Cover Page

Official title: A phase 3, national, multi-centre, 4-week, prospective, randomised, controlled, parallel group, open trial of LEO 90100 foam versus Dovobet® ointment
LEO Pharma number: LP0053-1422
NCT number: NCT03806790
Date: 06-Nov-2018

Clinical Trial Protocol

Efficacy and safety of LEO 90100 foam in Japanese subjects with psoriasis vulgaris

A phase 3, national, multi-centre, 4-week, prospective, randomised, controlled, parallel-group, open trial of LEO 90100 foam versus Dovobet® ointment

ICH GCP statement: *The clinical trial will be conducted in compliance with the clinical trial protocol, ICH-GCP, J-GCP and the applicable regulatory requirement(s).*

LEO Pharma A/S	**Trial ID:**	**LP0053-1422**
	Date:	**06-Nov-2018**
	Version:	**1.0**

1 Clinical Trial Protocol Statements

1.1 Approval Statement LEO Pharma A/S

Electronic signatures made within eTMF LEO are considered to be a legally binding equivalent of traditional handwritten signatures. The following persons have approved this clinical trial protocol by using electronic signatures as presented on the last page of this document:

PPD , MSc Stat
Biostatistics Lead, Global Clinical Operations

PPD , MD
Vice President, Medical Sciences

PPD , MSc Pharm
Clinical Operations Lead, Global Clinical Operations

1.2 Approval Statement signatory investigator

The signatory investigator approves the clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by manually signing the Signatory Investigator Clinical Trial Protocol Approval Form, which is a separate document adjoined to this document.

The following person has approved this clinical trial protocol:

PPD , MD, PhD
Signatory investigator

1.3 Acknowledgement Statement Investigators

Each participating investigator must agree to the approved clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by signing an Agreement for Conducting Clinical Trial - Japan form.

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List of Abbreviations and Definition of Terms

ADR	adverse drug reaction
AE	adverse event
ACE	angiotensin converting enzyme
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area
BUN	blood urea nitrogen
CDISC	clinical data interchange standards consortium
CMO	Contract Manufacturing Organisation
CRF	case report form
CRO	contract research organisation
CTCAE	common terminology criteria for adverse events
EU	European Union
GCP	good clinical practice
GGT	gamma-glutamyl transpeptidase
GMP	good manufacturing practice
HbA1c	average blood glucose level
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	investigational medicinal product
IRB	institutional review board
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
Overall improvement rate	A ‘substantial resolution’ of clinical signs or at least ‘moderately improved’ in the general change in the target lesion
PDE4i	phosphodiesterase 4 inhibitor
PUVA	psoralen plus UVA
RBC	red blood cell
SAE	serious adverse event
SDTM	study data tabulation model
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase

Substantial resolution	A clinical score for thickness and scaliness of 0 and a clinical score for redness of 1 or less in the severity of clinical signs of the target lesion
SUSAR	suspected unexpected serious adverse reaction
UVA	ultraviolet light A
UVB	ultraviolet light B
WBC	white blood cell
WHO	World Health Organisation

2 Trial Identification

LP0053-1422

The clinical trial protocol will be registered on clinicaltrials.gov, jRCT (Japan Registry of Clinical Trials) and JAPIC (Japan Pharmaceutical Information Center).

3 Introduction and Rationale

This Phase 3 clinical trial is being conducted as part of the clinical development programme to obtain marketing approval of LEO 90100 foam (a combination of calcipotriol hydrate plus betamethasone dipropionate) in Japan.

3.1 Psoriasis

Psoriasis vulgaris is one of the most common chronic skin diseases, with a prevalence generally estimated at between 1 to 3% of the world's population (1, 2). The prevalence of the disease in Japan could be low (3). It is characterised by sharply marginated areas of affected skin which appear thickened, red and scaly. The scalp, elbows, knees, lower back, hands, feet and nails are commonly affected sites. About 80% of affected patients complain of pruritus (4). Psoriasis is a significant problem in everyday life for the affected patients and has a significant impact on their health-related quality of life, an impact that increases with increasing skin involvement (5).

Psoriasis is a dermatological disease which is characterised by an immune inflammatory reaction, proliferation of epidermal keratinocytes and a disorder of differentiation. 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 (6,7). Activated T-cells (Th17 and Th1) as well as dendritic cells play an important role among immune and inflammatory reactions in psoriasis. Cytokines (IL-23 and IL-12) produced by dendritic cells are involved in T-cell proliferation and differentiation. Also, IL-22 and IL-17 produced by activated Th17 cause epidermal keratinocyte growth as well as abnormal keratinisation. Therefore, the target of psoriasis treatment is epidermal keratinocytes and immune cells, as well as cytokines produced by these cells. The investigational drug in this trial (LEO 90100 foam) contains two active ingredients with different mechanisms of action: a vitamin D_3 analogue and a corticosteroid. The vitamin D_3 analogue (calcipotriol) is mainly targeted at the epidermal keratinocyte, and the corticosteroid (betamethasone dipropionate) targets immune cells (8).

Treatment of psoriasis

Psoriasis vulgaris is a chronic disease for which there is currently no cure. Treatment is targeted at reducing the signs of redness, thickness and scaliness, and associated symptoms such as pruritus. Psoriasis treatments can be divided into three main types: topical treatments, phototherapy and systemic treatments. Each has its own advantages and disadvantages, and several treatment options, for example monotherapy and combination therapy, can be considered in medical practice (9-11). Topical treatment is well-recognised as the first-line medication. Phototherapy [Photochemotherapy (PUVA: psoralen combined with a long-wavelength ultraviolet radiation A, UVA) and middle-wavelength ultraviolet radiation B, UVB (narrow-band or broad-band)] and systemic treatments [such as methotrexate (which is out of insurance-reimbursement in Japan), retinoids and ciclosporin] are generally used in extensive, therapy-resistant and socially disabling disease and in the serious forms of erythro-dermic and pustular psoriasis (3,12). Among the most recently approved therapies in Japan are the biological agents, which reduce the effect of T-cells inducing psoriasis, either by a direct effect on the T-cells or by inhibition of their secreted cytokines. Currently 7 such biological products (adalimumab, infliximab, ustekinemab, brodalumab, secukinumab, ixekizumab and guselkumab) have been approved in Japan for the treatment of moderate to severe psoriasis.

For the first-line therapy of psoriasis, topical corticosteroids and vitamin D_3 analogues (such as calcipotriol, tacalcitol and maxacalcitol) are effective and the two most commonly used therapies for psoriasis vulgaris. Vitamin D_3 analogues do not act as quickly and have to be applied for more than six weeks in order that similar efficacy to corticosteroids can be obtained (13).

“Guidelines of care for the management and treatment of psoriasis with topical therapies” in the US (14) refers to the efficacy of the combination therapy of topical corticosteroids and vitamin D_3 analogues. It is very common in Japan to apply both topical corticosteroids and vitamin D_3 analogues on the same area simultaneously, to make the best clinical use of each drug. The efficacy of the combination therapy of topical corticosteroids and vitamin D_3 analogues in patients with psoriasis vulgaris has been reported by a number of clinical trials performed both in and outside Japan (15-21). In addition to the simultaneous application by patients of topical drugs, combined topical drugs prepared by physicians or pharmacists are often provided to patients in medical practice. Ozawa presented the residual ratio of active vitamin D_3 and corticosteroid after the mixing of various types of topical corticosteroids and vitamin D_3 analogues and indicated that some inappropriate combinations causing degradation of each of the drugs were observed (22). The compatibility of topical vitamin D_3 analogues with topical corticosteroids was also investigated in overseas trials and the results showed

calcipotriol had been degraded substantially when it was mixed with some corticosteroids. This indicates that mixing of vitamin D_3 analogues and corticosteroids without regard for this incompatibility should be avoided (23). In addition, as regards to combined drugs prepared by physicians or pharmacists, there are concerns about potential risk of contamination in preparation and the lack of established standard regimes.

Moreover, the issue that increasingly attracts attention is that topical treatment becomes a source of stress for psoriasis patients due to the time taken to apply it. The stress caused by topical treatment is an important factor contributing not only to the decrease of the patients' quality of life, but also to the reduction of drug compliance and therefore to the clinical effectiveness.

To reduce the patient's burden of topical treatment and realise a significant improvement over the currently available treatment, it is essential to decrease time and frequency required to apply the treatments (24-26). For these reasons, a stable and pre-fixed product of an appropriately combined topical corticosteroid and vitamin D_3 analogue was developed (Dovobet® ointment), and this was approved in 2014 for use in Japan. Also, the gel formulation which contains the same active ingredients at the same concentration as the Dovobet® ointment was approved in February 2018 for use in Japan.

3.2 Experience with Investigational Medicinal Product

In October 2015, LEO 90100 foam was approved in the US as the first country for the topical treatment of plaque psoriasis in patients 18 years of age and older. Overall, the product has been approved in 36 countries, hereof the majority in EU. The foam was launched in US and EU in 2016.

LEO 90100 foam contains the same fixed combination of calcipotriol hydrate 52.2 µg/g (equivalent to 50.0 µg/g calcipotriol) plus betamethasone dipropionate 0.643 mg/g as in the ointment and gel formulations that have been marketed for treatment of psoriasis vulgaris for years. Moreover, both active substances (and the combination thereof) are well established topical treatments for psoriasis.

The safety profile from the marketed combination products (ointment, gel and foam) is based on more than 21,000 subjects involved in LEO Pharma A/S sponsored clinical trials as well as extensive postmarketing experience.

For the ointment and gel formulations, various skin reactions have been reported. The following common and uncommon adverse drug reactions (ADRs) have been reported: pruritus, skin exfoliation, folliculitis, skin infection, skin atrophy, exacerbation of psoriasis,

dermatitis, erythema, rash, purpura or ecchymosis, skin burning sensation, skin irritation, application site pigmentation changes, application site pain, eye irritation, acne and dry skin.

The most frequently reported adverse events (AEs) related to LEO 90100 foam in trials conducted outside Japan were application site reactions. Also, the following uncommon ADRs have been reported: folliculitis, hypersensitivity, hypercalcaemia, skin hypopigmentation, rebound effect, application site pruritus and application site irritation (Investigator's Brochure section 4.8).

The toxicological profiles of calcipotriol and betamethasone dipropionate are well characterised and as expected for the respective drug classes (i.e. vitamin D_3 analogue and corticosteroid).

For Dovobet® ointment, no differences in the safety profile have been observed in Japan during the clinical development programme and postmarketing surveillance compared to overseas.

There has been one trial completed so far with LEO 90100 foam in Japanese subjects (27). Twenty healthy Japanese male adults received LEO 90100 foam and its vehicle as each single application on two sites on their back and the skin irritation and photo irritation were evaluated. As a result, only one AE occurred in one subject in the LEO 90100 foam skin irritation test site, which was assessed as 'only slight erythema' on Day 4. No other safety issues related to LEO 90100 foam or vehicle of LEO 90100 foam were reported. Thus, the results indicate safety of LEO 90100 foam in healthy Japanese male subjects.

3.3 Trial Rationale

As described above, Dovobet® ointment was approved in Japan in 2014 for the treatment of psoriasis vulgaris. Medicated ointments are generally considered to be the most effective type of formulation for the treatment of inflammatory skin disease with dry or scaly skin such as psoriasis. However, patients may consider ointment formulations greasy, messy and time consuming to apply which often results in poor adherence to therapy and a poor treatment outcome.

To meet patient preferences, a foam formulation of Dovobet® (called LEO 90100 foam) was developed. The formulation is expected to be more convenient and less time consuming to apply than an ointment formulation and is therefore expected to have an improved compliance.

The LEO 90100 foam contains the same strength of active pharmaceutical ingredients and excipients as the Dovobet® ointment dissolved in a mixture of the propellants butane and dimethyl ether. The propellants evaporate immediately after application. The foam provides a novel solution for easy and convenient application of topical treatment for psoriasis.

To obtain approval of LEO 90100 foam for treatment of psoriasis in Japan, a clinical development programme is being conducted in Japan and this trial is part of that programme.

