group and 30.53% in the Calcipotriol plus BDP ointment group.

The adjusted change in m-PASI from baseline to each visit is graphically presented in Figure 7.

**Table 31: Adjusted mean percentage change in m-PASI from baseline to weeks 1 (Visit 2) and 4 (Visit 4): full analysis set**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Percentage change in PASI</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VISIT 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-39.02</td>
<td>-32.95</td>
<td>-17.42</td>
<td>-23.82</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>23.90</td>
<td>24.11</td>
<td>27.33</td>
<td>28.40</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>-40.00</td>
<td>-30.84</td>
<td>-20.00</td>
<td>-18.14</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>-91.7</td>
<td>-87.5</td>
<td>-75.0</td>
<td>-80.1</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>57.1</td>
<td>28.8</td>
<td>87.5</td>
<td>68.3</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>138</td>
<td>132</td>
<td>49</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td><strong>Statistical analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted mean pct change</td>
<td>-43.36</td>
<td>-30.53</td>
<td>-22.28</td>
<td>-26.55</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-47.63 to -39.10</td>
<td>-35.03 to -26.04</td>
<td>-29.50 to -15.07</td>
<td>-33.73 to -19.36</td>
<td></td>
</tr>
<tr>
<td><strong>VISIT 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-70.54</td>
<td>-64.62</td>
<td>-29.64</td>
<td>-27.89</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>26.01</td>
<td>28.30</td>
<td>31.37</td>
<td>40.86</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>-75.52</td>
<td>-70.37</td>
<td>-31.58</td>
<td>-27.92</td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>-100.0</td>
<td>-100.0</td>
<td>-100.0</td>
<td>-91.1</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>13.0</td>
<td>53.3</td>
<td>36.0</td>
<td>96.4</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>138</td>
<td>127</td>
<td>47</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td><strong>Statistical analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted mean pct change</td>
<td>-74.18</td>
<td>-63.23</td>
<td>-35.32</td>
<td>-31.35</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-78.73 to -69.63</td>
<td>-68.08 to -58.38</td>
<td>-45.74 to -24.89</td>
<td>-41.63 to -21.06</td>
<td></td>
</tr>
</tbody>
</table>

5 t22pasi.doc
The percentage of subjects with a 75% reduction in PASI at week 4 is shown in Figure 8 and the results of the statistical analysis are shown in Table 32. A greater proportion of subjects in the LEO 90100 group achieved PASI 75 (50.4%) compared to the Calcipotriol plus BDP ointment group (40.7%). However, the difference did not reach statistical significance (OR 1.7; 95% CI 1.0 to 2.7; p=0.052).
Figure 8: Percentage of subjects with PASI 75 at weeks 1, 2, and 4: full analysis set
Table 32: Analysis of Percentage of subjects with PASI 75 at week 4: full analysis set

<table>
<thead>
<tr>
<th>PASI75 at week 4</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Yes</td>
<td>71</td>
<td>50.4</td>
<td>55</td>
<td>40.7</td>
</tr>
<tr>
<td>No</td>
<td>70</td>
<td>49.6</td>
<td>80</td>
<td>59.3</td>
</tr>
<tr>
<td>Total</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Statistical analysis**

- **Difference (%)**
  - 9.6
- **95% CI**
  - -2.1 to 21.3
- **Odds ratio**
  - 1.7
- **95% CI**
  - 1.0 to 2.7
- **CMH test p-value**
  - 0.052
- **Breslow-Day test p-value**
  - 0.85

---

1) Cochran-Mantel-Haenszel odds ratio for Controlled disease (LEO90100 relative to Cal B/D Ointment) 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
The results for PASI 50 are presented in Figure 9 and the statistical analysis in Table 33. As for PASI 75, there was also a greater proportion of subjects with 50% reduction in PASI in the LEO 90100 group (80.9%) compared to the Calcipotriol plus BDP ointment group (74.8%) but the difference was not statistically significant (OR 1.5; 95% CI 0.8 to 2.8; p=0.17).

**Figure 9: Percentage of subjects with PASI50 at weeks 1, 2, and 4: full analysis set**
Table 33: Analysis of Percentage of subjects with PASI 50 at week 4: full analysis set

<table>
<thead>
<tr>
<th>PASI50 at week 4</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Yes</td>
<td>114</td>
<td>80.9</td>
<td>101</td>
<td>74.8</td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>19.1</td>
<td>34</td>
<td>25.2</td>
</tr>
<tr>
<td>Total</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Statistical analysis

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference (%)</td>
<td>6.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>-3.8 to 15.8</td>
</tr>
<tr>
<td>Odds ratio¹</td>
<td>1.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.8 to 2.8</td>
</tr>
<tr>
<td>CMH test p-value²</td>
<td>0.17</td>
</tr>
<tr>
<td>Breslow-Day test p-value³</td>
<td>0.67</td>
</tr>
</tbody>
</table>

1) Cochran-Mantel-Haenszel odds ratio for Controlled disease (LEO90100 relative to Cal B/D Ointment) 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
The percentage of subjects with PASI 75 and PASI 50 at visits 2, 3 and 4 (weeks 1, 2, and 4) is presented in Table 34 and Table 35 respectively. Similar to the IGA, in the groups receiving active treatment the proportion of subjects with PASI 75 increased throughout the trial period; from 5.1% at week 1 to 50.7% at week 4 in the LEO 90100 group and from 6.1% to 43.3% in the Calcipotriol plus BDP ointment group. A similar pattern was seen for PASI50 with an increase from 34.8% at week 1 to 81.2% at week 4 in the LEO 90100 group and from 25.8% to 77.2% in the Calcipotriol plus BDP ointment group.

See Appendix 16.2.6 for individual subject data on the investigator’s assessment of extent and severity of clinical signs.

Table 34: Percentage of subjects with PASI 75 at weeks 1 (Visit 2), 2 (Visit 3) and 4 (Visit 4): full analysis set

<table>
<thead>
<tr>
<th>Visit</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>VISIT 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No</td>
<td>131</td>
<td>124</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>132</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>VISIT 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>25</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>99</td>
<td>104</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>129</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>VISIT 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>70</td>
<td>55</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>No</td>
<td>68</td>
<td>72</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>127</td>
<td>47</td>
<td>48</td>
</tr>
</tbody>
</table>
**Table 35: Percentage of subjects with PASI 50 at weeks 1 (Visit 2), 2 (Visit 3) and 4 (Visit 4): full analysis set**

<table>
<thead>
<tr>
<th>Visit</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>VISIT 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48</td>
<td>34.8</td>
<td>34</td>
<td>25.8</td>
</tr>
<tr>
<td>No</td>
<td>90</td>
<td>65.2</td>
<td>98</td>
<td>74.2</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>100.0</td>
<td>132</td>
<td>100.0</td>
</tr>
<tr>
<td>VISIT 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>93</td>
<td>67.4</td>
<td>73</td>
<td>56.6</td>
</tr>
<tr>
<td>No</td>
<td>45</td>
<td>32.6</td>
<td>56</td>
<td>43.4</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>100.0</td>
<td>129</td>
<td>100.0</td>
</tr>
<tr>
<td>VISIT 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>112</td>
<td>81.2</td>
<td>98</td>
<td>77.2</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
<td>18.8</td>
<td>29</td>
<td>22.8</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>100.0</td>
<td>127</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**11.4.1.4 Patient Reported Outcomes**

The patient reported outcomes in this trial included patient’s global assessment of psoriasis, assessment of itch and assessment of treatment satisfaction by the use of TSQM.

**11.4.1.4.1 Patient’s Assessment of Disease Severity at Week 4**

The percentage of subjects who achieved ‘controlled disease’ according to the Patient’s Global Assessment of disease severity at week 4 is presented in Table 36. There was no difference between the LEO 90100 group (61.6%) and the Calcipotriol plus BDP ointment group (59.8%) (OR: 1.1; 95% CI 0.6 to 1.8; p=0.76).
Table 36: Analysis of “Controlled disease” (Patient’s Global Assessment) at week 4: full analysis set

<table>
<thead>
<tr>
<th></th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Disease</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>at week 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled Disease</td>
<td>85</td>
<td>61.6</td>
<td>76</td>
<td>59.8</td>
</tr>
<tr>
<td>Non-controlled Disease</td>
<td>53</td>
<td>38.4</td>
<td>51</td>
<td>40.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>138</strong></td>
<td><strong>100.0</strong></td>
<td><strong>127</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

**Statistical analysis**

<table>
<thead>
<tr>
<th></th>
<th>1.8</th>
<th>-10.0 to 13.5</th>
<th>0.6 to 1.8</th>
<th>0.24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMH test p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breslow-Day test p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) Cochran-Mantel-Haenszel odds ratio for Controlled disease (LEO90100 relative to Cal B/D Ointment) 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
### 11.4.1.4.2 Subject’s Assessment of Itch

The subject’s assessment of itch using VAS is shown for all visits in Table 37 and the mean change in itch from baseline to visits 2, 3, and 4 is shown in Figure 10 and Table 38. All treatment groups had similar VAS scores at baseline (47.57 to 52.71). As the trial progressed, both LEO 90100 and Calcipotriol plus BDP ointment reduced itch and similar scores were reported at each visit.

#### Table 37: Analysis of Patient’s itching at weeks 1, 2 and 4 adjusted for baseline itch (Visual Analogue Scale): full analysis set

<table>
<thead>
<tr>
<th>Itching</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>Ointment Vehicle (n=49)</th>
<th>LEO 90100 Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>52.71</td>
<td>52.05</td>
<td>51.65</td>
<td>47.57</td>
</tr>
<tr>
<td>Week 1</td>
<td>24.83</td>
<td>28.96</td>
<td>39.82</td>
<td>35.44</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Difference¹,²</td>
<td>-5.0</td>
<td>-9.8 to -0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-value³</td>
<td>0.036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>18.50</td>
<td>18.88</td>
<td>36.43</td>
<td>34.14</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Difference¹,²</td>
<td>-0.8</td>
<td>-5.6 to 4.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-value³</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>13.46</td>
<td>14.51</td>
<td>31.06</td>
<td>31.17</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Difference¹,²</td>
<td>-1.6</td>
<td>-6.4 to 3.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-value³</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) LEO90100 minus Cal B/D Ointment
2) Adjusted for the effect of pooled centre and baseline itch
3) T-test for adjusted difference
Figure 10: Mean change in itching (VAS score) from baseline to weeks 1, 2 and 4: full analysis set
Table 38: Mean change in itching from baseline (Visual Analogue Scale) at weeks 1 (Visit 2), 2 (Visit 3) and 4 (Visit 4): full analysis set

<table>
<thead>
<tr>
<th>Change in itching</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>Ointment Vehicle (n=49)</th>
<th>LEO 90100 Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 2</td>
<td>-27.79</td>
<td>-22.47</td>
<td>-12.34</td>
<td>-12.04</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>23.51</td>
<td>28.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>20.11 to 26.91</td>
<td>25.14 to 31.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 3</td>
<td>-34.51</td>
<td>-32.52</td>
<td>-16.60</td>
<td>-13.84</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>17.69</td>
<td>18.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>14.27 to 21.12</td>
<td>15.01 to 21.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 4</td>
<td>-39.81</td>
<td>-36.54</td>
<td>-20.76</td>
<td>-15.91</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>13.05</td>
<td>14.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>9.66 to 16.45</td>
<td>11.19 to 18.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11.4.1.4.3 Treatment Satisfaction Questionnaire of Medication at End of Trial

The subject’s assessment of treatment satisfaction was performed at the end of trial (visit 4) by means of the TSQM. The TSQM consists of 4 domains: effectiveness (2 items), side effects (3 items), convenience (3 items) and global satisfaction (2 items). Scores in each domain range from 0 to 100 with higher scores indicating greater satisfaction. A summary of the four scores at week 4 is presented in Table 39. In general mean scores for all 4 domains were high in the active treatment groups (ranging from 77.51 to 99.08) and apart from ‘Side effects’ which was consistently high in all 4 groups (96.99 to 99.02) both LEO 90100 and Calcipotriol plus BDP scored higher than the vehicle groups. There was no statistically significant difference between LEO 90100 and Calcipotriol plus BDP ointment in any of the 4 domains.

See Appendix 16.2.6 for subject’s individual scores of items in the TSQM.
Table 39: Analysis of Summary of the four scores in TSQM at week 4: full analysis set

<table>
<thead>
<tr>
<th>Individual score</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
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<tr>
<td><strong>Effectiveness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>77.51</td>
<td>77.93</td>
<td>53.90</td>
<td>51.22</td>
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<tr>
<td>SD</td>
<td>25.87</td>
<td>24.13</td>
<td>26.57</td>
<td>27.77</td>
</tr>
<tr>
<td>Median</td>
<td>83.33</td>
<td>83.33</td>
<td>50.00</td>
<td>50.00</td>
</tr>
<tr>
<td>Minimum</td>
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</tr>
<tr>
<td>Maximum</td>
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<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Number</td>
<td>136</td>
<td>128</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td><strong>Statistical Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value¹</td>
<td></td>
<td>0.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Side-effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>99.02</td>
<td>99.08</td>
<td>96.99</td>
<td>97.83</td>
</tr>
<tr>
<td>SD</td>
<td>7.03</td>
<td>7.66</td>
<td>11.71</td>
<td>8.86</td>
</tr>
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<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
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<tr>
<td>Minimum</td>
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<td>16.7</td>
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<td>50.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Number</td>
<td>136</td>
<td>127</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td><strong>Statistical Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value¹</td>
<td></td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Convenience</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>80.58</td>
<td>79.09</td>
<td>73.52</td>
<td>71.41</td>
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<td>SD</td>
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<td>18.73</td>
<td>17.69</td>
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<td>83.33</td>
<td>77.78</td>
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<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Number</td>
<td>136</td>
<td>127</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td><strong>Statistical Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value¹</td>
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<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Global Satisfaction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>81.00</td>
<td>81.64</td>
<td>59.22</td>
<td>55.38</td>
</tr>
<tr>
<td>SD</td>
<td>24.21</td>
<td>21.31</td>
<td>26.76</td>
<td>28.12</td>
</tr>
<tr>
<td>Median</td>
<td>83.33</td>
<td>83.33</td>
<td>58.33</td>
<td>58.33</td>
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<tr>
<td>Minimum</td>
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<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Number</td>
<td>136</td>
<td>128</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td><strong>Statistical Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value¹</td>
<td></td>
<td>0.61</td>
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</table>
11.4.2 Statistical/Analytical Issues

The analyses were conducted according to the protocol and the SAPU as summarised in Section 9.7.1 and further changes as described in Section 9.8.

11.4.2.1 Adjustments for Covariates

For the primary endpoint, subjects with ‘controlled disease’ at week 4 an analysis was carried out, adjusting for baseline IGA as well as controlling for pooled centres.

For the secondary endpoints m-PASI at weeks 1 and 4 as well as VAS-score for itch at weeks 1, 2, and 4 the analyses incorporated baseline value of m-PASI and VAS-score for itch respectively.

11.4.2.2 Handling of Dropouts or Missing Data

For the primary endpoint, ‘controlled disease’ at week 4, the statistical analysis was carried out using LOCF. This means that an IGA-value missing at week 4 was imputed by the last non-missing IGA-value prior to week 4. The same approach was used for the secondary endpoints m-PASI at week 1 and 4, respectively.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analysis was planned nor performed.

11.4.2.4 Multi-Site Clinical Trials

To facilitate aggregation of results from the LEO 90100-7 and LEO 90100-35 trials it was decided to pool centres common to both trials based on their geographical location, rather than on the number of subjects randomised in a particular trial, as stated in the protocol. For details about the pooling strategy see the SAPU (Appendix 16.1.9).

11.4.2.5 Multiple Comparison/Multiplicity

There was only one primary endpoint and only two treatments to be compared, so no adjusting of p-values was necessary.

11.4.2.6 Use of an “Efficacy Subset” of Subjects

Not applicable.
11.4.2.7 Active-Control Studies Intended to Show Equivalence
Not applicable.

11.4.2.8 Examination of Subgroups
Not applicable.

11.4.3 Tabulation of Individual Response Data
Not applicable.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response
Not applicable

11.4.5 Drug-Drug and Drug-Disease Interactions
Not applicable.

11.4.6 By-Subject Displays
Not applicable.

11.4.7 Efficacy Conclusions

- The proportion of ‘controlled disease’ at week 4 (primary endpoint) was 54.6% in the LEO 90100 group compared with 43.0% in the Calcipotriol plus BDP ointment group, 6.1% in the LEO 90100 vehicle group, and 7.8% in the Ointment vehicle group. LEO 90100 was superior to Calcipotriol plus BDP ointment in the treatment of psoriasis vulgaris over 4 weeks (OR 1.7; 95% CI 1.1 to 2.8; p=0.025).

- The proportion of ‘controlled disease’ at week 1 was overall low; 3.6% in the LEO 90100 group, 6.1% in the Calcipotriol plus BDP ointment group, 2.0% in the LEO 90100 vehicle group, and 4.0% in the Ointment vehicle group. The statistical analysis of ‘controlled disease’ at week 1 showed no difference between LEO 90100 and Calcipotriol plus BDP ointment.

- Both at week 4 and week 1, mean m-PASI scores were statistically significantly lower (indicating greater improvement) for LEO 90100 than for Calcipotriol plus BDP ointment.
The percentage of subjects with PASI 75 at week 4 and PASI 50 at week 4 was higher in the LEO 90100 group compared to the Calcipotriol plus BDP group (54.0% vs. 40.7% for PASI 75, and 80.9% vs. 74.8% for PASI 50) however the comparisons were not statistically significant.

According to the Patient’s Global Assessment at week 4, similar proportion of subjects in the LEO 90100 group (61.6%) assessed their disease as ‘controlled’, as compared with the Calcipotriol plus BDP ointment group (59.8%) (OR: 1.1; 95% CI 0.6 to 1.8; p=0.76).

There was a similar improvement in itching over time between the LEO 90100 and Calcipotriol plus BDP ointment groups.

Treatment satisfaction scores were overall higher in the LEO 90100 and the Calcipotriol plus BDP ointment groups than in the vehicle groups. There was no difference between the two active treatment groups.
12 Safety Evaluation

The analysis of safety was based on the safety analysis set.

12.1 Extent of Exposure

The duration and extent of exposure to treatment is summarised in Table 40 and the amount of trial medication used between visits is presented in Table 41.

The mean duration of treatment was similar in all treatment groups; approximately 4 weeks. Due to the randomisation ratio 3:3:1:1 the overall extent of exposure (subject-treatment days) was much higher in the LEO 90100 and Calcipotriol plus BDP ointment groups (571 and 526 weeks respectively) compared to the vehicle groups (194 and 202 weeks respectively).

The mean amount of trial medication used per week over the total treatment period was similar in all treatment groups, ranging from 28.8 g in the Ointment vehicle group to 31.6 g in the LEO 90100 group.

The total average weekly use is shown versus BSA involvement in Figure 11. There was no clear pattern in the relationship between BSA involvement at baseline and the total average weekly use of trial medication.

For individual subject data on trial medication used see Appendix 16.2.5.
Table 40: Duration and extent of exposure to treatment: safety analysis set

<table>
<thead>
<tr>
<th>Duration of treatment (weeks)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
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<tbody>
<tr>
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<td>3.9</td>
<td>4.0</td>
<td>4.0</td>
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<td>0.9</td>
<td>0.7</td>
<td>0.8</td>
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<tr>
<td>Minimum</td>
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<td>5</td>
</tr>
<tr>
<td>Number</td>
<td>141</td>
<td>134</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>

Extent of exposure to treatment (subject-treatment-weeks)

|                         | 571               | 526                       | 194                      | 202                     |
Table 41: Average weekly amount of trial medication used between visits: safety analysis set

<table>
<thead>
<tr>
<th>Visit Interval</th>
<th>Trial medication used (g per week)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
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<td></td>
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<td>30.4</td>
<td>29.9</td>
<td>32.2</td>
<td>25.6</td>
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<td>24.2</td>
<td>24.7</td>
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<tr>
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<td>20.6</td>
<td>22.3</td>
<td>25.0</td>
<td>21.3</td>
</tr>
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<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Maximum</td>
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</tr>
<tr>
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<td>50</td>
</tr>
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<td><strong>Visit 2 to Visit 3</strong></td>
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<td>31.1</td>
<td>34.3</td>
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<tr>
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<td>24.8</td>
<td>26.2</td>
<td>21.2</td>
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<tr>
<td>Median</td>
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<td>24.1</td>
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<td>Minimum</td>
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<td>49</td>
</tr>
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<td>35.8</td>
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<td>28.2</td>
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<td>Maximum</td>
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<td>91.5</td>
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<td><strong>Total treatment period</strong></td>
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<tr>
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<tr>
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<td>23.4</td>
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<td>87.7</td>
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<td>50</td>
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</table>
Figure 11: BSA at baseline versus total average weekly use of IP: full analysis set
12.2 Adverse Events (AEs)

This section gives an overview of all treatment emergent AEs, (i.e., those that started after the first application of the trial medication, or started before this and worsened in intensity after) It summarises the overall frequency of AEs by treatment group. The summary is done on the preferred term level, which means that multiple occurrences of AEs within the same preferred term and SOC involving the same subject count as one occurrence. For a given preferred term, intensity is taken as the worst intensity recorded and relationship is taken from the last available assessment.