This trial will be performed as an open trial because the trial medications are different formulations, and a double-dummy design would be difficult on a practical basis. The trial design and endpoints are similar to those of a similar trial performed in Japan to compare different topical formulations of the same active ingredient (28). In addition to the target lesion, subjects will be instructed to treat any other psoriasis lesions they may have with the trial medication, apart from those on the scalp, face, genitals and skin folds, providing that all lesions are limited to a total area of less than or equal to 30% body surface area (BSA). This is for the convenience of the subjects, as they do not have to use a different medication on lesions other than the target lesion, and to prevent possible accidental use of this different medication on the target lesion which could impact both the efficacy and safety assessments. When the clinical trial for Dovobet® ointment, comparator of this trial, was conducted, scalp was excluded from the application and the evaluation, and Dovobet® ointment was approved based on the data.

Subjects will be provided with 60g of medication per week. Approximately 20.2g of ointment covers the whole body (29). Hence, approximately 6.1g of ointment covers 30% BSA, the maximum area to which medication can be applied in this trial. This is equal to 42.7g per week as the maximum once daily dosage of ointment. Since LEO 90100 foam has the same composition as Dovobet® ointment, with the exception of the propellants, it should be able to cover at least the same area as the ointment. Therefore, 60g per week should be an adequate amount of medication to provide to the subjects.

3.4 Ethical Consideration Statement

The purpose of this trial is to compare LEO 90100 foam and Dovobet® ointment in the treatment of psoriasis in Japanese subjects. The data obtained from this trial will contribute to the development of LEO 90100 foam, a therapy expected to be a useful treatment for psoriasis in the Japanese population.

Even though LEO 90100 foam is a different formulation of the approved product Dovobet® ointment, it contains the same active ingredients at the same concentration and is therefore expected to have a similar safety and efficacy profile. The results of the clinical trials

conducted with Dovobet® ointment in Japan were similar to the results of the clinical trials conducted overseas. Postmarketing surveillance has not revealed any signals indicating a difference between Japanese subjects and non-Japanese subjects.

Subjects participating in the trial will be under the careful supervision of an experienced dermatologist during the entire course of the trial.

Considering the above, this trial is assumed to involve a minimal risk to the participating subjects.

4 Trial Objectives

4.1 Primary Objective

To compare the efficacy of LEO 90100 foam with Dovobet® ointment in the treatment of psoriasis in Japanese subjects.

4.2 Secondary Objectives

To compare the safety of LEO 90100 foam with Dovobet® ointment in the treatment of psoriasis in Japanese subjects.

4.3 Exploratory Objectives

To investigate the subjects' own assessments of the use of LEO 90100 foam compared to previous psoriasis treatments for non-naïve subjects.

5 Trial Endpoints

5.1 Primary Endpoint

The primary endpoint is 'overall improvement rate' for the target lesion at Visit 4 (end of Week 4), defined as 'substantial resolution' of clinical signs or at least 'moderately improved' in the general change in the target lesion. 'Substantial resolution' is defined as a clinical score for thickness and scaliness of 0 and a clinical score for redness of 1 or less in the severity of clinical signs of the target lesion.

5.2 Secondary Endpoints

The 'overall improvement rate' for the target lesion at Visits 2 and 3 (end of Weeks 1 and 2).

The change in the total sign score from Visit 1 to Visit 4; total sign score is defined as the sum of the scores from the 3 clinical signs assessing severity in the target lesion.

The change in the sum of the scores (total sign score) for the severity of the three clinical signs (thickness, scaliness, redness) from Visit 1 to the sum of the scores at Visit 4 (end of Week 4) for the target lesion.

The number of adverse events.

5.3 Exploratory Endpoints

The following will be analysed as exploratory efficacy endpoints.

- The 'substantial resolution' of clinical signs for the target lesion for each visit
- The change in the total sign score for the target lesion from Visit 1 to Visits 2 and 3 (end of Weeks 1 and 2)
- The change in score for the severity of each clinical sign for the target lesion from Visit 1 to each subsequent visit

For those subjects who have previously used topical treatment for their psoriasis, the following will be analysed as exploratory endpoints evaluating subject assessment on the use medication:

- 'time spent for application' compared to the previous treatment (less time, slightly less time, unchanged, slightly more time, more time) at Visit 4 (end of Week 4)
- 'ease of application' (very easy, easy, difficult, very difficult) at Visit 4 (end of Week 4)

Exposure and standard safety data will be analysed as described in sections 11.3.3 and 11.3.8.

6 Trial Design

6.1 Overall Trial Design

A phase 3, national, multi-centre, 4-week, prospective, randomised, controlled, parallel-group, open trial of LEO 90100 foam versus Dovobet® ointment (each containing calcipotriol hydrate 52.2 µg/g [equivalent to 50.0 µg/g calcipotriol] plus betamethasone dipropionate 0.643 mg/g) in Japanese subjects with psoriasis vulgaris.

Screening period

Prior to randomisation at Visit 1, a screening period will be required to ensure that the subject is eligible to participate. The screening period will last for a maximum of 4 weeks and a minimum of 3 days (the latter to allow time for the site to receive the laboratory results from the samples taken at the Screening Visit). Subjects must give written informed consent either

before or at the Screening Visit. Subjects providing informed consent are considered to be enrolled in the trial, and eCRF should be completed for all such subjects.

Treatment period

The treatment period will last for up to 4 weeks. Trial visits will be performed on Day 1 (Visit 1) and after 1, 2 and 4 weeks (Visits 2, 3 and 4). Visit 2 and Visit 3 should be performed within ± 1 day of the scheduled time (Day 7-9 and Day 14-16, respectively), and Visit 4 should be performed within ± 2 days of the scheduled time (Day 27-31), in all cases relative to Visit 1. If they are outside this window, the (sub)investigator should record the reason in the patient's medical record.

At Visit 1, subjects will be randomised to receive treatment with either LEO 90100 foam or Dovobet® ointment. Trial medication will be applied once daily to psoriasis on a target lesion of the body. After this application on the target lesion, subjects will also apply trial medication to any other areas of psoriasis, excluding psoriasis on the scalp, face, genitals, and skin folds (axillae, groin, infra-mammary, those around the buttocks and the perianal area).

On the assessment day of the target lesion (Visit 1, Visit 2, Visit 3 and Visit 4), subject should not apply any topical treatment including emollients on the target lesion before the visit. Showering or bathing should also be avoided.

Subjects with the target lesion achieving 'substantial resolution', as defined in section 5, before the end of 4 weeks' treatment will complete the trial at this time (although they will still be required to attend the follow-up visit up to 14 days later, if applicable; see below).

Follow-up period

Follow up is only required if there is an AE present at the last visit which is of possible or probable relationship to trial medication or is a serious adverse event (SAE). For non-serious AEs of possible or probable relationship to trial medication, the subject will return 14 days after the subject's last visit or when the final outcome has been established, whichever comes first. If the visit is outside this 14-day window, the reason should be recorded in the subject's medical record, but LEO Pharma does not need to be notified. All related and not related SAEs must be followed up until a final outcome has been established, i.e. the follow-up may continue beyond the end of the clinical trial.

Planned date of enrolment of first subject: Q1 2019
Planned date of completion of last subject: Q2 2019
Estimated number of trial sites and country allocation: 20 trial sites in Japan

6.2 Sample Size

A total of 180 subjects will be randomised in a 1:1 ratio to the two treatment groups, i.e. 90 in each treatment group in order to provide at least 80 subjects per group who complete the trial. It is anticipated that approximately 200 subjects will be screened in order to provide 180 randomised subjects.

The sample size is not based on power calculations, but is based on regulatory considerations, as 80 subjects per treatment group is the number that has been used for a similar trial in Japan to compare different topical formulations of the same active ingredient (28).

6.3 Randomisation

Subjects will be randomly assigned to either LEO 90100 foam or Dovobet® ointment in a 1:1 ratio using a randomisation stratified by investigator site.

6.4 Blinding

An open trial will be performed because the trial medications are different formulations, and a double-dummy design would be difficult on a practical basis.

In order to ensure that there is no selection bias in the randomisation of subjects to treatment, sealed envelopes will be used to randomily assign the treatment.

6.5 End of Trial Definition

A subject is considered to have completed the trial if they have completed all periods of the trial, including the last visit or the subjects was cleared, ‘substantial resolution’, of the target lesion as defined in section 5, before the end of 4 weeks’ treatment.

The end of the trial is defined as the date of the last visit of the last subject in the trial.

Final collection of data for the primary endpoint occurs at Week 4.

6.6 Software

CDISC controlled terminology version 22-Dec-2017 was used for definition of controlled terminology used throughout this protocol and will be used for statistical programming and output. SDTM version 3.2 will be used for data tabulations.

7 Trial Population and Withdrawal Criteria

7.1 Subject Eligibility

The (sub)investigator should only randomise subjects who meet all eligibility criteria, are not put at undue risk by participating in the trial and can be expected to comply with the protocol.

The subject's eligibility for the clinical trial must be checked according to the inclusion and exclusion criteria at Visit 1 before randomisation.

Any implementation of national requirements/law for the subject's participation in the clinical trial must be ensured and described in the submission documentation to authorities/IRBs, as applicable.

7.2 Inclusion Criteria

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.
2. Japanese subjects
3. Aged 20 years or above
4. Clinical diagnosis of psoriasis vulgaris amenable to topical treatment of less than or equal to 30% BSA (excluding psoriasis on the face/genitals/skin folds)
5. A target psoriasis lesion on the body, which is of a minimum size of 10 cm^2 and scoring at least 2 (mild) for each of the clinical signs (redness, thickness and scaliness). The lesion must not be on the scalp, face, genitals or skin folds.
6. Females of childbearing potential must have a negative result for a urine pregnancy test at Day 1 (Visit 1) and must agree to use an adequate method of birth control, as judged by the (sub)investigator, during the trial. The contraceptive method should have started an adequate amount of time before the pregnancy test, which is dependent on the particular method used and as judged by the (sub)investigator, and must continue for at least 1 week after the last application of trial medication. 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).
7. Able to communicate with the (sub)investigator and understand and comply with the requirements of the trial.

7.3 Exclusion Criteria

1. Systemic use of biological treatments with a potential effect on psoriasis vulgaris within the following time periods prior to randomisation:

   - etanercept, adalimumab, infliximab, guselkumab, brodalumab – 3 months
   - ustekinumab – 4 months
   - secukinumab – 5 months
   - other products – 3 months/5 half-lives (whichever is longer).

2. Systemic treatments with all therapies other than biological treatments with a potential effect on psoriasis vulgaris (e.g., PDE4i, corticosteroids, vitamin D_3 analogues, retinoids, immunosuppressants such as ciclosporin and methotrexate) within 4 weeks prior to randomisation.

3. PUVA therapy, UVB therapy or UVA therapy on the full body or on the target lesion within 4 weeks prior to randomisation.

4. Topical treatment of psoriasis on the areas to be treated with trial medication within 2 weeks prior to randomisation (use of emollients, and corticosteroids of a strength up to Japanese classification III (strong) on psoriasis lesion other than the target lesion are allowed during this 2-week period, but not after randomisation).

5. Topical treatment of psoriasis on the face, genitals or skin folds with vitamin D_3 analogues (e.g. calcipotriol, tacalcitol, maxacalcitol) Japanese classification I and II (very strong to strongest) corticosteroids or immunosuppressants within 2 weeks prior to randomisation.

6. Topical treatment of conditions other than psoriasis with vitamin D_3 analogues (e.g. calcipotriol, tacalcitol, maxacalcitol), Japanese classification I and II (very strong to strongest) corticosteroids or immunosuppressants within 2 weeks prior to randomisation.

7. Planned initiation of, or changes in, concomitant medication that may affect psoriasis vulgaris (e.g., beta-blockers, antimalaria drugs, lithium and ACE inhibitors) during the trial.

8. Patients with any of the following disorders (a) or symptoms (b) present on the areas to be treated with trial medication: (a) viral (e.g., herpes or varicella) lesions of the skin, fungal, spirochetal or bacterial skin infections, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, rosacea, acne vulgaris, atrophic skin, striae atrophicae, ichthyosis, acne rosacea, ulcers, burns, frostbite, wounds, animal skin disease (scabies, crabs, lice, etc.) or (b) fragility of skin veins.