12.2.1 Brief Summary of Adverse Events

The incidence of AEs in this trial was low. Similar numbers were reported in the groups receiving active treatment; 20 AEs reported by 16 subjects (11.3%) in the LEO 90100 group, and 23 AEs reported by 14 subjects (10.4%) in the Calcipotriol plus BDP ointment group. In the vehicle groups, only 2 AEs were reported in each group; by 1 subject (2.0%) in the LEO 90100 vehicle group, and by 2 subjects (3.9%) in the Ointment vehicle group. The majority of AEs were mild and only 5 AEs were judged as probably or possibly related to treatment. There was 1 AE of severe intensity in the Calcipotriol plus BDP ointment group leading to withdrawal from the trial (heart rate increased). A total of 3 SAEs were reported by 2 subjects; all in the Calcipotriol plus BDP ointment group.

12.2.2 Display of Adverse Events

All AEs are presented by MedDRA primary SOC and preferred term in Table 42.

Overall the number of AEs was low and there were no major differences between LEO 90100 and Calcipotriol plus BDP ointment.

The most common SOC was infections or infestations, reported by 5 subjects (3.5%) in the LEO 90100 group and 5 subjects (3.6%) in the Calcipotriol plus BDP ointment group. Except for nasopharyngitis, reported by 2 subjects (1.5%), all individual AEs in this SOC were reported by single subjects.

Gastrointestinal disorders were the next most common types of AEs and were reported by 4 subjects (2.8%) in the LEO 90100 group and 1 subject (0.7%) in the Calcipotriol plus BDP ointment group. All individual AEs in this SOC were reported by single subjects.
There were no AEs coded to the SOC skin and subcutaneous tissue disorders in the LEO 90100 group while 4 subjects (2.9%) in the Calcipotriol plus BDP ointment group reported this type of AEs. Apart from pruritus, reported for 2 subjects (1.5%), all other AEs in this SOC were reported for single subjects.

All lesional/perilesional AEs (Table 65, EoT) were considered by the investigator to be ADRs, see Section 12.2.3.2.

Table 42: AEs by MedDRA primary SOC and preferred term: safety analysis set

<table>
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<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
</tr>
</thead>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>Nausea</td>
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<td>Application site pain</td>
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<tr>
<td></td>
<td>Application site pain</td>
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<td>Pyrexia</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Laryngitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Staphylococcal infection</td>
<td>0</td>
<td>0</td>
<td>1</td>
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</tr>
</tbody>
</table>
Table 42: AEs by MedDRA primary SOC and preferred term: safety analysis set
(Continued...)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract</td>
<td></td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>1</td>
<td>0.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Viral pharyngitis</td>
<td></td>
<td></td>
<td>1</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Excoriation</td>
<td></td>
<td></td>
<td>1</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Facial bones fracture</td>
<td></td>
<td></td>
<td>1</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Muscle strain</td>
<td></td>
<td></td>
<td>1</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate increased</td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysplastic naevus</td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Seborrhoeic keratosis</td>
<td></td>
<td></td>
<td>1</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Presyncope</td>
<td></td>
<td></td>
<td>1</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollakiuria</td>
<td></td>
<td></td>
<td>1</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal pruritus</td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td></td>
<td></td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
</tbody>
</table>

Continued...
Table 42: AEs by MedDRA primary SOC and preferred term: safety analysis set (Continued...)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal pain</td>
<td>1</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Swelling face</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
</tr>
<tr>
<td>Total number of adverse events²</td>
<td>20</td>
<td>23</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>16</td>
<td>11.3</td>
<td>14</td>
<td>10.4</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value³</td>
<td>0.81</td>
<td>0.026</td>
<td>0.091</td>
<td></td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.0.
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.
3) Treatment comparison by Chi-squared test.

12.2.3 Analysis of Adverse Events

12.2.3.1 Adverse Events by Severity

All AEs were to be assessed for intensity (mild, moderate, or severe). The intensity of AEs is presented by MedDRA primary SOC and preferred term in Table 67 (EoT). The majority of AEs were mild. One subject in the Calcipotriol plus BDP ointment group (CRF 0020_48) experienced one event of severe bronchitis and one event of severe hypertension that were judged by the investigator to be not related to trial medication. Both events were reported as SAEs, see narrative in Section 12.3.2.
12.2.3.2 Adverse Drug Reactions

All AEs were to be assessed for causal relationship to the investigational product, as judged by the investigator. Adverse drug reactions (AEs for which the investigator did not describe the causal relationship to trial medication as ‘not related’) are summarised in Table 43. Only 1 ADR was reported in the LEO 90100 group (application site pruritus). A total of 5 ADRs were reported by 4 subjects (3.0%) in the Calcipotriol plus BDP ointment group; 1 reaction each of application site dryness, application site pain, and psoriasis and 2 reactions of pruritus. No ADRs were reported in the vehicle groups. All ADRs were reported as lesional/perilesional (Table 66).

The causal relationship of all AEs is presented by MedDRA primary SOC and preferred term in Table 68 (EoT).
Table 43: ADRs by MedDRA primary SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>0.0</td>
<td>1.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Application site dryness</td>
<td>0.0</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Application site pain</td>
<td>0.0</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>1.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>0.0</td>
<td>2.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.0</td>
<td>1.5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>0.0</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total number of drug reactions²</td>
<td>1.0</td>
<td>4.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>0.7</td>
<td>3.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>P-value³</td>
<td>0.15</td>
<td>0.44</td>
<td>0.43</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.0.
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.
3) Treatment comparison by Chi-squared test.

12.2.4 Listing of Adverse Events by Subject

For individual subject data on AEs see Appendix 16.2.7

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

All SAEs and discontinuations due to AEs are listed in Appendix 16.2.7.
### 12.3.1.1 Deaths

There were no deaths in this trial.

### 12.3.1.2 Other Serious Adverse Events

The SAEs are summarised in Table 44 by MedDRA SOC and preferred term. The incidence of SAEs was low. Overall 3 SAEs were reported by 2 subjects in the Calcipotriol plus BDP ointment group; 1 event of bile duct stone reported by subject CRF, and 1 event of hypertension and 1 event of bronchitis reported by subject CRF. Narratives are provided in Section 12.3.2.

**Table 44: SAEs by MedDRA primary SOC and preferred term: safety analysis set**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>LEO 90100 Ointment (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile duct stone</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total number of SAEs</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>0</td>
<td>2</td>
<td>1.5</td>
<td>0</td>
</tr>
</tbody>
</table>

1) Classification according to MedDRA version 15.0.

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.
12.3.1.3 Other Significant Adverse Events

One subject (CRF [Redacted]) in the Calcipotriol plus BDP ointment group discontinued from the trial due to increased heart rate. A narrative is provided in Section 12.3.2.2.

12.3.2 Narratives of Deaths, other Serious Adverse Events and Other Significant Adverse Events

12.3.2.1 Serious Adverse Event Narratives

Calcipotriol plus BDP ointment group

CRF Number: [Redacted]; Bile Duct Stone (Mild intensity)

A [Redacted] was enrolled into the trial, randomised to the Calcipotriol plus BDP ointment group and started treatment on [Redacted].

The subject had a medical history of coronary artery disease, hypercholesterolemia, gout, hypertension, open heart surgery, stent placement, aneurysm, and aorta surgery. Concomitant medication included atorvastatin calcium, clopidogrel, lisinopril, metoprolol, indomethacin, and acetylsalicylic acid.

On [Redacted] the subject called the site with complaint of increased sleeping, weakness, nausea and vomiting, and aching kidneys that started on [Redacted]. The subject went to the emergency room on [Redacted] and was hospitalised from [Redacted] to [Redacted]. The subject was diagnosed with choledocholithiasis (bile duct stone) with chronic cholecystitis. Trial medication was discontinued from [Redacted] to [Redacted]. On [Redacted], the patient had an open cholecystectomy with intraoperative cholangiogram. The subject recovered from the event and was discharged on [Redacted]. The subject was not withdrawn from the trial due to the event and last received trial treatment on [Redacted], as [Redacted] completed the trial.

The investigator considered the event to be not related to the trial medication.
A[REDACTED] was enrolled into the trial, randomised to the Calcipotriol plus BDP ointment group and started treatment on[REDACTED].

The subject had a medical history of insomnia, hypertension, angina, depression, seizures, torn rotator cuff, diabetes, hypercholesterolemia, stroke, water retention, proteinuria, celiac sprue, allergy to beta blockers and ACE inhibitors, spondylolisthesis, carpal tunnel surgery, cervical and lumbar implants, and craniotomy. Concomitant medication included zolpidem tartrate, amlopidine, citalopram, clonazepam, valsartan, acetylsalicylic acid, gabapentin, levetiracetam, metformin, metoprolol, simvastatin, furosemide, potassium chloride, vitamins, magnesium oxide, and isosorbide dinitrate.

On[REDACTED], the subject experienced hypertension and a bronchial infection and was hospitalised. On multiple occasions thereafter the site tried to contact the subject, by phone, email + certified letter but with no response. Last date of trying to contact the subject was[REDACTED] but the subject was lost to follow-up. Outcome of the events and date for last dose of trial medication was reported as unknown.

The causality of both events was initially considered ‘not assessable’ by the investigator due to lack of information about the events and they were first reported as SUSARs. In a later follow-up the investigator degraded the events to be not related to the trial medication and the events were consequently reported as SAEs.

12.3.2.2 Narratives of Adverse Event Leading to Discontinuation

Calcipotriol plus BDP ointment group

A[REDACTED] was enrolled into the trial, randomised to the Calcipotriol plus BDP ointment group and started treatment on[REDACTED]

The subject had a medical history of stab wound. Concomitant medication included albuterol, ibuprofen and nicorette.
On the subject experienced increased heart rate. Trial medication was discontinued on the same day and the subject was withdrawn from the trial due to the event. The subject recovered on.

The investigator considered the event to be not related to the trial medication.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

There were no deaths during this trial. Only 3 SAEs were reported for 2 subjects, all in the Calcipotriol plus BDP ointment group and all were considered not related to trial medication. Two SAEs (hypertension and bronchitis) were first reported as SUSARs due to lack of information about the events. The subject was unblinded by LEO GPV but the investigator remained blinded. The causality was later in a follow-up degraded to ‘not related’ by the investigator and the events were reported as SAEs, see narrative in Section 12.3.2.