9. Other inflammatory skin diseases (e.g., seborrhoeic dermatitis, contact dermatitis and cutaneous mycosis) that may confound the evaluation of psoriasis vulgaris.
10. Erythrodermic, exfoliative or pustular psoriasis on the areas to be treated with trial medication.
11. Planned excessive exposure of areas to be treated with trial medication to either natural or artificial sunlight (including tanning booths, sun lamps, etc) during the trial.
12. Known or suspected disorders of calcium metabolism associated with hypercalcaemia, or albumin-corrected serum calcium above the reference range from the sample taken during screening.
13. Known severe renal insufficiency, severe hepatic disorders or severe heart disease that is equivalent to greater than or equal to Grade 3 (CTCAE Ver.5.0, 27-Nov-2017).
14. Known or suspected hypersensitivity to any components of the IMPs.
15. Clinical signs or symptoms of Cushing's disease or Addison's disease
16. Subjects who have received treatment with any non-marketed drug substance (i.e. an agent which has not yet been made available for clinical use following registration) within the 4 weeks prior to randomisation, or longer if the class of substance requires a longer washout as defined in exclusion criterion number 1 for biological treatments.
17. History of cancer within the last 5 years (Except for completely cured skin cancer)
18. Current participation in any other interventional clinical trial
19. Previously randomised in this trial
20. Females who are pregnant, wishing to become pregnant or are breast-feeding
21. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
22. Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.

7.4 Subject Screening Log

The investigator will maintain a log of all subjects considered for screening, whether they have provided written informed consent or not (Subject Screening Log). The log should contain such information as date of screening, subject's age, sex, reason for not enrolled and CRF subject number for enrolled subject. A copy of the log will be provided to the sponsor.

7.5 Subject Identification List

The (sub)investigator must maintain a list of all subjects enrolled at the trial site including each subject's identity, date of enrolment and corresponding subject ID so that any subject may be identified if required for any reason. The list is kept by the investigator and must not be copied to or retained by LEO Pharma.

At enrolment, each subject must be assigned a unique subject ID (eCRF number) to protect the subject's identity and which will be used in lieu of the subject's name when the (sub)investigator reports trial-related data.

7.6 Restrictions during Trial

Use of concomitant treatment must be recorded in the subject's medical record and the eCRF (treatment/drug name, dose, indication and dates of start and stop).

Treatments requiring a washout before Visit 1 are listed below, with the required washout period given in brackets:

- Systemic use of biological treatments with a potential effect on psoriasis vulgaris:
  - etanercept, adalimumab, infliximab, guselkumab, brodalumab (3 months)
  - ustekinumab (4 months)
  - secukinumab (5 months)
  - other products (3 months/5 half-lives, whichever is longer)
- Systemic treatments with all therapies other than biological treatments with a potential effect on psoriasis vulgaris, e.g., corticosteroids, vitamin D_3 analogues, retinoids, immunosuppressants such as ciclosporin and methotrexate (use of systemic antihistamines and nasal and inhaled corticosteroids is allowed) (4 weeks)
- PUVA therapy, UVB therapy or UVA therapy on the full body or on the target lesion (4 weeks)
- Topical treatment of psoriasis on areas to be treated with trial medication (2 weeks), but use of emollients, and weak to strong corticosteroids (Japanese Classifications V and III) on psoriasis lesion other than the target lesion are allowed.
- Topical treatment of other areas with vitamin D_3 analogues (e.g. calcipotriol, tacalcitol, maxacalcitol), immunosuppressants, very strong to strongest corticosteroids (Japanese Classifications I and II) (2 weeks).
- Treatment with any non-marketed drug substance, i.e. an agent which has not yet been made available for clinical use following registration (4 weeks, or longer if the class of substance requires a longer washout as defined above for biological treatments).

Treatments which cannot be used during the trial (Visits 1-4) are the same as those requiring a washout, as listed previously, with the addition that the following are not allowed:

- Use of an emollient on areas to be treated with trial medication
- Initiation of, or changes in, concomitant medication that may affect psoriasis vulgaris (e.g., beta-blockers, antimalaria drugs, lithium and ACE inhibitors)
- Excessive exposure of areas treated with trial medication to either natural or artificial sunlight (including tanning booths, sun lamps, etc)

Hence, during the trial (Visits 1-4), psoriasis lesions will be treated with the trial medication, apart from those on the scalp, face, genitals and skin folds. For treatment of psoriasis lesions on the scalp, corticosteroids up to a 'very strong' classification (Japanese classification II) are allowed. Bath oils, moisturizing soaps, nasal antihistamines are allowed.

During the follow-up period, there are no restrictions on the use of concomitant treatment.

7.7 Withdrawal Criteria

Subjects **may** withdraw from the trial for any of the following reasons:

1. *Unacceptable treatment efficacy:* the (sub)investigator is free to withdraw the subject at any time based on a medical judgement.
2. *Unacceptable AEs:* any AE that the (sub)investigator or the subject considers unacceptable.
3. *Exclusion criteria:* any exclusion criteria which emerge/become apparent during the subject's participation in the clinical trial.
4. *Voluntary withdrawal:* subjects are free to withdraw from the clinical trial at any time and for any reason.
5. *Other reasons:* other reasons than stated above which require the subject to (be) withdraw(n) should be specified.

Subjects **must** be withdrawn if they are found to have become pregnant.

Subjects with the target lesion achieving 'substantial resolution', as defined in section 5, before the end of 4 weeks' treatment will complete the trial at this time (although will still be required to attend the follow-up visit up to 14 days later if applicable)

Subjects who are discovered, after randomisation, not to have fulfilled all inclusion/exclusion criteria at the time of randomisation, should be withdrawn from treatment unless the (sub)investigator finds withdrawal inappropriate, based on clinical and ethical evaluation.

Reason(s) for withdrawal will be recorded in the eCRF. Withdrawn subjects will not be substituted.

Completion of trial is defined as:

A subject who attends Visit 4 on Day 29 or later

or

A subject who attends Visit 4 earlier than Day 29, but the reason for attending earlier than Day 29 is not because (a) the (sub)investigator wishes to withdraw the subject, or (b) the subject wishes to withdraw

or

Subjects with the target lesion achieving ‘substantial resolution’, as defined in section 5, before the end of 4 weeks treatment.

8 Trial Schedule and Assessments

8.1 Schedule of Trial Procedures

Visits	**Screening**	**1**	**2**	**3**	**4/EoT**	**Unscheduled/early withdrawal**	**Follow up[d]**
Days	**-28 to -3[a]**	**1**	**8**	**15**	**29**		**Up to +14**
Visit Window[e]	**-**	**-**	**+/- 1**	**+/- 1**	**+/- 2**		**-**
Informed consent	x						
Demographics/baseline characteristics	x						
Medical history/concurrent diagnoses	x						
Concurrent procedures	x	x	x	x	x	x	x
Concurrent medication	x	x	x	x	x	x	x
Selection of a target lesion	x						
Laboratory assessment	x	x			x	x	
Adverse events	x	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x	x
Pregnancy test[b]		x			x	x	
Inclusion/exclusion criteria check	x	x					
Randomisation		x					
Investigator's assessment – sign score of target lesion		x	x	x	x	x	
Investigator's assessment – general change in target lesion			x	x	x	x	
Subject's assessment: time spent for application[f]					x	x	
Subject's assessment: ease of application[f]					x	x	
Supply IMP		x	x	x			
Collect unused IMP			x	x	x	x	
Compliance check			x	x	x	x	
Completion of End of trial form	x[c]				x	x[c]	

a The minimum time between Screening Visit and Visit 1 is 3 days

b For females of child-bearing potential

c For screening failures and early withdrawals only

d Follow-up only if ongoing related AEs present at last on-treatment visit; to be done 14 days after this visit, or when final outcome established, whichever comes first

e Relative to Visit 1

f Compared to previous topical treatment

8.2 Informed Consent

The subject must provide signed and dated informed consent before any trial related activity is carried out, including activities relating to the screening period such as washout. The End of Trial form in the eCRF must be completed for all subjects who have signed the informed consent.

8.3 Demographics and Baseline Characteristics

Date of birth, sex, height, weight, duration of psoriasis and concurrent diagnoses will be recorded at the Screening Visit.

8.3.1 Medical History

Relevant medical history must be recorded:

- Skin disease history: all past and current skin disease history should be collected for each diagnosis within the previous 12 months; the start date and stop date will be recorded (it will also be recorded if the diagnosis is ongoing). For topical treatments, record whether the disease has been present in the current treatment area.
- Other medical and surgical history including concurrent diagnoses within the previous 12 months. For each condition, diagnosis or surgical procedure, the start date and stop date will be recorded (it will also be recorded if the condition, diagnosis or surgical procedure is ongoing).

Relevant medical history also includes diseases which are specifically listed as exclusion criteria and diseases for which specific treatments are listed as exclusion criteria.

8.4 Concurrent Medication and Concurrent Procedures

Concurrent medication will be recorded at the Screening Visit (treatment/drug name, dose, indication and dates of start/stop). Any changes in concurrent medication will be recorded at subsequent visits.

Similarly, any concurrent procedure must also be recorded in the subject's medical record and the eCRF. The following details will be recorded: procedure, body location, diagnosis, and start and stop date (it will also be recorded if the procedure is ongoing).

8.5 Selection of Target Lesion

A target lesion on the body will be selected at the Screening Visit. The location of the target lesion will be recorded in the eCRF as trunk, arm excluding elbow, leg excluding knee, elbow or knee. Location of the lesion will be specified in more detail in the subject records to allow identification of the lesion at subsequent visits. The target lesion will be assessed again at Visit 1, when the inclusion/exclusion criteria are checked, in order to check whether it meets the necessary requirements for size and severity at this time (see section 8.10).

8.6 Laboratory Assessments

A total of 4.5 mL of venous blood and a urine sample will be taken at the Screening Visit, Visit 1 and at Visit 4, hence 13.5 mL of blood in total for the trial. If a subject withdraws from or completes the trial at Visits 2 or 3, samples should be taken at this time in lieu of the Visit 4 samples. The samples will be analysed for the following parameters:

Haematology, whole blood
Haemoglobin, haematocrit, platelets, RBC count, WBC count, HbA1c

Chemistry, serum
Calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total bilirubin, total protein, albumin, SGOT (AST), SGPT (ALT), GGT, LDH, alkaline phosphatase.

Urine, semi-quantitatively
Urine Glucose, urine protein

The central laboratory will provide the material and instructions necessary for the collection and transport of the samples, analyse the samples.

If any laboratory results are clinically abnormal, the (sub)investigator should follow-up the subject as clinically appropriate. Any laboratory abnormality assessed as clinically significant by the (sub)investigator must be recorded as an AE in eCRF.

8.7 Adverse Events

AEs must be assessed and recorded as specified in section 9.

8.8 Physical Examination

A physical examination will be performed from Screening Visit to follow-up. If a subject withdraws from or completes the trial at Visits 2 or 3, the examination should be made at this

time in lieu of the one at Visit 4. The extent of the physical examination will be at the discretion of the (sub)investigator and will include general appearance and dermatological examination of the skin. Any abnormal findings will be recorded.

8.9 Pregnancy Test

A urine pregnancy test will be performed at the trial site at Visit 1 (prior to randomisation) and Visit 4 in female subjects of child-bearing potential. If a subject withdraws from or completes the trial at Visits 2 or 3, the test should be done at this time in lieu of the one at Visit 4. The test kits will be provided by the central laboratory.

8.10 Inclusion/Exclusion Criteria

Subjects' eligibility for the clinical trial will be checked during screening and re-checked at Visit 1 before randomisation (when results of laboratory test at screening are available). After results of laboratory test at Visit 1 becomes available and if any clinically significant abnormality which meets exclusion criteria is found, the subject will be withdrawn from the trial (see section 7.7).

8.11 Randomisation

Subjects will be randomised at Visit 1 when all inclusion/exclusion criteria are satisfied, as specified in section 10.6.

8.12 Investigator's Assessment of Target Lesion

The (sub)investigator must make the following assessments of the target lesion. All assessments for a subject should be made by the same (sub)investigator. In case the same (sub)investigator is not able to assess the same subject, measures should be taken at the site ensure consistent assessments by the (sub)investigators.