One subject experienced increased heart rate and was withdrawn from the trial due to this event.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject (16.2.8)

See Appendix 16.2.8 for individual subject data on laboratory measurements.

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Albumin-corrected serum calcium and change from baseline to week 4 is summarised in Table 45 and the urinary calcium:creatinine ratio (from spot urine samples) and change from baseline to week 4 is summarised in Table 46.

The mean values of albumin-corrected serum calcium and urinary calcium:creatinine ratio were similar across the treatment groups and were within the normal range at both baseline and week 4. The summary data show only small mean changes from baseline for both parameters; -0.011 to 0.009 mmol/L for albumin-corrected serum calcium and -0.310 to 0.480 mmol/g for urinary calcium:creatinine ratio. The changes were not considered to be of clinical significance.
Table 45: Summary of albumin-corrected serum calcium and change from baseline (Visit 1) to week 4 (Visit 4, end-of-treatment): safety analysis set

<table>
<thead>
<tr>
<th>Albumin corrected serum calcium (mmol/L)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VISIT 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.284</td>
<td>2.307</td>
<td>2.310</td>
<td>2.314</td>
</tr>
<tr>
<td>SD</td>
<td>0.082</td>
<td>0.078</td>
<td>0.099</td>
<td>0.085</td>
</tr>
<tr>
<td>Median</td>
<td>2.280</td>
<td>2.300</td>
<td>2.315</td>
<td>2.330</td>
</tr>
<tr>
<td>Minimum</td>
<td>2.08</td>
<td>2.15</td>
<td>2.10</td>
<td>2.15</td>
</tr>
<tr>
<td>Maximum</td>
<td>2.53</td>
<td>2.55</td>
<td>2.53</td>
<td>2.50</td>
</tr>
<tr>
<td>Number</td>
<td>139</td>
<td>131</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td><strong>VISIT 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.295</td>
<td>2.301</td>
<td>2.301</td>
<td>2.301</td>
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<tr>
<td>SD</td>
<td>0.092</td>
<td>0.086</td>
<td>0.076</td>
<td>0.085</td>
</tr>
<tr>
<td>Median</td>
<td>2.290</td>
<td>2.300</td>
<td>2.300</td>
<td>2.290</td>
</tr>
<tr>
<td>Minimum</td>
<td>2.10</td>
<td>2.05</td>
<td>2.18</td>
<td>2.13</td>
</tr>
<tr>
<td>Maximum</td>
<td>2.53</td>
<td>2.58</td>
<td>2.48</td>
<td>2.55</td>
</tr>
<tr>
<td>Number</td>
<td>138</td>
<td>127</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td><strong>Change from Visit 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VISIT 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.009</td>
<td>-0.005</td>
<td>-0.008</td>
<td>-0.011</td>
</tr>
<tr>
<td>SD</td>
<td>0.096</td>
<td>0.081</td>
<td>0.077</td>
<td>0.093</td>
</tr>
<tr>
<td>Median</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Minimum</td>
<td>-0.25</td>
<td>-0.23</td>
<td>-0.20</td>
<td>-0.30</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.35</td>
<td>0.20</td>
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<td>0.18</td>
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<tr>
<td>Number</td>
<td>136</td>
<td>125</td>
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</table>
Table 46: Summary of urinary calcium:creatinine ratio and change from baseline (Visit 1) to week 4 (Visit 4, end-of-treatment): safety analysis set

<table>
<thead>
<tr>
<th>Urine Calcium creatinine (mmol/g)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Vehicle (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
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<tbody>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VISIT 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.516</td>
<td>2.969</td>
<td>2.559</td>
<td>2.759</td>
</tr>
<tr>
<td>SD</td>
<td>1.863</td>
<td>2.487</td>
<td>1.626</td>
<td>2.095</td>
</tr>
<tr>
<td>Median</td>
<td>2.050</td>
<td>2.120</td>
<td>2.050</td>
<td>2.450</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.25</td>
<td>0.22</td>
<td>0.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Maximum</td>
<td>12.00</td>
<td>14.82</td>
<td>6.80</td>
<td>8.72</td>
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<td>Number</td>
<td>141</td>
<td>133</td>
<td>47</td>
<td>51</td>
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<tr>
<td><strong>VISIT 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>2.956</td>
<td>2.730</td>
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<td>2.644</td>
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<td>2.270</td>
<td>1.620</td>
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<td>0.07</td>
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<td>Maximum</td>
<td>33.32</td>
<td>7.82</td>
<td>7.80</td>
<td>9.22</td>
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<tr>
<td>Number</td>
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<td>128</td>
<td>47</td>
<td>47</td>
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<tr>
<td><strong>Change from Visit 1</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VISIT 4</strong></td>
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</tr>
<tr>
<td>Mean</td>
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<td>-0.189</td>
<td>-0.310</td>
<td>-0.129</td>
</tr>
<tr>
<td>SD</td>
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<td>1.977</td>
<td>1.642</td>
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<tr>
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<td>-0.150</td>
<td>-0.200</td>
<td>-0.100</td>
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<tr>
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<td>-8.80</td>
<td>-5.50</td>
<td>-6.32</td>
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<td>Maximum</td>
<td>32.85</td>
<td>5.30</td>
<td>5.13</td>
<td>6.85</td>
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<tr>
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<td>127</td>
<td>45</td>
<td>47</td>
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</tbody>
</table>

12.4.2.2 Individual Subject Changes

A shift table comparing baseline (Visit 1) with end-of-treatment (Visit 4) with respect to normal reference ranges is given in Table 47 for albumin-corrected serum calcium and in Table 48 for urinary calcium:creatinine ratio from spot urine samples.

**Albumin-corrected serum calcium**

The majority of subjects in all treatment groups had albumin-corrected serum calcium values
within the normal reference range at baseline (2.15 to 2.55 mmol/L) and did not record a shift at the end of treatment. For the few subjects that recorded a shift, the pattern of shifts was largely similar across the treatment groups.

None of the subjects treated with LEO 90100 (or any of the vehicles) developed albumin-corrected serum calcium above the normal reference range, as compared with 1 subject treated with Calcipotriol plus BDP ointment.

In total 10 subjects had baseline values below the normal range; 7 in the LEO 90100 group and 3 in the LEO 90100 vehicle group. All 3/3 subjects in the vehicle group and 5/7 subjects in the LEO 90100 group recorded a shift to normal at the end of treatment.

**Urinary calcium:creatinine**

The majority of subjects in all treatment groups had urinary calcium:creatinine values within the normal reference range at baseline (0.300 to 6.100 mmol/g in men and 0.225 to 8.200 mmol/g in women) and did not record a shift at the end of treatment. For subjects that recorded a shift the pattern of shifts was similar in the LEO 90100 and Calcipotriol plus BDP ointment groups, and included both increases and decreases.

A shift from normal at baseline to high at end of treatment was recorded by a similar proportion of subjects in all treatment groups: 4 subjects in LEO 90100, 3 subjects in Calcipotriol plus BDP ointment and 1 subject in each of the vehicle groups.

In total 5 subjects had urinary calcium:creatinine values below the normal range at baseline. Four of these subjects recorded a shift to normal levels at the end of treatment: 2/2 in the LEO 90100 group, 1/2 in the Calcipotriol plus BDP ointment group, and 1/1 in the Ointment vehicle group.
Table 47: Shift tables for albumin-corrected serum calcium from Visit 1 (baseline) to Visit 4 (End of Treatment): safety analysis set

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Baseline category&lt;sup&gt;1&lt;/sup&gt;</th>
<th>LOW</th>
<th>NORMAL</th>
<th>HIGH</th>
<th>End of treatment category&lt;sup&gt;1&lt;/sup&gt;</th>
<th>LOW</th>
<th>NORMAL</th>
<th>HIGH</th>
<th>End of treatment category&lt;sup&gt;1&lt;/sup&gt;</th>
<th>LOW</th>
<th>NORMAL</th>
<th>HIGH</th>
<th>End of treatment category&lt;sup&gt;1&lt;/sup&gt;</th>
<th>LOW</th>
<th>NORMAL</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin Corrected</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Cal B/D Ointment (n=134)</td>
<td></td>
<td></td>
<td></td>
<td>LEO 90100 Vehicle (n=49)</td>
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<td></td>
<td></td>
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<tr>
<td>Serum Calcium Low</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>3</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
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<tr>
<td>Normal</td>
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<td>2</td>
<td>122</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

1) Number of subjects with laboratory parameters below, within or above the reference range.
Table 48: Shift tables for urinary calcium:creatinine ratio from Visit 1 (baseline) to Visit 4 (End of Treatment): safety analysis set

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Baseline category</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>End of treatment category</td>
<td>End of treatment category</td>
<td>End of treatment category</td>
<td>End of treatment category</td>
</tr>
<tr>
<td>Calcium/Creatinine</td>
<td>Low</td>
<td>0 2 0</td>
<td>1 1 0</td>
<td>0 0 0</td>
<td>0 1 0</td>
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<td></td>
<td>Normal</td>
<td>1 124 4</td>
<td>1 115 3</td>
<td>0 43 1</td>
<td>0 41 1</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>0 3 2</td>
<td>0 5 1</td>
<td>0 1 0</td>
<td>0 4 0</td>
</tr>
</tbody>
</table>

1) Number of subjects with laboratory parameters below, within or above the reference range.
12.4.2.3 Individual Clinically Significant Abnormalities

As mentioned above, there were sporadic elevations in clinical laboratory variables, but none of the abnormal laboratory values were considered clinically significant and none were reported as AE.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

12.5.1 Vital Signs

Blood pressure and heart rate were assessed at baseline (Visit 1) and at the end of treatment (Visit 4). Individual subject data are listed in Appendix 16.2.7.

Change in heart rate and blood pressure from baseline to end of treatment are summarised in Table 69 (EoT). No clinically relevant changes in blood pressure or heart rate were observed.

12.5.2 Local Safety and Tolerability

Local safety and tolerability was evaluated by scoring of application site skin reactions at Visits 2 to 4. Due to the inconsistency of reporting local safety and tolerability across centres (described in Section 9.8) these assessments were summarised by centre only and no overall values (pooled over all centres) are presented. Individual scores by centre for each treatment group are presented EoT in Table 70 (investigator’s assessments) and Table 71 (subject’s assessment).

Review of the per-centre data indicated no increased incidence or severity of application skin reactions of any kind in the LEO 90100 group compared with the Calcipotriol plus BDP group. While the results indicate good tolerability and raise no concerns with regard to local safety of LEO 90100 compared to Calcipotriol plus BDP ointment, they must nevertheless be interpreted with caution for the reasons cited above.