Severity of clinical signs of target lesion

The severity will be recorded for each of the signs of redness, thickness and scaliness at Visits 1-4, according to the 9-point scales below:

Redness		
0	=	none (no erythema)
0.5*		
1	=	slight (faint erythema, pink to very light red)
1.5*		
2	=	mild (definite light red erythema)

2.5*
3 = moderate (dark red erythema)
3.5*
4 = severe (very dark red erythema)

Thickness
0 = none (no plaque elevation)
0.5*
1 = slight (slight, barely perceptible elevation)
1.5*
2 = mild (definite elevation but not thick)
2.5*
3 = moderate (definite elevation, thick plaque with sharp edge)
3.5*
4 = severe (very thick plaque with sharp edge)

Scaliness
0 = none (no scaling)
0.5*
1 = slight (sparse, fine scale, lesions only partially covered)
1.5*
2 = mild (coarser scales, most of lesions covered)
2.5*
3 = moderate (entire lesion covered with coarse scales)
3.5*
4 = severe (very thick coarse scales, possibly fissured)

* intermediate intervals (0.5, 1.5, 2.5, 3.5) are to serve as mid-points between the defined grades (0, 1, 2, 3, 4). See 'Appendix 9: Descriptors for intermediate intervals in severity score of clinical signs of target lesion' which shows descriptors for the intermediate intervals for the purposes of data coding.

General change in target lesion

At Visits 2-4, the general change in the target lesion from Visit 1 will be recorded according to the 5-point scale below.

Markedly improved	+++	A very definite improvement (approx. 75% or more)
Moderately improved	++	A definite improvement (approx. 50%)
Slightly improved	+	Some definite improvement (approx. 25%), however, significant signs remain
Unchanged	+/-	No change
Aggravated	-	Worsened

8.13 Subject's Assessments

At Visit 4, the subject will make the following assessments. If a subject withdraws from or completes the trial at Visits 2 or 3, the assessment should be done at this time in lieu of the one at Visit 4.

Time spent for application, scored as less time, slightly less time, unchanged, slightly more time, more time as compared to previous topical treatments.

Ease of application, scored as very easy, easy, difficult, very difficult as compared to previous topical treatments.

8.14 Supply/Return of IMP and Compliance

Refer to sections 10.7.1 and 10.7.3

9 Adverse Events

- AEs and SAEs are defined in Appendix 3: Definitions of Adverse Events and Serious Adverse Events.
- Classification of AEs in terms of severity, causality and outcome are defined in Appendix 4: Classification of Adverse Events.

9.1 Collection of Adverse Events

AEs must be collected from the signing of the informed consent form until the last trial visit.

AEs must be assessed by (sub) investigators who are medically qualified.

At all visits, the (sub)investigator should ask the subject a non-leading question to the effect of: "How have you felt since I saw you last?" No specific symptoms should be asked for. It is important that the (sub)investigator also observes the subject for any changes not reported by the subject and records these changes.

If there are no AEs to record, no further questions should be asked and "NO" should be ticked in the eCRF. In case there are one or more AEs to record, "YES" should be ticked.

9.2 Reporting of Adverse Events in the eCRF

AEs reported by the subject or observed by the (sub)investigator must be recorded on the AE form of the eCRF and should be described in the following manner:

The *AE term* will be in precise English medical terminology (i.e. not necessarily the exact words used by the subject). Whenever possible, a specific diagnosis should be stated (e.g. allergic contact dermatitis).

For cutaneous AEs, the *location* must be part of the AE description and will be described as either:

- lesional/perilesional (≤ 2 cm from the border of lesion(s) treated with IMP), or
- distant (>2 cm from the lesion border)

The *duration* of the AE must be reported as the start date and stop date of the event (it will also be recorded if the event is ongoing). In addition, it must be recorded whether the AE started prior to start of trial medication.

AEs must be classified in terms of severity, causality and outcome according to the definitions in Appendix 4: Classification of Adverse Events.

9.2.1 Actions Taken as a Consequence of an AE

Action taken with trial treatment: Any action taken with trial medication as a consequence of the AE must be recorded (dose not changed, dose reduced, dose increased, drug interrupted, drug withdrawn, not applicable, unknown).

Other action taken: Any other action taken as a result of the AE must be recorded (none, concomitant medication, concurrent procedure).

Withdrawn due to AE: It must be recorded whether the AE leads to withdrawal from the trial.

9.3 Other Events to be Reported

9.3.1 Pregnancy

Any pregnancy occurring after first exposure to IMP and until the subject has completed the trial must be reported to LEO Pharma K.K. within 24 hours of first knowledge using the (paper) Pregnancy Form (Part I). All such pregnancies must be followed up until delivery or

termination and final outcome must be reported on the (paper) Pregnancy Form (Part II) within 24 hours of first knowledge.

The completed Pregnancy Forms must be faxed or scanned and e-mailed to LEO Pharma K.K. using the following fax number or e-mail address:

Fax number: +81 3 6735 7767
E-mail address: drug.safetyjp@leo-pharma.com

Please also confer with section 7.7, Withdrawal Criteria.

9.3.2 Overdose

An overdose is defined as a subject receiving a quantity of IMP per administration or per week which is in excess of that specified in this protocol. An overdose is either accidental or intentional.

For Dovobet® ointment and LEO 90100 foam, overdose is defined as application of >90g/week, based upon the package insert of the already marketed Dovobet® ointment.

The term ‘overdose’ including a specification of why it occurred (accidental or intentional) must be recorded on the AE form of the eCRF. In addition, AEs originating from overdose must be recorded as separate events. If the AE originating from the overdose qualifies as an SAE, expedited reporting is required (Section 9.4).

If the overdose is accidental and due to a device deficiency, the device deficiency must be reported as a product complaint as described in Section 10.9.

9.3.3 Medication Error

Medication error refers to any unintentional error in the dispensing or administration of a medicinal product while in the control of the (sub)investigator or subject. Broadly, medication errors fall into four categories: wrong medication, wrong dose (including strength, form, concentration, amount), wrong route of administration or wrong subject.

The medication error must be documented on the AE form of the eCRF. In addition, AEs originating from a medication error must be documented on a separate line specifying the category of error (see definitions above).

If the medication error is due to a device deficiency, the device deficiency must be reported as a product complaint as described in Section 10.9.

9.3.4 Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

The term ‘misuse’ must be documented on the AE form of the eCRF. In addition, AEs originating from misuse must be documented on a separate line. If the AE originating from misuse qualifies as an SAE, expedited reporting is required (Section 9.4).

9.3.5 Abuse

Abuse relates to the sporadic or persistent, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects.

The term abuse must be documented on the AE form of the eCRF. In addition, AEs originating from abuse must be documented on a separate line.

9.3.6 Aggravation of Condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s), compared to baseline, must be reported as an AE.

9.4 Additional Reporting Requirements for Serious Adverse Events

9.4.1 Investigator Reporting Responsibilities

Any SAE must be reported to LEO Pharma K.K on the LEO Serious Adverse Event Form (paper) - Clinical Trials within 24 hours of first knowledge.

This report should contain an assessment of available information on seriousness, severity, causal relationship to the IMP, comparator or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

The completed SAE form must be faxed or scanned and e-mailed to LEO Pharma K.K. using the following fax number or e-mail address:

Fax number: +81 3 6735 7767
E-mail address: drug.safetyjp@leo-pharma.com

It may be relevant for the (sub)investigator to enclose other information with the SAE form, such as anonymised reports of diagnostic procedures, hospital records, autopsy reports, etc.

Additionally, Global Safety, LEO Pharma A/S may request further information in order to fully assess the SAE. The (sub)investigator must forward such information to Global Safety, LEO Pharma A/S via LEO Pharma K.K. upon request by fax or e-mail (see contact details above).

The investigator must report SAEs to the director of the trial site. The director of the trial site must notify the local IRB(s) of SAEs as required by current applicable legislation for the concerned country.

SAEs occurring after the completion of the clinical trial, including the protocol required post-treatment follow-up period, should not be routinely sought or collected. However, such events should be reported to LEO Pharma K.K. if the (sub)investigator becomes aware of them.

9.4.2 LEO Pharma Reporting Responsibilities

Global Safety, LEO Pharma A/S is responsible for assessing whether or not a SAE is expected. The relevant reference document for those randomised to LEO 90100 foam is the current version of the Investigator's Brochure for LEO 90100 foam. For those randomised to Dovobet® ointment, the relevant reference document is the Japanese package insert for Dovobet® ointment.

Global Safety, LEO Pharma A/S and LEO Pharma K.K. (collectively called as 'LEO Pharma') will notify the regulatory authorities and concerned investigators of SAEs according to the current applicable legislation for the concerned country.

The IRB(s) will be notified of SAEs according to the current applicable legislation for the concerned country. For Japanese sites, the investigator and LEO Pharma K.K. will be notified of the IRB review outcome by the director of the trial site.

All SAEs which are assessed as causally related to the IMP(s) by either the investigator or LEO Pharma A/S, and which are not expected (Suspected, Unexpected Serious Adverse Reactions (SUSARs)) are subject to expedited reporting to regulatory authorities and IRB(s) according to the current applicable legislation in the concerned country. Investigators will be notified of these on an ongoing basis. In addition, in Japan all SAEs which are assessed as causally related to the IMP(s) by either the investigator or LEO Pharma A/S and are subject to expedited reporting in Japan, will be reported to regulatory authorities, IRB(s) and investigators according to the current applicable legislation in Japan.

9.5 Follow-up for Final Outcome of Adverse Events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as of possible/probable relationship to the IMP for 14 days or until the final outcome is determined, whichever comes first. All related and not related SAEs must be followed up until a final outcome has been established, i.e. the follow-up may continue beyond the end of the clinical trial.

9.6 Handling of an Urgent Safety Measure

An Urgent Safety Measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined within the EU Directive as "*...the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.*" (Article 10(b) of Directive 2001/20/EC).

If the investigator becomes aware of information that necessitates an immediate change in the clinical trial procedure or a temporary halt to the clinical trial in order to protect clinical trial subjects from any immediate hazard to their health and safety, the investigator can do so without prior approval from LEO Pharma, regulatory authority(ies) or IRB(s).

The investigator must immediately inform LEO Pharma K.K. of this change in the clinical trial procedure or of the temporary halt providing full details of the information and the decision making process leading to the implementation of the urgent safety measure.

LEO Pharma K.K. must act immediately upon receipt of the urgent safety measure notification in accordance with the internal procedures and local legislation.

10 Investigational Medicinal Products

10.1 Investigational Medicinal Product Description

Finished product (brand) name (if available)/name of IMP	LEO 90100 foam
Formulation	Foam
Active ingredient name/concentration	Calcipotriol hydrate 52.2 µg/g (equivalent to 50.0 µg/g calcipotriol) plus betamethasone dipropionate 0.643 mg/g
Excipients	Paraffin, white soft Paraffin, liquid Polyoxyproylene stearyl ether All-rac-alpha-tocopherol Propellants: Dimethyl ether Butane
Pack size	60 g can
Sites involved in manufacturing, labelling or release	• LEO Laboratories Ltd, 285 Cashel Road, Crumlin, Dublin 12, Ireland • LEO Pharma A/S, Industriparken 55 2750 Ballerup, Denmark • Colep Laupheim GmbH & Co. KG, Fockestraβe 12, 88471 Laupheim, Germany • Klifo A/S, Smedeland 36, DK 2600 Glostrup, Denmark

Finished product (brand) name (if available)/name of IMP	Dovobet® ointment
Formulation	Ointment
Active ingredient name/concentration	Calcipotriol hydrate 52.2 µg/g (equivalent to 50.0 µg/g calcipotriol) plus betamethasone dipropionate 0.643 mg/g
Excipients	Paraffin, white soft Paraffin, liquid Polyoxyproylene stearyl ether All-rac-alpha-tocopherol
Pack size	30g tube
Sites involved in manufacturing, labelling or release	• LEO Laboratories Ltd, 285 Cashel Road, Crumlin, Dublin 12, Ireland • LEO Pharma A/S, Industriparken 55 2750 Ballerup, Denmark • Klifo A/S, Smedeland 36, DK 2600 Glostrup, Denmark

10.2 Administration of Investigational Medicinal Products

Route of administration	Topical
Dosing range	Depending on the size of psoriasis lesion
Dosing frequency	Once daily
Weekly maximum	60g

The instructions for use, as detailed on the subject treatment instructions, are as follows:

For subjects receiving tubes:

- Remove the cap and break the seal of the tube using the point in the back of the cap. Turn the cap round while still pushing to create a round hole.
- Squeeze the ointment onto a clean finger
- Apply with the fingertips

For subjects receiving cans:

- Keep the cans in the supplied outer carton, to protect from light.
- The can should be shaken for a few seconds before use.
- Application can be performed by either applying after spraying directly on the affected areas or by spraying in the palm and applying on to the affected areas with the fingertips.
- Use enough to cover each lesion. Apply gently with fingertips
- Apply the study medication by holding the spray can at least 3cm from the skin and spray.

For both groups of subjects:

- Apply the trial medication to psoriasis once daily.
- Apply trial medication first to the 'target lesion', as instructed by the trial doctor, and then apply to other lesions to the extent possible for lesions that may be hard to reach, namely on the back.
- Take care not to spread the medication onto unaffected skin
- Avoid accidental contact to the face, eyes or mouth
- Wash hands after each application
- Do not use the trial medication on any psoriasis on the face, scalp, genitals or skin folds (armpits, groin, under the breasts, those around the buttocks and the perianal area)
- Do not use any other treatments on psoriasis, apart from medication which the (sub)investigator may prescribe for use on psoriasis on the face, scalp, genitals or skin folds
- If taking a bath/shower or washing hair around the time of medication application, apply the medication afterwards (to avoid washing it off). However, do not apply trial

medication or emollients on the target lesion before coming to the site on the day of the Visits.
- Do not bandage or otherwise cover or wrap the treated areas
- Avoid excessive exposure of treated areas to either natural or artificial sunlight (including tanning booths, sun lamps, etc.)
- Keep the medication out of the sight and reach of children and pets
- The medication is for external use only
- Return all medication at each visit
- After applying, avoid contact with textiles which are easily stained by grease, e.g. silk

The subject treatment instructions will be explained to the subject at Visit 1, and the subject will be given a copy. A subject trial card will also be given out at Screening visit.

Subjects with the target lesion achieving 'substantial resolution', as defined in section 5, before the end of 4 weeks' treatment will complete the trial at this time (although will still be required to attend the follow-up visit up to 14 days later, if applicable).

10.3 Precautions/Over dosage

Calcipotriol

Calcipotriol may cause hypercalcaemia. Serum calcium is quickly normalised, however, when treatment is discontinued. In addition, calcipotriol may cause decline in kidney function associated with hypercalcaemia. The major symptoms of hypercalcaemia include malaise, feelings of weakness, anorexia, nausea, vomiting, enlarged feeling of abdomen, abdominal pain, headache, dizziness, muscle pain and muscle weakness.

Betamethasone dipropionate

AEs found in connection with systemic corticosteroid treatment, such as adrenocortical suppression or impact on the metabolic control of diabetes mellitus, may occur also during topical corticosteroid treatment due to systemic absorption.

There may be a risk of generalised pustular psoriasis or of rebound effects when discontinuing treatment. Medical supervision should therefore continue in the post-treatment period.

10.4 Packaging of Investigational Medicinal Products

The IMPs will be packaged in individually numbered kits. Primary and secondary packaging materials will be individually labelled. The details of the primary and secondary packaging are described in the trial product manual.

The labelling of IMPs must be in accordance with EU GMP Annex 13, local regulations and trial requirements.

10.5 Storage of Investigational Medicinal Products

All LEO Pharma supplied IMPs must be stored in a secure and restricted area under the conditions specified on the label. At the investigational site, they should not be stored above 30°C, and not stored in a freezer. IMPs must remain in the original container until dispensed. The cans of LEO 90100 foam must be dispensed to the subject in the carton each can is supplied in, in order to protect it from light.

10.6 Treatment Assignment and Dispensing

At Visit 1, subjects who have been found to comply with all the inclusion and exclusion criteria will be randomised to receive treatment with either LEO 90100 foam or Dovobet® ointment. Treatment assignment will be pre-planned according to a computer-generated randomisation schedule in a 1:1 ratio, stratified by investigator site. Randomisation will be performed by a sealed envelope method at site. After confirming subject's eligibility criteria, (sub)investigator opens only the corresponding envelope that contains treatment assignment in the predefined order, i.e. by specifying which of the two treatments the subject should receive. The person who opened the envelope writes the date, time and name on the envelope. The site can then choose any available outer box with the assigned medication for the subject. Full details of this randomisation procedure will be given in a separate document.

From this outer box, IMP is dispensed to the subject at Visits 1, 2 and 3. At Visit 1, the carton labelled 'Week 1' is dispensed. At Visit 2, the carton labelled 'Week 2' is dispensed. At Visit 3, the cartons labelled 'Week 3' and 'Week 4' are dispensed, and the subject should be instructed to use the medication labelled 'Week 3' for the next week, and then the medication labelled 'Week 4' for the subsequent week.

At Visits 2, 3 and 4, the medication dispensed at Visits 1, 2 and 3, respectively, should be returned by the subject, including any empty cans/tubes, and retained by the site for collection.

10.6.1 Randomisation Code List

The randomisation schedule will be prepared by LEO Pharma A/S or CRO. It must not be provided to investigator site staff.

10.7 Drug Accountability and Compliance Checks

10.7.1 Drug Accountability

The director of the trial site is fully responsible for the IMPs at the trial site and the IMP administrator is responsible for maintaining adequate control of the IMPs and for documenting all transactions with them in Trial Medication Inventory Log.

At Visit 2, 3 and 4, the IMP (including empty containers) dispensed at Visits 1, 2 and 3, respectively, must be returned by the subject. An inventory at subject level must be kept of the IMP given to and returned by each subject in the trial. This inventory must be available for inspection during monitoring visits and will be checked by the monitor to ensure correct dispensing of the IMP.

All IMPs supplied by the Contract Manufacturing Organisation (CMO) on behalf of LEO Pharma must be returned to the CMO. Prior to their return, they must be fully accounted for by the monitor with the help of the person responsible for dispensing the IMPs. Accountability must be documented by using drug accountability forms. IMPs will be returned from the trial site to the CMO. The IMP returned to the CMO will be reconciled with the Trial Medication Inventory Log.

10.7.2 Investigational Medicinal Product Destruction

Used and unused IMPs will be destroyed by the CMO according to LEO Pharma procedures.

10.7.3 Treatment Compliance

At Visits 2, 3 and 4, the subject should be asked if she/he has used the IMP as prescribed. If a subject is found to be non-compliant, the (sub)investigator should remind the subject of the importance of following the instructions given including using the trial products as prescribed. The degree of non-compliance (number of applications missed, or other deviation) and the reason for it must be recorded in the eCRF. Subjects will be provided with a diary for recording of this information.

10.8 Provision for Subject Care following Trial Completion

In order to ensure appropriate treatment of the subjects after they have completed the trial, the subjects will be treated at the investigator’s discretion or referred to other physician(s) according to standard practice.

10.9 Reporting Product Complaints

Any defects or issues with the IMP must be reported to LEO Pharma K.K. on the trial specific (paper) Complaint Form within 3 days of first knowledge.

Critical complaints (defined as any defect or issue that has or potentially could have a serious impact for the subject [e.g., SAE]) must be reported to LEO Pharma K.K. within 24 hours of first knowledge.

Complaint forms should contain a detailed description of the defect or issue, including whether it led to an AE. (S)AEs which occur due to a defect or issue with the IMPs will be reported by the investigator as described in sections 9.2 and 9.4.

During the investigation of the product complaint, the IMP(s) must be stored at labelled conditions unless otherwise instructed; the trial site will be notified whether the IMP(s) needs to be returned for further investigation or may be destroyed.

LEO Pharma K.K. contact information for reporting product complaints:

Fax number: +81 3 6735 7767
E-mail address: drug.safetyjp@leo-pharma.com

10.10 Emergency Unblinding of Individual Subject Treatment

Not applicable as this trial is open-label.

11 Statistical Methods

11.1 Determination of Sample Size

The sample size is not based on power calculations (section 6.2), but is based on regulatory considerations, as 80 subjects per treatment group is the number that has been used for a similar trial in Japan to compare different topical formulations of the same active ingredient (28).

11.2 Definition of Trial Analysis Sets

All subjects enrolled in the trial (i.e. subjects for whom informed consent has been obtained and who have been registered in a clinical trial) will be accounted for in the clinical trial report.

All randomised subjects are included in the full analysis set and will be analysed for efficacy. Exclusions from the full analysis set can be considered in special cases as described in ICH

E9, section 5.2.1., Full Analysis Set. Any exclusion of subjects from the full analysis set will be justified.

A per protocol analysis set will be defined by excluding subjects from the full analysis set who had less than 75% compliance or based on a review of protocol deviations with justification.

A safety analysis set will be defined by excluding randomised subjects who either received no treatment with IMP and/or for whom no post-baseline safety evaluations are available.

The decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented in the analysis set definition document.

11.3 Statistical Analysis

11.3.1 Disposition of Subjects

The reasons for leaving the trial will be presented for all randomised subjects by last visit attended and by treatment group.

11.3.2 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects and by treatment group.

Demographics include age and sex. Other baseline characteristics include height, weight, BMI, duration of psoriasis, baseline severity of clinical signs, location of target lesion on the body, concurrent diagnoses (including indications for concomitant medication) and concomitant medication.

Presentations of age, sex, and baseline severity of clinical signs by treatment group will also be given by site.

11.3.3 Exposure and Treatment Compliance

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

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

The percentage of missed applications will be allocated to one of the following categories: ≤10%, >10% to ≤25%, >25% to ≤40%, >40% to ≤50%, >50%.

11.3.4 Analysis of Primary Efficacy Endpoint

The primary endpoint, as defined in section 5, will be analysed for the full analysis set and for the per protocol analysis set. The analysis using the full analysis set will be regarded as primary, while the per protocol analysis set will act as supportive.

Rates of subjects with the event defined by the primary endpoint, 'overall improvement rate' for the target lesion at Visit 4 (end of Week 4), will be compared between treatment groups by means of Fisher's exact test. Estimated rates, odds ratio and its 95% CI will be presented, together with the p-value from Fisher's exact test. The number and percentage of subjects with the event will be tabulated for each treatment group and also presented for each site by treatment group.

11.3.5 Analysis of Secondary Efficacy Endpoints

The secondary endpoints, as defined in section 5, will be analysed for the full analysis set and for the per protocol analysis set. The analysis using the full analysis set will be regarded as primary, while the per protocol analysis set will act as supportive.

The number and percentage of subjects with 'overall improvement rate' will be tabulated for Visits 2 and 3 (end of Weeks 1 and 2) and by treatment group.

Descriptive statistics for observed values and change from baseline to Visit 4 (end of Week 4) for the total sign score for the target lesion will be summarised as mean, SD, median, minimum and maximum values for each treatment group.

In addition, for the change in the total sign score, the estimated difference between the treatment groups in the mean change (LEO 90100 foam group – Dovobet® ointment group) will be calculated with 95% confidence interval. The treatment difference of the change in the total sign score at Visit 4 will be estimated with an ANOVA with treatment as fixed effect.

11.3.6 Exploratory Analysis of Efficacy

The following will be tabulated for the full analyses set.

The number and percentage of subjects with 'substantial resolution' of clinical signs for the target lesion will be tabulated by visit and treatment group.

The general change in target lesion will be tabulated by treatment group and visit. The clinical signs for the target lesion from baseline to all subsequent visits will be tabulated by treatment group, as both the number and percentage of subjects in each category (markedly improved, moderately improved, slightly improved, unchanged and aggravated). Further, the number and percentage of subjects with a change of 'moderately improved' or better will be tabulated by treatment group and visit.

The change in total sign score for the target lesion from baseline to Visits 2 and 3 (end of Weeks 1 and 2) by treatment will be summarised as mean, SD, median, minimum and maximum values.

The change in score for the severity of each clinical sign for the target lesion from baseline to each subsequent visit by treatment will be summarised as mean, SD, median, minimum and maximum values. In addition, the estimated difference between the treatment groups (LEO 90100 foam group – Dovobet® ointment group) in the mean change from baseline to Visit 4 (end of Week 4) will be calculated for each clinical sign with 95% confidence interval.

11.3.7 Exploratory Analysis of Subject Assessments

The number and percentage of subjects in each category for 'time spent for application' (less time, slightly less time, unchanged, slightly more time, more time) and 'ease of application' (very easy, easy, difficult, very difficult) will be tabulated at Visit 4 (end of Week 4) by treatment group.