12.6 Safety Conclusions

- There were no deaths in the trial, and no SAEs or AEs leading to discontinuation in the LEO 90100 group. There were 3 SAEs and one AE that led to discontinuation in the Calcipotriol plus BDP ointment group; all were considered unrelated to study treatment.
The incidence of AEs was comparable between the LEO 90100 and Calcipotriol plus BDP ointment groups, with 16 (11.3%) subjects in the LEO 90100 group and 14 (10.4%) subjects in the Calcipotriol plus BDP ointment group. Adverse drug reactions were reported for 1 (0.7%) subject in the LEO 90100 group and 4 subjects (3.0%) in the Calcipotriol plus BDP ointment group.

There were no indications of effect on calcium homeostasis based on measurement of albumin-corrected serum calcium and spot urinary calcium:creatinine ratio.
13 Discussion and Overall Conclusions

13.1 Discussion

The primary objective of this trial was to compare the efficacy of treatment with LEO 90100 with Calcipotriol plus BDP ointment for up to 4 weeks in subjects with psoriasis vulgaris. The primary response criterion was the proportion of subjects with ‘controlled disease’ according to the IGA at week 4. The IGA is a static skin scoring system, consisting of a five point scale from clear to severe, recommended by the US regulatory authority as the most appropriate approach to primary efficacy assessment (22). Controlled disease was defined as clear or almost clear for subjects with at least moderate disease at baseline and clear for subjects with mild disease at baseline, i.e. a two-grade improvement on the global scale was required to be considered a treatment success. The comparison of efficacy at week 1, and comparison of safety were the secondary objectives.

There were no amendments to the Clinical Study Protocol. A total of 376 subjects were randomised and 358 subjects (95.2%) completed the trial, thus the withdrawal rate in the trial was low. Compliance with treatment instructions was high and over 90% of subjects in all treatment groups applied trial medication as instructed or only missed 10% or less of applications.

LEO 90100 was demonstrated to be superior to the currently marketed Calcipotriol plus BDP ointment in the proportion of subjects achieving ‘controlled disease’ at week 4 according to the IGA (54.6% vs. 43.0%, p=0.025). All treatment groups had low response rates at week 1 and there was no statistically significant difference between LEO 90100 and Calcipotriol plus BDP ointment (3.6% vs. 6.1%, p=0.29). A larger increase in the proportion of subjects with ‘controlled disease’ was seen between week 1 and week 2 in the LEO 90100 group compared to the Calcipotriol plus BDP ointment group. Although no statistical analysis was performed for week 2 it appears as if LEO 90100 has a more rapid onset than Calcipotriol plus BDP ointment.

PASI is a well established assessment that has been used in all previous psoriasis trials conducted by LEO. It was included as a secondary response criterion to enable comparison of results across several trials and also to assess the development of response to treatment over time. LEO 90100 was superior to Calcipotriol plus BDP ointment in the mean adjusted
m-PASI at week 4 (1.86 vs. 2.46, p=0.005). In contrast to the IGA there was also a statistically significant difference already at week 1 (3.95 vs. 4.64, p=0.001).

The results for the patient reported outcomes showed no major differences between LEO 90100 and Calcipotriol plus BDP ointment. The proportion of subjects assessing their disease as controlled at week 4 was similar (61.8% vs. 59.8%), treatment satisfaction scores were overall high in both groups and both treatments reduced itch considerably more than vehicle.

The incidence of AEs and ADRs in this trial was low and comparable between LEO 90100 and Calcipotriol plus BDP ointment. None of the 3 SAEs reported in the trial were in the LEO 90100 group. There was only one AE leading to withdrawal from the trial (heart rate increased in the Calcipotriol plus BDP ointment group) and this was considered not related to treatment The AE profile of LEO 90100 was similar to the AE profile of Calcipotriol plus BDP ointment.

A potential concern of systemic exposure to calcipotriol is its effects on calcium metabolism including increased blood and urine calcium levels. In this trial, the majority of subjects had albumin-corrected serum calcium as well as urinary calcium:creatinine levels within the normal range both at baseline and end of treatment. None of the subjects treated with LEO 90100 developed albumin-corrected serum calcium levels above the normal range after treatment, as compared to 1 subject treated with Calcipotriol plus BDP ointment. However, some subjects in the LEO 90100 group as well as in the vehicle group had baseline levels below the normal range. Most of these subjects shifted to normal after treatment; this was seen in both groups. A few subjects developed urinary calcium:creatinine values higher than the normal range, or shifted from low at baseline to normal after treatment, but the numbers were similar in the LEO 90100 and Calcipotriol plus BDP groups. Overall, there were no clinically significant changes in serum or urinary calcium levels after exposure to LEO 90100.

Vitamin D has a well-known role in calcium metabolism. In this trial levels of 25-hydroxy vitamin D were measured at baseline and it appeared that approximately 90% of all randomised subjects had levels below the normal reference range. This is not an unexpected finding given the fact that vitamin D insufficiency is very common in the USA and Europe where its prevalence is estimated to be as high as 50-80% in the general population, and there are studies to suggest that vitamin D deficiency may be even more common in patients with psoriasis (25-27).
13.2 Overall Conclusions

- LEO 90100 was more effective than Calcipotriol plus BDP ointment in the treatment of psoriasis vulgaris over 4 weeks.
- LEO 90100 was safe and well tolerated. The safety profile of LEO 90100 was comparable to that of Calcipotriol plus BDP ointment.
### 14 Tables, Figures and Graphs Referred to but not included in the Text

#### 14.1 Trial Population

**Table 49: Study period by centre: enrolled subjects**

<table>
<thead>
<tr>
<th>Centre</th>
<th>Date of first subject visit</th>
<th>Date of last subject visit</th>
<th>Duration of study (weeks)</th>
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</thead>
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**All enrolled subjects**

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<th>Date of first subject visit</th>
<th>Date of last subject visit</th>
<th>Duration of study (weeks)</th>
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Figure 12: Subject recruitment: number of enrolled subjects vs time
### 14.2 Demographic Data

Table 50: Subject enrolment and randomisation by centre: enrolled subjects and randomised subjects

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<thead>
<tr>
<th>Centre</th>
<th>Total number of subjects enrolled (n=427)</th>
<th>Total number of subjects randomised (n=376)</th>
<th>Total number of subjects assigned treatment</th>
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<tr>
<td></td>
<td>LEO 90100 (n=141)</td>
<td>Cal B/D Ointment (n=135)</td>
<td>LEO 90100 Vehicle (n=49)</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td>6</td>
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</tr>
<tr>
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Table 50: Subject enrolment and randomisation by centre: enrolled subjects and randomised subjects (Continued...)

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Table 51: Reasons for withdrawal by last on-treatment visit for which data are recorded: randomised subjects

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¹ Other reasons included: one withdrawal of consent to start methotrexate again, one was unable to complete visits 2 and 3 and one missed visit 2
Table 52: Investigator’s assessment of clinical signs at baseline: randomised subjects

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<tr>
<th>Location</th>
<th>Clinical sign Assessment</th>
<th>All subjects (n=376)</th>
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<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
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<td>%</td>
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Table 52: Investigator’s assessment of clinical signs at baseline: randomized subjects (Continued...)

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Table 52: Investigator’s assessment of clinical signs at baseline: randomized subjects (Continued...)

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4JAN13:18:47:06 LEO90100 35 t48signs.doc Continued...
Table 52: Investigator’s assessment of clinical signs at baseline: randomized subjects (Continued...)

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<td>13 9.2</td>
<td>3 2.2</td>
<td>3 6.1</td>
<td>2 3.9</td>
</tr>
<tr>
<td></td>
<td>50-69%</td>
<td>6 1.6</td>
<td>1 0.7</td>
<td>3 2.2</td>
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<td>1 2.0</td>
</tr>
<tr>
<td></td>
<td>70-89%</td>
<td>2 0.5</td>
<td>1 0.7</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>1 2.0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>376 100.0</td>
<td>141 100.0</td>
<td>135 100.0</td>
<td>49 100.0</td>
<td>51 100.0</td>
</tr>
<tr>
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<td>Inv Assessment of Severity of Redness</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>151 40.2</td>
<td>54 38.3</td>
<td>52 38.5</td>
<td>24 49.0</td>
<td>21 41.2</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>47 12.5</td>
<td>16 11.3</td>
<td>14 10.4</td>
<td>7 14.3</td>
<td>10 19.6</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>139 37.0</td>
<td>55 39.0</td>
<td>53 39.3</td>
<td>15 30.6</td>
<td>16 31.4</td>
</tr>
<tr>
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<td>Severe</td>
<td>35 9.3</td>
<td>14 9.9</td>
<td>16 11.9</td>
<td>1 2.0</td>
<td>4 7.8</td>
</tr>
<tr>
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<td>Very severe</td>
<td>4 1.1</td>
<td>2 1.4</td>
<td>0 0.0</td>
<td>2 4.1</td>
<td>0 0.0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>376 100.0</td>
<td>141 100.0</td>
<td>135 100.0</td>
<td>49 100.0</td>
<td>51 100.0</td>
</tr>
<tr>
<td></td>
<td>Inv Assessment of Severity of Thickness</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>None</td>
<td>154 41.0</td>
<td>54 38.3</td>
<td>54 40.0</td>
<td>24 49.0</td>
<td>22 43.1</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>76 20.2</td>
<td>29 20.6</td>
<td>24 17.8</td>
<td>10 20.4</td>
<td>13 25.5</td>
</tr>
<tr>
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<td>117 31.1</td>
<td>46 32.6</td>
<td>46 34.1</td>
<td>12 24.5</td>
<td>13 25.5</td>
</tr>
<tr>
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<td>Severe</td>
<td>26 6.9</td>
<td>12 8.5</td>
<td>8 5.9</td>
<td>3 6.1</td>
<td>3 5.9</td>
</tr>
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Table 52: Investigator’s assessment of clinical signs at baseline: randomized subjects (Continued...)