In addition, a difference between the two treatment groups will be calculated for each subject assessment with odds ratio and 95% confidence interval.

11.3.8 Analysis of Safety

The analysis of safety will be based on the safety analysis set.

11.3.8.1 Adverse Events

AEs will be coded during the course of the trial according to MedDRA. AEs will be presented by preferred terms and primary system organ class.

Only treatment emergent AEs will be tabulated but all AEs recorded during the course of the trial will be included in the subject data listings. An event will be considered emergent with the trial treatment if started after the first application of IMP or if started before the first

application of IMP and worsened in severity thereafter. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary system organ class.

An overall summary of AEs and number (percentage) of subjects with any AEs, SAEs, premature discontinuations from the trial due to AEs, treatment related AEs and AEs stratified by severity will be presented.

The number of AEs and number (percentage) of subjects for each type of AE will be tabulated by treatment group. A similar tabulation will be made for AEs stratified by severity.

The causal relationship to trial medication for each type of AEs will be tabulated by treatment group. Where there are several recordings of causal relationship to the IMP for a given type of AE for a subject, causal relationship will be taken as the most-related recording from the last report of that AE, since that is when the (sub)investigator will be in possession of most information and so best able to judge causal relationship.

Related AEs are defined as AEs for which the (sub)investigator has not described the causal relationship to IMP as ‘not related’. The number of subjects experiencing each type of related AE will be tabulated regardless of the number of times each related AE is reported by each subject.

Cutaneous AEs will be tabulated, similarly stratified as ‘lesional/perilesional’ or ‘distant’.

SAEs will be evaluated separately and a narrative for each will be given.

AEs leading to withdrawal from trial or discontinuation of IMP will be listed.

11.3.8.2 Clinical Laboratory Evaluation

The observed values and change from baseline in each of the haematology and chemistry laboratory parameters will be summarised as mean, geometric mean, coefficient of variation, SD, median, minimum and maximum values.

The haematology and chemistry laboratory parameters will also be classified as ‘low’, ‘normal’ or ‘high’, depending on whether the value is below, within or above the reference range, respectively. Urine glucose and protein will be classified as ‘absent’ or ‘present’. Shift tables will be produced showing the categories at Visit 1 (baseline) against those at Visit 4 (end of Week 4).

Laboratory parameters outside the reference range will be indicated in the subject data listings.

11.3.9 Interim Analysis

No interim analyses are planned.

11.3.10 General Principles

All significance tests will be two-sided using the 5% significance level. All confidence intervals will be presented with 95% degree of confidence.

An observed cases approach will be used for tabulations of data by visit (i.e. involving only those subjects who attended each specific visit).

Categorical data will be summarised using the number and percentage of subjects in each category and treatment group. Continuous data will be summarised using the mean, median, standard deviation (SD), minimum and maximum values. For laboratory data, the geometric mean and coefficient of variation will be included.

'Baseline' value is defined as the value from the latest assessment before treatment, i.e. at Visit 1 (Day 1) before randomisation.

Any changes from the statistical analysis planned in this clinical trial protocol will be described and justified in a protocol amendment/the statistical analysis plan and/or in the clinical trial report dependent on the type of deviation.

11.3.11 Handling of Missing Values

In this trial the imputation approach will be the Last Observation Carried Forward (LOCF) as we expect no or very few subjects to drop out. Overseas many trials have been conducted with LEO 90100 where the dropout rate was very low. There is no evidence to support that psoriasis is a different disease in Japan than is the rest of the world. This is consistent with the procedure for determining the primary endpoint for subjects who have substantial resolution of the target lesion before the end of 4 weeks of treatment.

Sensitivity analyses where missing values of the primary endpoint are imputed by either achieving or not achieving 'overall improvement rate', will be done. Imputement will be done for each treatment group separately and with two treatment groups and two outcomes, there will be four sensitivity analyses in total. These sensitivity analyses will define the range to which the result of the primary analysis would belong, in case no missing values had been present.

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List of Appendices

13 Appendix 1: Protocol Summary

Name of finished/ investigational medicinal product	LEO 90100 foam
Name of active substance	Calcipotriol hydrate and betamethasone dipropionate
Title of trial/trial ID	Efficacy and safety of LEO 90100 foam in Japanese subjects with psoriasis vulgaris / LP0053-1422
Coordinating investigator	Hidemi Nakagawa, MD, PhD
Sponsor's name/ address	LEO Pharma A/S, Denmark, Ballerup. LEO Pharma K.K. is the sponsor of the clinical trial in Japan on behalf of LEO Pharma A/S. LEO Pharma K.K., Tokyo, Japan.
Estimated number of trial sites and distribution	Twenty trial sites in Japan
Trial period	Q1 2019 to Q3 2019
Main objectives and endpoints	**Objectives** Primary objective: To compare the efficacy of LEO 90100 foam with Dovobet® ointment in the treatment of psoriasis in Japanese subjects. Secondary objective: To compare the safety of LEO 90100 foam with Dovobet® ointment in the treatment of psoriasis in Japanese subjects. **Endpoints** Primary endpoint: 'Overall improvement rate' for the target lesion at Visit 4 (end of Week 4), defined as 'substantial resolution' of clinical signs or at least 'moderately improved' in the general change in the lesion. 'Substantial resolution' is defined as a clinical score for thickness and scaliness of 0 and a clinical score for redness of 1 or less in the severity of clinical signs of the lesion.

	Secondary endpoint: Subjects with 'overall improvement rate' for the target lesion at Visits 2 and 3 (end of Weeks 1 and 2) The change in the sum of the scores (total sign score) for the severity of the three clinical signs (thickness, scaliness, redness) from Visit 1 to Visit 4 (end of Week 4) for the target lesion.
Final collection of data for the primary endpoint	Visit 4 (end of Week 4)
Methodology	A phase 3, national, multi-centre, 4-week, prospective, randomised, controlled, parallel-group, open trial of LEO 90100 foam versus Dovobet® ointment (each containing calcipotriol hydrate 52.2 µg/g [equivalent to 50.0 µg/g calcipotriol] plus betamethasone dipropionate 0.643 mg/g) in Japanese subjects with psoriasis vulgaris. Each subject will have one target lesion of psoriasis identified on the body. Subjects will be randomised to treat psoriasis with either LEO 90100 foam or Dovobet® ointment for 4 weeks.
Number of subjects to be enrolled	A total of 180 subjects will be randomised in a 1:1 ratio to the two treatment groups, i.e. 90 in each treatment group in order to provide at least 80 subjects per group who complete the trial. It is anticipated that approximately 200 subjects will be enrolled in order to provide 180 randomised subjects
Main criteria for inclusion	1. Japanese subjects aged 20 years or more 2. Clinical diagnosis of psoriasis vulgaris of less than or equal to 30% BSA (excluding any psoriasis on the face/skin folds/genitals) 3. A target psoriasis lesion on the body, of a minimum size of 10 cm^2 and scoring at least 2 (mild) for each of redness, thickness and scaliness 4. Females of childbearing potential must have a negative result for a urine pregnancy test at Day 1 (Visit 1) and must agree to use an adequate method of birth control
Main criteria for exclusion	1. Use of systemic treatment with an effect on psoriaisis 2. Use of UV therapy on full body or on the target lesion 3. Use of topical treatment on areas to be treated with trial medication

	4. Topical treatment on areas other than treated areas with vitamin D analogues, immunosuppressants or strong/very strong corticosteroids 5. Skin diseases besides psoriasis on the areas to be treated with trial medication. 6. Disorders of calcium metabolism, hypercalcaemia, renal insufficiency, hepatic disorders, heart disease.
Investigational medicinal product	LEO 90100 foam (containing calcipotriol hydrate 52.2 µg/g [equivalent to 50.0 µg/g calcipotriol] plus betamethasone dipropionate 0.643 mg/g) applied to a target lesion and any other areas of psoriasis once daily
Investigational reference product	Dovobet® ointment (containing calcipotriol hydrate 52.2 µg/g [equivalent to 50.0 µg/g calcipotriol] plus betamethasone dipropionate 0.643 mg/g) applied to a target lesion and any other areas of psoriasis once daily
Duration of treatment	Screening period: up to 4 weeks Treatment period: up to 4 weeks Follow-up period (if required): up to 2 weeks
Main assessments	The severity of each clinical sign (redness, thickness, scaliness) of the target lesion on a 9-point scale, from 0 = none to 4 = severe The general change in the target lesion from baseline on 5-point scale (markedly improved, moderately improved, slightly improved, unchanged, aggravated)
Statistical methods	Fisher's exact test

14 Appendix 2: Japanese Package Insert for Dovobet® ointment

Revised in Feb/2018 (2nd edition)
Prepared in Sep/2014

Japan standard commodity classification number
872699

Powerful drug **Therapeutic drug for psoriasis vulgaris**

Prescription drug note

Dovobet® Ointment

Calcipotriol hydrate/Betamethasone Dipropionate Combination

Dovobet ® Ointment

Approval number	22600AMX00752
NHI price listing	September 2014
Initial marketing in Japan	September 2014
International birth date	March 2001

Storage: Stored at room temperature
Expiration date: Indicated on the carton, etc. (Two year after being manufactured)
Note) Cautions – Use only under description as directed by a physician

[Contraindications (This medication contraindicated in the following patients.)]

1. Patients who have a history of hypersensitivity to any ingredients of this product
2. Patients with bacterial, fungal, spirochetal or viral skin infection or with animal skin disease (scabies, crab lice, etc.) [these diseases may worsen.]
3. Ulcers (excluding Behcet's disease), deep burns of second or severer grade, and frostbite [skin regeneration may be suppressed, resulting in delayed healing.]

[Description]

Ingredients	Active Ingredients /amount (per 1 g)	Calcipotriol hydrate 52.2μg (equivalent to calcipotriol 50.0μg), betamethasone dipropionate 0.643mg
	Excipients	All-rac-α-tocopherol Liquid paraffin White soft paraffin Polyoxypropylene stearyl ether
Appearance/description		Yellowish white to yellow ointment

[Indication]

Psoriasis vulgaris

[Dosage and Administration]

Apply adequate amount of Dovobet® ointment to the affected area once daily.

<Precautions regarding dosage and administration>

The maximum weekly dose should not exceed 90 g.

[Precautions]

1 Careful administration (This medication should be carefully administered to the following patients.)

1. Patients with hypercalcemia and those who are at risk for hypercalcemia [serum calcium level may be increased more.]
2. Patients with renal dysfunction [the administration of this product may increase serum calcium levels.]

2. Important precautions

(1) This product is a combination drug containing calcipotriol hydrate and betamethasone dipropionate. Adverse drug reactions caused by the use of calcipotriol or betamethasone may occur, therefore appropriate use of this drug should be considered.

(2) This product is an active vitamin D_3 containing preparation. This medication may increase serum calcium level. Since hypercalcemia may induce a decrease in renal function, patients should be monitored for serum calcium level and renal function (e.g. creatinine and BUN) periodically (once at 2 - 4 weeks after the start of administration of the product and when deemed necessary thereafter). If any abnormality is observed in these values, the administration of the product should be discontinued until normal calcium levels are restored.

(3) Efficacy and safety when this product is applied more than 4 weeks have not been established [See section “Clinical results”]. The clinical course should be closely observed during treatment. Use of this product should not be continued aimlessly.

(4) Overdosage of the product may induce hypercalcemia. Hypercalcemia may also occur in patients using the product for eruption covering a large area of the body or in patients with deteriorated skin barrier function which may accelerate percutaneous absorption of the drug. If any abnormality suggestive of hypercalcemia is observed, the administration of the product should be discontinued immediately and the patient should be followed up by observing biochemical parameters such as serum and urinary calcium levels[1-3)] [See section 8. “Overdosage” for signs/symptoms of hypercalcemia].

(5) Local adverse reactions, such as skin atrophy, steroid flush, etc. may occur. Therefore, careful consideration should be given particularly when this medication is used for

eruptions on the neck, genitals and skin folds.

(6) This product contains a corticosteroid and concurrent treatment at the same treatment area with other steroids must be avoided. When use in large doses or for prolonged periods over a large surface area [particularly under the occlusive dressing technique (ODT)], symptoms such as those that are likely to occur in systemic administration of adrenocortical steroids may occur. Therefore, prolonged use in large doses or ODT should be avoided.

(7) This medication contains calcipotriol. The safety of the product, when applied by the occlusive dressing technique (ODT), has not been established (incidence of skin irritation is higher in ODT than plain application. ODT may enhance percutaneous absorption of the drug, and may increase the incidence of systemic adverse effects as compared with plain application).

3. Drug interactions

Precautions for coadministration (Dovobet® ointment should be administered with care when coadministered with the following drugs.)

Drugs	Signs, symptoms, and treatment	Mechanism and risk factors
Vitamin D and its analogues Alfacalcidol, calcitriol, tacalcitol, maxacalcitol, etc.	Hypercalcemia may be induced.	Additive effect
Cyclosporin		Increase of serum calcium level may easily be induced due to renal impairment by cyclosporine.

4. Adverse drug reactions

In clinical studies conducted in Japan before approval of Ointment and before approval of Gel, 17 adverse drug reactions were reported in 17 of the 445 treated patients (3.8%). Those adverse drug reactions were folliculitis in 5 patients, anaemia and glucose urine present in 2 patients each, and leukocytosis, oedema peripheral, hepatic function abnormal, herpes simplex, rash pustular, contusion, psoriasis aggravated and skin depigmentation in 1 patient each.

(1) Clinically significant adverse drug reactions

1) Hypercalcemia (information from Package Insert of calcipotriol, frequency unknown): Hypercalcemia and clinical symptoms that are considered to be due to hypercalcemia (malaise, feelings of weakness, anorexia, vomiting, abdominal pain and muscle weakness, etc.) may appear. If any abnormalities are noted, use of this medication should be discontinued, and biochemical tests including serum calcium and urine calcium should be conducted. If necessary, actions such as intravenous fluids should be taken.

2) Acute kidney injury (information from Package Insert of calcipotriol, frequency unknown): Acute kidney injury accompanied by serum calcium increased may appear. If any abnormalities such as serum creatinine increased and BUN increased are noted, use of this medication should be discontinued, and an appropriate action should be taken.

(2) Other adverse drug reactions

If the following adverse drug reactions are observed, appropriate measures should be taken.

	≥ 1%	< 1%	Unknown*
Hypersensitivity note1			Erythema/redness,
Skin note2		Psoriasis aggravated	Itch, pruritus, burning sensation, pricking skin feeling, skin irritation, dermatitis, Ichthyosis-like dermal changes, skin dryness, skin erosion, contact dermatitis, exfoliation, eruption, swelling
Skin infection note3	Folliculitis		Bacterial infection (infectious impetigo, furuncle, etc.), dermatomycosis (candidiasis, tinea, etc.), viral infection
Other skin symptoms note4		Rash pustular, Skin depigmentation	Skin pigmentation, pustular psoriasis, acneform eruption, rosacea-like dermatitis, steroid skin (skin atrophy, telangiectasis and purpura), hypertrichosis,
Hepatic		Hepatic function abnormal	Increased AST(GOT), increased ALT(GPT) increased γ-GTP, increased LDH, increased ALP, increased total bilirubin
Renal			Increased BUN, increased serum creatinine, increased urinary creatinine
Hematologic		Leukocytosis, anaemia	Leukopenia, leukocytosis, decreased haemoglobin, lymphopenia, monocytosis, neutropenia
Infection		Herpes simplex	
Function of pituitary adrenocortical system			Suppress the function of the pituitary adrenocortical system note5
Others		Oedema peripheral, Contusion, glucose urine present	Increased urinary calcium, increased serum calcium, increased serum phosphorus, decreased urinary phosphorus, increased serum $1\alpha,25(OH)_2D_3$, decreased serum phosphorus, decreased serum $1\alpha,25(OH)_2D_3$, rebound effect

The incidence is the sum of adverse drug reactions observed in clinical studies of Dovobet Ointment and Dovobet Gel conducted in Japan.

* ADRs from overseas studies, calcipotriol preparation or betamethasone diproprionate preparation, therefore frequency is unknown in Japanese patients.

note 1: Discontinue application of this medicine if any symptom is observed.

note 2: Discontinue application of this medicine if the adverse drug reactions occur severely.

note 3: When any of these symptoms are observed, this medication should be used in combination with a suitable antibacterial drug or antifungal drug, and if the symptom does not disappear promptly, the administration of this medication should be discontinued. [Such symptoms are liable to occur when used under the occlusive dressing technique (ODT).]

note 4: When any of these symptoms occur after long term application, the use of this medication should be avoided, and changed over to some other drug(s) not containing adrenocortical steroid.

note 5: Event due to application in large doses, usage for prolonged periods over a large surface area or used under the occlusive dressing technique (ODT) in application of betamethasone diproprionate. Since acute adrenocortical insufficiency may occur by the discontinuation of this medication, the dose should be gradually reduced under close observation of the patient's conditions when the administration of this medication is discontinued.

5. Use in the elderly

In general, elderly patients have a deterioration of physiological functions. Therefore, attention should be given to overuse in elderly patients.

6. Use during pregnancy, delivery and lactation

(1) Pregnant women, etc.:

It is desirable not to use this medication in pregnant women or women who may be pregnant [safety in application during pregnancy has not been established. It has been reported that calcipotriol is transferred to fetuses via the placenta in an animal experiment (rats)[4]. It has been reported that betamethasone has teratogenic action in animal studies (mice, rats, rabbits)[5,6]] .

(2) Nursing women:

It is desirable to avoid the use of this medication in nursing women. If this medication is used in nursing women by necessity, patients should be instructed to refrain from breastfeeding [It has been reported that calcipotriol is excreted in milk in an animal experiment (rats)[4]] .

7. Use in children, etc.

Safety in low birth weight infants, neonates, nursing infants, infants and children has not been established (there is no experience).

8. Overdosage

Signs and symptoms: The major symptoms of hypercalcemia include malaise, feelings of weakness, anorexia, nausea, vomiting, enlarged feeling of abdomen, abdominal pain, headache, dizziness, muscle pain and muscle weakness, etc.

[See Section (2), (4) of "Important precautions".]

Treatment: Use of this medication should be discontinued immediately. Biochemical tests including serum calcium and urine calcium should be conducted. If necessary, treatments such as intravenous fluids should be taken.

[See Section (2), (4) of "Important precautions".]

9. Precautions concerning use

(1) Application sites:

1) This medication should not be applied to the face.
2) This medication should not be used for ophthalmic application.
3) This medication should not be applied to any sites except for the affected areas.

(2) At the time of use: Be careful not to touch the face and wound sites with hands exposed to this medication.

(3) After use:

1) Wash your hands thoroughly after using this medication to avoid the transference

of this medication to the face, etc.

2) It is not recommended to take a shower or bath immediately after application of this medication.

(4) At the time of delivery of this medication: Special attentions should be given to the storage of this medication to prevent inappropriate use (oral use, etc.). Especially, this medication should be kept out of reach of children. If a patient takes this medication orally by mistake, the patient should be instructed to take appropriate action such as consulting a medical institution because systemic adverse drug reactions such as hypercalcemia may occur.
[See Section "Overdosage".]

10. Other precautions

(1) It has been reported that in a study using male and female albino hairless mice to which light (xenon lamp) was irradiated for 40 weeks and calcipotriol solution was applied, the irradiation time required for inducing skin tumor was shortened significantly in males. However, in a study in which only the drug solution was applied to mice, no skin tumor was induced.

(2) It has been reported that erythrodermic psoriasis, pustular psoriasis, etc. occurred during or after discontinuation of application of this medicine.

[Pharmacokinetics]

In the study where this product once daily was applied to 13 Japanese subjects with severe psoriasis vulgaris, plasma concentration of calcipotriol, and betamethasone dipropionate were BLQ (below 50.0 pg/mL and 30.0 pg/mL, respectively) in almost all subjects. The ranges of C_{max} and AUC_{last} for the two subjects with quantitative concentration of calcipotriol were 56.1 to 159 pg/mL and 28.1 to 311 h•pg/mL, respectively. The C_{max} and AUC_{last} for the one subject with quantitative concentration of betamethasone dipropionate were 39.6 pg/mL and 41.24 h•pg/mL, respectively.[7)]

Plasma concentration of main metabolite of calcipotriol was quantified in 1 to 3 subjects at each time point. The ranges C_{max} and AUC_{last} for those subjects were 26.4 to 151 pg/mL and 27.9 to 736 h•pg/mL, respectively. Plasma concentration of main metabolite of betamethasone dipropionate was quantified in 5 to 11 subjects at each time point. The ranges C_{max} and AUC_{last} for those subjects were 30.3 to 910 pg/mL and 15.91 to 4732 h•pg/mL, respectively.[7)]

[Clinical results]

The clinical efficacy of this product once daily application for 4 weeks was confirmed in the double-blind comparative study with the calcipotriol (twice daily application) and betamethasone dipropionate (once daily application) in Japanese psoriasis vlugaris patients. Mean percentage change in m-PASI from baseline is shown in the following table. Once daily application of this medication for 4 weeks showed the excellent therapeutic effect compared with comparators.[8)]

	Calcipotriol hydrate/ Betamethasone dipropionate (n=226)	Calcipotriol (n=227)	Betamethasone dipropionate (n=223)
Mean percentage change in m-PASI from baseline to Week 4 (±SD)	-64.3% (24.7)	-50.5% (32.1)	-53.6% (26.4)

(Calcipotriol hydrate/Betamethasone dipropionate vs Calcipotriol, Calcipotriol hydrate/Betamethasone dipropionate vs Betamethasone dipropionate, $p<0.0001$ for all comparison)

[Pharmacology]

1. Action of mechanism

Calcipotriol binds to the vitamin D receptor, and it has been reported that calcipotriol inhibits cell proliferation, regulates cell cycles and induces differentiation in various cell types, regulate abnormal expression of proinflammatory cytokines and control anti-microbial peptide expression [9-13)].

Betamethasone dipropionate acts by binding to and activating the glucocorticoid receptor in the target cells. After binding to the receptors, corticosteroids including betamethasone dipropionate inhibit the production of inflammatory cytokine as well as the expression of other types of inflammatory mediators including intercellular adhesion molecule-1, the enzymes phospholipase A2, cyclooxygenase type 2 and inducible nitric oxide synthase. Inhibition of the expression of these enzymes results in the attenuated production of inflammatory mediators [14-17)].

2. Effect of concomitant use

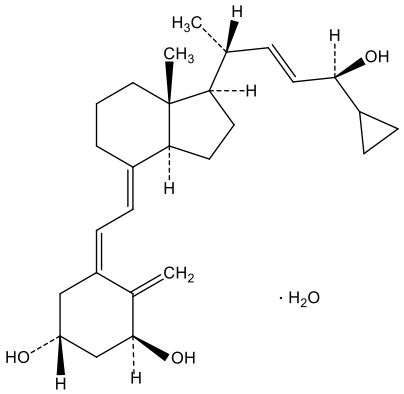
Treatment with the calcipotriol/betamethasone dipropionate combination significantly inhibited the differentiation and activity of human type 1 helper T (Th1) cell / IL-17 expressing helper T (Th17) cell. The inhibitory effect of treatment with the combination on differentiation and activity of Th1/Th17 cells was greater than either that of calcipotriol alone or betamethasone dipropionate alone [18)].

[Physicochemistry]

Calcipotriol hydrate

Nonproprietary name: Japanese description
Calcipotriol hydrate
Chemical name: (5*Z*,7*E*,22*E*,24*S*)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol monohydrate

Structure formula:



Molecular formula: $C_{27}H_{40}O_3 \cdot H_2O$

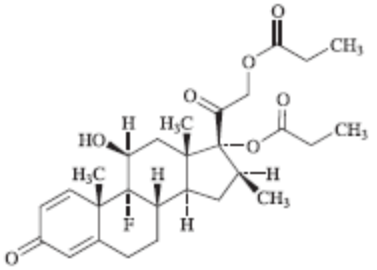
Molecular weight: 430.62

Description: White crystalline powder.

Freely soluble in methanol, in ethanol (95) and in 2-propanol. Soluble in propylene glycol. Sparingly soluble in ethyl acetate, in dichloromethane and in chloroform. Practically insoluble in liquid paraffin and in water (0.1% disodium hydrogen phosphate solution).