<table>
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<tr>
<th>Location</th>
<th>Clinical sign Assessment</th>
<th>All subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRUNK</td>
<td>Inv Assessment of Severity of Thickness</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Very severe</td>
<td>3</td>
<td>0.8</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>Total</td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
<td>100.0</td>
</tr>
<tr>
<td>Inv Assessment of Severity of Scaliness</td>
<td>None</td>
<td>154</td>
<td>41.0</td>
<td>54</td>
<td>38.3</td>
<td>53</td>
</tr>
<tr>
<td>Mild</td>
<td>83</td>
<td>22.1</td>
<td>34</td>
<td>24.1</td>
<td>27</td>
<td>20.0</td>
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<tr>
<td>Moderate</td>
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<td>26.2</td>
<td>50</td>
<td>37.0</td>
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<tr>
<td>Severe</td>
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<td>7.4</td>
<td>15</td>
<td>10.6</td>
<td>4</td>
<td>3.0</td>
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<tr>
<td>Very severe</td>
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<td>1</td>
<td>0.7</td>
<td>1</td>
<td>0.7</td>
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<td>Total</td>
<td>376</td>
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<td>141</td>
<td>100.0</td>
<td>135</td>
<td>100.0</td>
</tr>
<tr>
<td>Inv Assessment of Extent</td>
<td>No involvement</td>
<td>150</td>
<td>39.9</td>
<td>54</td>
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<tr>
<td>&lt;10%</td>
<td>166</td>
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<td>62</td>
<td>45.9</td>
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<tr>
<td>10-29%</td>
<td>49</td>
<td>13.0</td>
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<td>14.1</td>
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<tr>
<td>30-49%</td>
<td>10</td>
<td>2.7</td>
<td>6</td>
<td>4.3</td>
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<td>1.5</td>
</tr>
<tr>
<td>50-69%</td>
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<td>0.3</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>70-89%</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>376</td>
<td>100.0</td>
<td>141</td>
<td>100.0</td>
<td>135</td>
<td>100.0</td>
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Table 53: Summary of 25-hydroxy vitamin D at baseline: safety analysis set

<table>
<thead>
<tr>
<th>25-hydroxy vitamin D</th>
<th>All randomised subjects (n=375)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>330 (90.2%)</td>
<td>122 (89.1%)</td>
<td>122 (93.1%)</td>
<td>40 (85.1%)</td>
<td>46 (90.2%)</td>
</tr>
<tr>
<td>Normal</td>
<td>35 (9.6%)</td>
<td>14 (10.2%)</td>
<td>9 (6.9%)</td>
<td>7 (14.9%)</td>
<td>5 (9.8%)</td>
</tr>
<tr>
<td>High</td>
<td>1 (0.3%)</td>
<td>1 (0.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>366 (100.0%)</td>
<td>137 (100.0%)</td>
<td>131 (100.0%)</td>
<td>47 (100.0%)</td>
<td>51 (100.0%)</td>
</tr>
</tbody>
</table>
Table 54: Physical examination (weight, height, BMI): randomised subjects

<table>
<thead>
<tr>
<th>Physical examination</th>
<th>All randomised subjects (n=376)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>171.0</td>
<td>170.5</td>
<td>171.3</td>
<td>170.8</td>
<td>171.9</td>
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<tr>
<td>SD</td>
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<td>9.5</td>
<td>10.8</td>
<td>9.1</td>
<td>11.6</td>
</tr>
<tr>
<td>Median</td>
<td>170.2</td>
<td>170.2</td>
<td>170.2</td>
<td>170.2</td>
<td>172.7</td>
</tr>
<tr>
<td>Minimum</td>
<td>140.0</td>
<td>148.0</td>
<td>140.0</td>
<td>149.9</td>
<td>149.9</td>
</tr>
<tr>
<td>Maximum</td>
<td>213.4</td>
<td>198.1</td>
<td>213.4</td>
<td>190.5</td>
<td>213.4</td>
</tr>
<tr>
<td>Number</td>
<td>375</td>
<td>140</td>
<td>135</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>90.2</td>
<td>92.0</td>
<td>88.5</td>
<td>87.8</td>
<td>91.8</td>
</tr>
<tr>
<td>SD</td>
<td>21.2</td>
<td>22.3</td>
<td>18.0</td>
<td>23.6</td>
<td>23.3</td>
</tr>
<tr>
<td>Median</td>
<td>88.5</td>
<td>90.7</td>
<td>86.2</td>
<td>87.1</td>
<td>87.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>42.4</td>
<td>42.4</td>
<td>49.0</td>
<td>47.6</td>
<td>49.9</td>
</tr>
<tr>
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<td>204.1</td>
<td>152.0</td>
<td>154.2</td>
<td>143.8</td>
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<tr>
<td>Number</td>
<td>375</td>
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<td>135</td>
<td>49</td>
<td>51</td>
</tr>
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<td>Body Mass Index</td>
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</tr>
<tr>
<td>Mean</td>
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<td>31.7</td>
<td>30.2</td>
<td>30.1</td>
<td>30.9</td>
</tr>
<tr>
<td>SD</td>
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<td>7.8</td>
<td>6.0</td>
<td>7.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Median</td>
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<td>29.8</td>
<td>29.4</td>
<td>28.0</td>
<td>30.0</td>
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<tr>
<td>Minimum</td>
<td>18.3</td>
<td>19.4</td>
<td>19.1</td>
<td>18.3</td>
<td>20.8</td>
</tr>
<tr>
<td>Maximum</td>
<td>79.7</td>
<td>79.7</td>
<td>56.5</td>
<td>52.4</td>
<td>45.2</td>
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<tr>
<td>Number</td>
<td>375</td>
<td>140</td>
<td>135</td>
<td>49</td>
<td>51</td>
</tr>
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</table>
Table 55: Relevant medical history and concurrent diagnoses at baseline by MedDRA primary SOC: randomised subjects

<table>
<thead>
<tr>
<th>System Organ Classification</th>
<th>All randomised subjects (n=375)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>2</td>
<td>2</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>17</td>
<td>14</td>
<td>3.7</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td>1</td>
<td>1</td>
<td>0.3</td>
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<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>8</td>
<td>5</td>
<td>1.3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Endocrine disorders</td>
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<td>2</td>
<td>0.5</td>
<td>2</td>
<td>2</td>
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<td>Eye disorders</td>
<td>22</td>
<td>22</td>
<td>5.9</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>16</td>
<td>13</td>
<td>3.5</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>8</td>
<td>8</td>
<td>2.1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
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<td>1.6</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Immune system disorders</td>
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<td>61</td>
<td>16.3</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>15</td>
<td>14</td>
<td>3.7</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>14</td>
<td>11</td>
<td>2.9</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Investigations</td>
<td>25</td>
<td>18</td>
<td>4.8</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>31</td>
<td>23</td>
<td>6.1</td>
<td>11</td>
<td>11</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
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<td>39</td>
<td>10.4</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (including cysts and polyps)</td>
<td>24</td>
<td>20</td>
<td>5.3</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

Continued...
Table 55: Relevant medical history and concurrent diagnoses at baseline by MedDRA primary SOC: randomised subjects (Continued...)

<table>
<thead>
<tr>
<th>System Organ Classification</th>
<th>All randomised subjects (n=375)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
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</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
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</tr>
<tr>
<td>Total number of diagnoses²</td>
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<td>236</td>
<td>4.0</td>
<td>211</td>
<td>71</td>
</tr>
<tr>
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<td>44</td>
<td>31.2</td>
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</table>

1) Classification according to MedDRA version 15.0.
2) Different diagnoses within the same preferred term and involving the same subject have been counted as one. A subject could appear in multiple classes.
Table 56: Concomitant medication at baseline: randomised subjects

<table>
<thead>
<tr>
<th>ATC classification index level</th>
<th>All randomised subjects (n=375)</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>No. Drugs</td>
<td>No. Subj</td>
<td>%</td>
<td>No. Drugs</td>
<td>No. Subj</td>
</tr>
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<td>82</td>
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<td>4</td>
<td>4</td>
</tr>
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<td>2</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>BLOOD AND BLOOD FORMING ORGANS</td>
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<td>59</td>
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<td>29</td>
</tr>
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<td>51</td>
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<td>47</td>
<td>12.5</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
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<td>30</td>
<td>26</td>
<td>6.9</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>MUSCULO–SKELETAL SYSTEM</td>
<td>60</td>
<td>49</td>
<td>13.1</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>NERVOUS SYSTEM</td>
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<td>93</td>
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<td>60</td>
<td>39</td>
</tr>
<tr>
<td>RESPIRATORY SYSTEM</td>
<td>73</td>
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</tr>
<tr>
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<td>0.8</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS</td>
<td>21</td>
<td>21</td>
<td>5.6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>VARIOUS</td>
<td>28</td>
<td>18</td>
<td>4.8</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total number of drugs taken</strong></td>
<td>943</td>
<td>397</td>
<td>319</td>
<td>86</td>
<td>141</td>
</tr>
<tr>
<td><strong>Total number of subjects taking drugs</strong></td>
<td>236</td>
<td>62.9</td>
<td>98</td>
<td>69.5</td>
<td>75</td>
</tr>
</tbody>
</table>

1) Drugs with the same Anatomical Therapeutic Chemical (ATC) classification level 4 code and generic name/preferred term name which have been taken by the same subject have been counted as one.
Table 57: Compliance with treatment instructions: randomised subjects

<table>
<thead>
<tr>
<th>Visit Missed applications</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vist 2</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>No</td>
<td>125</td>
<td>121</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>&lt;= 10% applications missed</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10% and &lt;=20% applications missed</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20% and &lt;=30% applications missed</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>&gt;30% and &lt;=40% applications missed</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;40% and &lt;=50% applications missed</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;50% applications missed</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>132</td>
<td>49</td>
<td>50</td>
</tr>
</tbody>
</table>

28JAN13:14:39:22 LEO90100 35 t53comp.doc
### Table 57: Compliance with treatment instructions: randomised subjects (Continued...)

<table>
<thead>
<tr>
<th>Visit Missed applications</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>VISIT 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>119</td>
<td>88.1</td>
<td>118</td>
<td>91.5</td>
</tr>
<tr>
<td>&lt;= 10% applications missed</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>&gt;10% and &lt;=20% applications missed</td>
<td>11</td>
<td>8.1</td>
<td>5</td>
<td>3.9</td>
</tr>
<tr>
<td>&gt;20% and &lt;=30% applications missed</td>
<td>2</td>
<td>1.5</td>
<td>3</td>
<td>2.3</td>
</tr>
<tr>
<td>&gt;30% and &lt;=40% applications missed</td>
<td>2</td>
<td>1.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;40% and &lt;=50% applications missed</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;50% applications missed</td>
<td>1</td>
<td>0.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>135</td>
<td>100.0</td>
<td>129</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 57: Compliance with treatment instructions: randomised subjects (Continued...)

<table>
<thead>
<tr>
<th>Visit Missed applications</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>VISIT 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>111</td>
<td>82.2</td>
<td>107</td>
<td>83.6</td>
</tr>
<tr>
<td>&lt;= 10% applications missed</td>
<td>13</td>
<td>9.6</td>
<td>14</td>
<td>10.9</td>
</tr>
<tr>
<td>&gt;10% and &lt;=20% applications missed</td>
<td>8</td>
<td>5.9</td>
<td>4</td>
<td>3.1</td>
</tr>
<tr>
<td>&gt;20% and &lt;=30% applications missed</td>
<td>2</td>
<td>1.5</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;40% and &lt;=50% applications missed</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;50% applications missed</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td>135</td>
<td>100.0</td>
<td>128</td>
<td>100.0</td>
</tr>
</tbody>
</table>

28JAN13:14:33:22 LEO90100 35 t55comp.doc
### 14.3 Efficacy Data

**Table 58: Analysis of Percentage of subjects with “Controlled disease” (IGA) at week 4 adjusted for baseline IGA (LOCF): full analysis set**

<table>
<thead>
<tr>
<th>Controlled Disease at week 4</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Disease</td>
<td>77</td>
<td>58</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Non-controlled Disease</td>
<td>64</td>
<td>77</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>141</td>
<td>135</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>

**Statistical analysis**

**LEO90100 vs. Cal B/D**
- **Odds ratio**
  - 1.8
  - 95% CI: 1.1 to 3.1
  - Wald test p-value: 0.020

**Baseline**
- **Odds ratio**
  - 2.9
  - 95% CI: 1.6 to 5.7
  - Wald test p-value: < 0.001

**Pooled Centre**
- Wald test p-value: 0.19

---

1) Logistic regression odds ratio for Controlled disease (LEO90100 relative to Cal B/D Ointment) adjusted for pooled centre and baseline IGA
2) Test for the hypothesis of odds ratio equal to 1
3) Logistic regression odds ratio for increase of 1 on IGA scale adjusted for treatment and pooled centre
4) Test for homogeneity of odds ratios across pooled centres
<table>
<thead>
<tr>
<th>Week 4</th>
<th>Pooled centre</th>
<th>OR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEO90100 vs CAL B/D Ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>not calculable</td>
<td>not calculable</td>
<td></td>
</tr>
<tr>
<td>0.0 ( to )</td>
<td>0.1 (0.0 to 1.5)</td>
<td></td>
</tr>
<tr>
<td>0.5 (0.1 to 3.4)</td>
<td>0.7 (0.1 to 5.1)</td>
<td></td>
</tr>
<tr>
<td>1.0 (0.2 to 5.4)</td>
<td>1.3 (0.2 to 7.6)</td>
<td></td>
</tr>
<tr>
<td>1.5 (0.2 to 13.2)</td>
<td>1.7 (0.2 to 13.2)</td>
<td></td>
</tr>
<tr>
<td>1.9 (0.5 to 7.3)</td>
<td>2.0 (0.1 to 29.8)</td>
<td></td>
</tr>
<tr>
<td>2.7 (0.2 to 45.1)</td>
<td>2.7 (0.2 to 45.1)</td>
<td></td>
</tr>
<tr>
<td>4.0 (0.3 to 60.3)</td>
<td>6.7 (0.5 to 91.3)</td>
<td></td>
</tr>
<tr>
<td>18.0 (1.3 to 255.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Table 60: Percentage of subjects with “Controlled disease” (IGA) at week 4 by pooled centre: full analysis set

<table>
<thead>
<tr>
<th>Pooled site</th>
<th>Controlled Disease</th>
<th>Non-controlled Disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEO 90100</td>
<td>Number of subjects</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>(n=141)</td>
<td>6</td>
<td>54.5</td>
<td>11</td>
</tr>
<tr>
<td>Cal B/D Ointment</td>
<td>Number of subjects</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>(n=135)</td>
<td>5</td>
<td>50.0</td>
<td>10</td>
</tr>
<tr>
<td>LEO 90100 Vehicle</td>
<td>Number of subjects</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>(n=49)</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td>Ointment Vehicle</td>
<td>Number of subjects</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>(n=51)</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pooled site</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled Disease</td>
<td>6</td>
<td>54.5</td>
<td>5</td>
<td>50.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Non-controlled Disease</td>
<td>5</td>
<td>45.5</td>
<td>5</td>
<td>50.0</td>
<td>4</td>
<td>100.0</td>
<td>2</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>100.0</td>
<td>10</td>
<td>100.0</td>
<td>4</td>
<td>100.0</td>
<td>2</td>
<td>100.0</td>
</tr>
</tbody>
</table>

| Controlled Disease | 4         | 80.0 | 3         | 60.0 | 0         | 0.0 | 0         | 0.0 |
| Non-controlled Disease | 1        | 20.0 | 2         | 40.0 | 2         | 100.0 | 2         | 100.0 |
| Total       | 5       | 100.0 | 5         | 100.0 | 2         | 100.0 | 2         | 100.0 |

| Controlled Disease | 3         | 57.1 | 6         | 66.7 | 0         | 0.0 | 0         | 0.0 |
| Non-controlled Disease | 3        | 42.9 | 3         | 33.3 | 3         | 100.0 | 3         | 100.0 |
| Total       | 7       | 100.0 | 9         | 100.0 | 3         | 100.0 | 3         | 100.0 |

| Controlled Disease | 6         | 50.0 | 0         | 0.0 | 0         | 0.0 | 0         | 0.0 |
| Non-controlled Disease | 6        | 50.0 | 8         | 100.0 | 2         | 100.0 | 2         | 100.0 |
| Total       | 12      | 100.0 | 8         | 100.0 | 2         | 100.0 | 2         | 100.0 |

| Controlled Disease | 5         | 55.6 | 5         | 62.5 | 0         | 0.0 | 2         | 50.0 |

(Continued...)
<table>
<thead>
<tr>
<th>Pooled site</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-controlled</td>
<td>4</td>
<td>44.4</td>
<td>3</td>
<td>37.5</td>
<td>2</td>
<td>100.0</td>
<td>2</td>
<td>50.0</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>100.0</td>
<td>8</td>
<td>100.0</td>
<td>2</td>
<td>100.0</td>
<td>4</td>
<td>100.0</td>
</tr>
<tr>
<td>Controlled Disease</td>
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<td>12.5</td>
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<td>0.0</td>
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<td>0.0</td>
</tr>
<tr>
<td>Non-controlled</td>
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<td>40.0</td>
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<td>100.0</td>
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<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>100.0</td>
<td>5</td>
<td>100.0</td>
<td>3</td>
<td>100.0</td>
<td>3</td>
<td>100.0</td>
</tr>
<tr>
<td>Controlled Disease</td>
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<td>40.0</td>
<td>1</td>
<td>20.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Non-controlled</td>
<td>3</td>
<td>60.0</td>
<td>4</td>
<td>80.0</td>
<td>1</td>
<td>100.0</td>
<td>3</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
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<td>100.0</td>
<td>5</td>
<td>100.0</td>
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<td>100.0</td>
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<td>100.0</td>
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<tr>
<td>Controlled Disease</td>
<td>12</td>
<td>63.2</td>
<td>8</td>
<td>53.3</td>
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<tr>
<td>Non-controlled</td>
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<td>46.7</td>
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<tr>
<td>Total</td>
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<td>15</td>
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<td>100.0</td>
<td>4</td>
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</tr>
<tr>
<td>Controlled Disease</td>
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<td>62.5</td>
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<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Non-controlled</td>
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<td>28.6</td>
<td>3</td>
<td>37.5</td>
<td>2</td>
<td>100.0</td>
<td>3</td>
<td>100.0</td>
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<tr>
<td>Total</td>
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<td>8</td>
<td>100.0</td>
<td>2</td>
<td>100.0</td>
<td>3</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 60: Percentage of subjects with “Controlled disease” (IGA) at week 4 by pooled centre: full analysis set (Continued...)

<table>
<thead>
<tr>
<th>Pooled site</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Controlled Disease</td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>62.5</td>
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<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>37.5</td>
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<tr>
<td>Total</td>
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<td>100.0</td>
</tr>
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<td>66.7</td>
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<tr>
<td>Total</td>
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<td>100.0</td>
<td>10</td>
<td>100.0</td>
</tr>
<tr>
<td>Controlled Disease</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>44.4</td>
<td></td>
<td>5</td>
<td>62.5</td>
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<td>55.6</td>
<td></td>
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<td>100.0</td>
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<td>100.0</td>
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<td>4</td>
<td>80.0</td>
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<td>75.0</td>
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<td>25.0</td>
</tr>
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<td>Total</td>
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<tr>
<td>Controlled Disease</td>
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<tr>
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<td>33.3</td>
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<td>6</td>
<td>66.7</td>
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<td>5</td>
<td>71.4</td>
</tr>
<tr>
<td>Pooled site</td>
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</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td></td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>100.0</td>
<td>7</td>
<td>100.0</td>
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<tr>
<td>Controlled Disease</td>
<td>2</td>
<td>33.3</td>
<td>4</td>
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<tr>
<td>Non-controlled Disease</td>
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<td>66.7</td>
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<tr>
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<td>100.0</td>
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Table 61: Percentage of subjects in each IGA-category at weeks 1 (Visit 2), 2 (Visit 3) and 4 (Visit 4): full analysis set

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<th>Visit</th>
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<th>Cal B/D Ointment (n=135)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
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<td></td>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
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<td>132</td>
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<td>10</td>
<td>7.9</td>
<td>20</td>
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<td></td>
<td>Severe</td>
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<td>0.0</td>
<td>1</td>
<td>0.8</td>
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<td>127</td>
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Table 62: Summary of m-PASI at baseline and change from baseline to weeks 1 (Visit 2), 2 (Visit 3) and 4 (Visit 4): full analysis set

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<th>LEO 90100 Vehicle (n=49)</th>
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</tr>
<tr>
<td></td>
<td>Number</td>
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<td>135</td>
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<td>51</td>
</tr>
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<td>-1.8</td>
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<td>-11</td>
<td>-13</td>
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<td>132</td>
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Table 63: Percentage of subjects in each Patient’s Global Assessment-category at weeks 1 (Visit 2), 2 (Visit 3) and 4 (Visit 4): full analysis set

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<th>%</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
<th>Number of subjects</th>
<th>%</th>
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<tr>
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<td>30</td>
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<td>18</td>
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<td>5</td>
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<td>2.1</td>
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<td>127</td>
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<td>100.0</td>
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Table 64: BSA involvement of psoriasis vulgaris at weeks 1 (Visit 2), 2 (Visit 3) and 4 (Visit 4): full analysis set

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<td>29</td>
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<td>Number</td>
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<td>50</td>
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<td>5.0</td>
<td>4.0</td>
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<td>1</td>
<td>1</td>
<td></td>
</tr>
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<tr>
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<td>138</td>
<td>127</td>
<td>47</td>
<td>48</td>
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14.4 Safety Data

Table 65: Lesional/perilesional AEs by MedDRA primary SOC and preferred term: safety analysis set

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<th>Preferred Term</th>
<th>LEO 90100 (n=141)</th>
<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
</tr>
</thead>
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<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
<td>%</td>
<td>Number of subjects</td>
</tr>
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<td>0.7</td>
</tr>
<tr>
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<td>Application site pain</td>
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<td>0.0</td>
<td>1</td>
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</tr>
<tr>
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<td>0.7</td>
<td>0</td>
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</tr>
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</tr>
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<td>0.0</td>
<td>1</td>
<td>0.7</td>
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</tbody>
</table>

| Total number of drug reactions | 1 | 5 |

| Total number of subjects | 1 | 0.7 | 4 | 3.0 | 0 | 0.0 | 0 | 0.0 |

1) Classification according to MedDRA version 15.0.
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.
Table 66: Lesional/perilesional ADRs by MedDRA primary SOC and preferred term: safety analysis set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
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<th>Cal B/D Ointment (n=134)</th>
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1) Classification according to MedDRA version 15.0.
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.
Table 67: Intensity of AEs by MedDRA primary SOC and preferred term: safety analysis set

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Table 67: Intensity of AEs by MedDRA primary SOC and preferred term: safety analysis set (Continued...)

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Table 67: Intensity of AEs by MedDRA primary SOC and preferred term: safety analysis set (Continued...)

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<th>System Organ Class</th>
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1) Classification according to MedDRA version 15.0.
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.
Table 68: Causal relationship of AEs by MedDRA primary SOC and preferred term: safety analysis set

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<td>PO^3</td>
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### Table 68: Causal relationship of AEs by MedDRA primary SOC and preferred term: safety analysis set (Continued...)

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*Continued...*
Table 68: Causal relationship of AEs by MedDRA primary SOC and preferred term: safety analysis set (Continued...)

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<td>Respiratory, thoracic and mediastinal disorders</td>
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Table continued...
Table 68: Causal relationship of AEs by MedDRA primary SOC and preferred term: safety analysis set (Continued...)

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<th>Preferred Term</th>
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<th>Cal B/D Ointment (n=134)</th>
<th>LEO 90100 Vehicle (n=49)</th>
<th>Ointment Vehicle (n=51)</th>
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<td>PO</td>
<td>NR</td>
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1) Classification according to MedDRA version 15.0.
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.
3) PR=Probably related, PO=Possible related, NR=Not related, NA=Not assessable
Table 69: Vital signs at Visit 1 (baseline) and Visit 4 (EOT) and change from Visit 1: safety analysis set

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<th>Vital sign</th>
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<th>Visit 4</th>
<th>Change</th>
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Table 69: Vital signs at Visit 1 (baseline) and Visit 4 (EOT) and change from Visit 1: safety analysis set (Continued...)

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Table 69: Vital signs at Visit 1 (baseline) and Visit 4 (EOT) and change from Visit 1: safety analysis set (Continued...)

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<td><strong>Mean</strong></td>
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Continued...
Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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# Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Continued...
Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

| LEO 90100 (n=141) | | | | | | | | | | | | | | | | | | | |
| Cal B/D Ointment (n=134) | | | | | | | | | | | | | | | | | | | |
| LEO 90100 Vehicle (n=49) | | | | | | | | | | | | | | | | | | | |
| Ointment Vehicle (n=51) | | | | | | | | | | | | | | | | | | | |
| Erythema | Absent | 0 (0.0) | 0 (0.0) | 4 (80.0) | 3 (60.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 1 (50.0) | 1 (50.0) | 2 (100.0) | | | | | |
| Mild | 0 (0.0) | 0 (0.0) | 1 (20.0) | 2 (40.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | | | | | |
| Total | 0 (0.0) | 0 (0.0) | 5 (100.0) | 5 (100.0) | 5 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 2 (100.0) | 2 (100.0) | 2 (100.0) | 2 (100.0) | | | | | | |
| Oedema | Absent | 0 (0.0) | 0 (0.0) | 5 (100.0) | 5 (100.0) | 5 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 2 (100.0) | 2 (100.0) | 2 (100.0) | | | | | | |
| Total | 0 (0.0) | 0 (0.0) | 5 (100.0) | 5 (100.0) | 5 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 2 (100.0) | 2 (100.0) | 2 (100.0) | 2 (100.0) | | | | | | |
| Dryness | Absent | 0 (0.0) | 0 (0.0) | 4 (80.0) | 4 (80.0) | 5 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 1 (50.0) | 0 (0.0) | | | | | | | | |
| Mild | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | | | | | | | | |
| Moderate | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | | | | | | | | |
| Total | 0 (0.0) | 0 (0.0) | 5 (100.0) | 5 (100.0) | 5 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 2 (100.0) | 2 (100.0) | 2 (100.0) | | | | | | | |
| Erosion | Absent | 0 (0.0) | 0 (0.0) | 5 (100.0) | 5 (100.0) | 5 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 2 (100.0) | 2 (100.0) | 2 (100.0) | | | | | | |
| Total | 0 (0.0) | 0 (0.0) | 5 (100.0) | 5 (100.0) | 5 (100.0) | 1 (100.0) | 1 (100.0) | 1 (100.0) | 2 (100.0) | 2 (100.0) | 2 (100.0) | 2 (100.0) | | | | | | |

Continued...
Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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<th>Visit 4 n (%)</th>
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**Erythema**

- **Absent**
  - LEO 90100: 0 (0.0) 2 (25.0) 6 (75.0) 0 (0.0) 2 (33.3) 3 (50.0) 0 (0.0) 1 (33.3) 2 (66.7) 0 (0.0) 0 (0.0) 0 (0.0)
  - Cal B/D Ointment: 8 (100.0) 6 (75.0) 2 (25.0) 6 (100.0) 4 (66.7) 3 (50.0) 1 (33.3) 0 (0.0) 1 (33.3) 1 (50.0) 1 (50.0)
  - LEO 90100 Vehicle: 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 2 (66.7) 2 (66.7) 0 (0.0) 1 (50.0) 1 (50.0)
  - Ointment Vehicle: 8 (100.0) 8 (100.0) 6 (100.0) 6 (100.0) 3 (100.0) 3 (100.0) 3 (100.0) 2 (100.0) 2 (100.0) 2 (100.0)

- **Mild**
  - LEO 90100: 8 (100.0) 6 (75.0) 2 (25.0) 6 (100.0) 4 (66.7) 3 (50.0) 1 (33.3) 0 (0.0) 1 (33.3) 1 (50.0) 1 (50.0)
  - Cal B/D Ointment: 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 2 (66.7) 2 (66.7) 0 (0.0) 1 (50.0) 1 (50.0)
  - LEO 90100 Vehicle: 8 (100.0) 8 (100.0) 6 (100.0) 6 (100.0) 3 (100.0) 3 (100.0) 3 (100.0) 2 (100.0) 2 (100.0) 2 (100.0)
  - Ointment Vehicle: 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 2 (66.7) 2 (66.7) 0 (0.0) 1 (50.0) 1 (50.0)

- **Moderate**
  - LEO 90100: 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 2 (66.7) 2 (66.7) 0 (0.0) 1 (50.0) 1 (50.0)
  - Cal B/D Ointment: 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 2 (66.7) 2 (66.7) 0 (0.0) 1 (50.0) 1 (50.0)
  - LEO 90100 Vehicle: 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 2 (66.7) 2 (66.7) 0 (0.0) 1 (50.0) 1 (50.0)
  - Ointment Vehicle: 8 (100.0) 8 (100.0) 6 (100.0) 6 (100.0) 3 (100.0) 3 (100.0) 3 (100.0) 2 (100.0) 2 (100.0) 2 (100.0)

**Total**

- Erythema: 8 (100.0) 8 (100.0) 6 (100.0) 6 (100.0) 3 (100.0) 3 (100.0) 3 (100.0) 2 (100.0) 2 (100.0) 2 (100.0)

**Oedema**

- Absent: 8 (100.0) 8 (100.0) 6 (100.0) 6 (100.0) 3 (100.0) 3 (100.0) 3 (100.0) 2 (100.0) 2 (100.0) 2 (100.0)

**Dryness**

- Absent: 8 (100.0) 8 (100.0) 6 (100.0) 6 (100.0) 3 (100.0) 3 (100.0) 3 (100.0) 2 (100.0) 2 (100.0) 2 (100.0)

**Erosion**

- Absent: 8 (100.0) 8 (100.0) 6 (100.0) 6 (100.0) 3 (100.0) 3 (100.0) 3 (100.0) 2 (100.0) 2 (100.0) 2 (100.0)

**Continued...**
Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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**Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)**

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## Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 70: Local safety and tolerability – investigator’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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Table 71: Local safety and tolerability – subject’s assessment, by centre: safety analysis set (Continued...)

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15 References


## 16 List of Appendices

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<th>App. No.</th>
<th>Appendix</th>
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<td></td>
<td><strong>16.1 STUDY INFORMATION</strong></td>
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<tr>
<td>16.1.1</td>
<td>Protocol and protocol amendments</td>
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<td>16.1.2</td>
<td>Sample case report form (unique pages only)</td>
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<td>16.1.3</td>
<td>List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for subject and sample consent forms</td>
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<td>16.1.4</td>
<td>List and description of investigators and other important participants in the trial, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical trial</td>
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<td>16.1.5</td>
<td>Signatures of principal or coordinating investigator(s) or sponsor’s responsible medical officer, depending on the regulatory authority's requirement</td>
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<td>16.1.6</td>
<td>Listing of subjects receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used</td>
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<td>Randomisation scheme and codes (subject identification and treatment assigned)</td>
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<td>16.1.8</td>
<td>Audit certificates (if available)</td>
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<td>16.1.9</td>
<td>Documentation of statistical methods</td>
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<td>Documentation of inter-laboratory standardisation methods and quality assurance procedures if used</td>
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<td>16.1.12</td>
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<td><strong>16.2 SUBJECT DATA LISTINGS</strong></td>
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<td>16.2.1</td>
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<td>Subjects excluded from the efficacy and safety analysis</td>
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<td>Demographic data</td>
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16.2.5 Compliance and/or drug concentration data (if available)  Enclosed
16.2.6 Individual efficacy response data  Enclosed
16.2.7 Adverse event listings (each subject)  Enclosed
16.2.8 Listing of individual laboratory measurements by subject, when required by regulatory authorities  Enclosed
16.2.9 Additional subject data listings  Enclosed

16.3 CASE REPORT FORMS

16.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE  Available upon request
16.3.2 Other CRFs submitted  N.A.
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