Betamethasone dipropionate

Nonproprietary name: Japanese description (JP)
Betamethasone dipropionate
Chemical name: 9-Fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropanoate
Structure formula:



Molecular formula: $C_{28}H_{37}FO_7$

Molecular weight: 504.59

Description: The product is a white to pale yellow crystalline powder without odor.
It is freely soluble in acetone, 1,4-dioxane and chloroform, soluble in methanol, sparingly soluble in ethanol (95), slightly soluble in ether and practically insoluble in water and hexane.
It gradually changes under light.

[Package]

15g×1, 15g×10, 30g×1

[References]

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18) Company data (LEO Pharma A/S)

[Request for literatures should be made to]

Please request for the company data as well as literature cited in the REFERENCE to the following.

Medical Information Office
Kyowa Hakko Kirin Co., Ltd.
1-6-1, Ohtemachi, Chiyoda-ku, Tokyo 100-8185, Japan
0120-850-150 (toll free)
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Fax: 03-3282-0102
Open: 9:00-17:30 (except Saturday, Sunday, national holidays and company holidays)

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15Appendix 3: Definitions of Adverse Events and Serious Adverse Events

15.1 Adverse Event Definition

An 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 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)).

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures unless these were planned before the subject consented to trial participation.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 8.6).

15.2 Serious Adverse Event Definition

A SAE is any untoward medical occurrence that

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation. Planned hospitalisation or planned prolonged hospitalisation do not fulfill the criteria for being an SAE but should be documented in the subject's medical record.
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect

or

- is a medically important condition. 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 are intensive treatment in an emergency room or at home for allergic broncospasm, blood dyscrasias and convulsions that do not result in hospitalization, development of drug dependency or drug abuse.

16 Appendix 4: Classification of Adverse Events

16.1 Severity

The *severity* of the AE should be described in terms of mild, moderate or severe according to the (sub)investigator's clinical judgement.

Mild	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

If the severity of an AE worsens, a new AE should be recorded.

16.2 Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probable, possible or not related according to the investigator's clinical judgement. The categories are defined below.

Probably related	Follows a reasonable temporal sequence from administration of the IMP. 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 IMP. Disappears or decreases on cessation or reduction in dose of the IMP. Reappears or worsens upon re-challenge.
Possibly related	Follows a reasonable temporal sequence from the administration of the IMP. 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 IMP.

Not related	Does not follow a reasonable temporal sequence from administration of the IMP. Is better explained by other factors like the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Does not reappear or worsen upon re-challenge. Does not follow a known pattern of response to the IMP.

16.3 Outcome

The *outcome* of the event according to the investigator's clinical judgement should be classified using the categories below

Recovered/ resolved	The event has stopped. The stop date of the event must be recorded.
Recovering/ resolving	The subject is clearly recovering from an event. The event is not yet completely resolved.
Not recovered/ not resolved	Event is still ongoing.
Recovered/ resolved 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 must be recorded. In case of a SAE, the sequelae should be specified.
Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE.
Unknown	Unknown to (sub)investigator, e.g. subject lost to follow-up.

Note that as per the above definition, LEO Pharma uses "recovered/resolved" only if an event has actually stopped. According to the CDISC definition, the category "recovered/resolved" also includes events which have improved. However, following the LEO Pharma definitions above, such an improved event will instead be classified as "not recovered/not resolved" or "recovering/resolving".

Similarly, it should be noted that as per the above definition, LEO Pharma uses "recovered/resolved with sequelae" only if an event has reached a state where the residual symptoms are assumed to persist. According to CDISC, an event is considered "with sequelae", if it has "retained pathological conditions". Consequently, it is likely that some of the events classified by LEO Pharma with the outcome "recovered/resolved with sequelae" could have been classified with the outcome "recovered/resolved" according to the CDISC definition.

For SAEs which have stabilised and from which the subject cannot be expected to recover during trial or the safety follow-up periods, for example chronic illnesses, the final outcome should be reported as 'recovered'; in addition, a statement that the SAE has stabilised or is chronic should be added to the narrative of the SAE on the SAE form.

17 Appendix 5: Trial governance considerations

Appendix 5A: Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki (30) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (31).
- Current version of applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines (32).
- EU's General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

The appropriate regulatory authority (PMDA) must be notified of/approve the clinical trial as required.

Any documents that the IRB may need to fulfil its responsibilities (such as the trial protocol, protocol amendments, Investigator's Brochure, subject information sheet and informed consent form(s), or advertisements) will be submitted to the IRB. These documents must be reviewed and approved by the IRB before the trial is initiated.

Written approval must be obtained from relevant IRBs prior to the signing of the CTA with the site and before enrolment of subjects.

Any amendments to the protocol must be approved by/receive favourable opinion from relevant regulatory authorities and IRBs, as required, prior to implementation.

The principal investigator will be responsible for the following, if required by local legislation:

- Providing written summaries of the status of the trial to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the local IRB of SAEs or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the trial at the trial site and ensuring adherence to applicable national and international legislation.

Appendix 5B: Informed consent process

Subjects will receive written and verbal information concerning the clinical trial. This information will emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

The subject's signed and dated informed consent to participate in the clinical trial will be obtained prior to any clinical trial related procedure being carried out in accordance with ICH GCP (4.8) and all applicable laws and regulations. The authorised person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the subject.

Subject card

At screening, subjects will be provided with a card stating that they are participating in a clinical trial and which contains contact address(es) and telephone number(s) of relevant trial site staff including the number for the investigator in case of emergency situations.

Appendix 5C: Subject and data confidentiality

This clinical trial protocol as well as all other information, data, and results relating to this clinical trial and/or to the IMP is confidential information of LEO and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that LEO may use any and all information, data, and results from this clinical trial in connection with the development of the IMPs and, therefore, may disclose and/or transfer information, data and/or results to other investigators, regulatory authorities and/or commercial partners.

Trial subjects will be assigned a unique identifier (subject ID) by LEO. Any subject's records or datasets that are transferred to LEO will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

Trial subjects must be informed and consent to that their personal trial-related data will be used by LEO in accordance with local data protection law.

Trial subjects must be informed and consent to that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by LEO, by appropriate IRB members, and by inspectors from regulatory authorities.

Processing of personal data

This protocol specifies the personal data on trial subjects (e.g. age, gender, health condition, medical history, test results, etc.) which shall be collected as part of the clinical trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator, LEO Pharma and third parties acting on behalf of LEO Pharma.

Processing of personal data on behalf of LEO Pharma requires a written agreement between LEO Pharma and the relevant party which covers collection, processing and transfer of personal data in the clinical trial. In certain cases an agreement on transfer of personal data may also be required.

Investigators and LEO Pharma must ensure that collection, processing and transfer of personal data are in compliance with applicable legislation on data protection and privacy, including but not limited to the EU General Data Privacy Regulation.

Subjects must be asked to consent to the collection, processing and transfer of their personal data to EU and non-EU countries for the purpose of conducting the clinical trial, research and development of new or existing products/services, improving existing products/services, applying for marketing authorisations for products/services, marketing of products/services and other related activities.

LEO Pharma has obtained the necessary authorisations for the processing of personal data collected in the trial.

Appendix 5D: Record keeping, quality control, and data handling

Source data

For all data recorded, the source document must be defined in a source document agreement or similar document at each trial site. There must only be 1 source defined at any time for any data elements. The eCRF cannot be a source document.

Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed and dated by medically qualified (sub)investigators.

If the worksheet does not become part of the subject's medical record, the following should as a minimum be added to the subject's medical record:

- Date(s) of conducting the informed consent process, including date of provision of subject information.
- A statement from the investigator to verify that each of the eligibility criteria are met and documented.
- Subject ID (eCRF number)
- Trial ID (LP0053-1422)
- Kit number of trial medication
- The fact that the subject is participating in a clinical trial in psoriasis involving 4 weeks treatment with LEO 90100 foam (containing calcipotriol and betamethasone dipropionate) or Dovobet® ointment (*it should be specified which one*).
- Other relevant medical information.

Trial monitoring

During the course of the trial, CRA(s) will visit the trial site. These visits have the following objectives: (i) to continually verify source data to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; (ii) to confirm that the safety and rights of subjects are being protected; and (iii) to confirm that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, J-GCP, and all applicable regulatory requirements.

The first monitoring visit should be performed as soon as after first subject first visit.

The monitoring visit intervals will depend on the trial site's recruitment rate and the compliance of the trial site with the protocol and ICH GCP/J-GCP.

In order to perform their role effectively, CRAs and persons involved in quality assurance and inspections will need direct access to source data, e.g. medical records, laboratory reports, appointment books, etc. If source data is kept in an electronic medical record and if this record does not have a visible audit trail, the investigator must provide the CRA with signed and dated printouts. In addition, relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

Protocol compliance

Protocol deviations will be documented and notified to the investigator. Protocol deviations will be assessed by LEO Pharma and major deviations described in the clinical trial report.

Sponsor audits, IRB review, and regulatory agency inspections

The clinical trial will be subject to audits conducted by LEO Pharma or inspections from domestic or foreign regulatory authorities or from IRBs. Audits and inspections may take

place during or after the trial. The investigator and the site staff as well as LEO Pharma staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify and reproduce any records and reports that are important to the evaluation of the trial.

If the trial site is contacted for an inspection by competent authorities, LEO Pharma must be notified immediately.

Risk Assessment

Risks in this trial will be evaluated and documented in a separate document.

Data handling

Data will be collected by means of electronic data capture unless transmitted electronically to LEO Pharma or designee (e.g., laboratory data). The investigator or staff authorised by the investigator will enter subject data into electronic CRFs (eCRFs). Data recorded in the eCRFs will be accessible to the trial site and LEO Pharma personnel immediately after entry. The eCRFs must be maintained in an up-to-date state by the trial site at all times.

The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require the re-signature by the investigator. The person making the change to the data, and the date, time and reason for the change will be identified in the audit trail.

Subject data should be entered into the eCRF no later than 5 working days after each visit, unless a different deadline is stated in the Clinical Trial Agreement. Queries for discrepant data will be generated automatically by the system upon entry or manually by the CRA, sponsor's medical expert, or the data manager. All queries will be raised electronically within the electronic data capture system. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

External data transfers from vendors to LEO Pharma will be transmitted and handled via a secure file transfer protocol site.

Archiving of trial documentation

The investigator/director at each trial site or the person responsible for document archiving at the site must make arrangements to store the essential trial documents, including the

investigator trial file (32). Essential trial documents must be stored until LEO Pharma informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

In addition, this person is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after the completion of the trial (for example in case of an inspection from regulatory authorities).

The person is required to ensure the continued storage of the documents even if the investigator or the person leaves the trial site or retires before the end of the required storage period.

No documents may be destroyed during the retention period without the written approval of LEO Pharma. No documents may be transferred to another location or party without written acceptance from LEO Pharma.

The destruction process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

For archiving purposes, each investigator will be supplied with an electronic copy of the eCRFs for all screened subjects at the trial site. This is done after completion of the trial and before access to the eCRF is revoked. Audit trail information will be included. eCRFs must be available for inspection by authorised representatives from LEO Pharma, from regulatory authorities and/or IRBs.

Appendix 5E: Registration, reporting and publication policy

Trial disclosure

LEO Pharma is committed to be transparent with respect to its clinical trials.

Basic information of this clinical trial will be registered in the global data registry, www.ClinicalTrials.gov before the first subject enters into the trial. The trial may also become registered in other online data registries, according to applicable law and regulations.

Results of this clinical trial will be posted on the corporate website of LEO Pharma in accordance with our Position on Public Access to Clinical Trial Information no later than 12 months after trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

LEO Pharma may also provide researchers access to anonymised patient level data for further research. Publication and access will be in accordance with the Position on Public Access to Clinical Trials which can be found on the LEO Pharma website.

Publications
The investigator shall be entitled to make publications of the results generated by investigator in accordance with the process described here.

A multi-centre publication will be submitted for publication within 18 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as database lock of the clinical trial. After such multi-centre publication is made public, or if no multi-centre publication has been submitted with the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

Prior to submission for publication or presenting a manuscript relating to the clinical trial, the investigator shall provide to LEO Pharma a copy of all such manuscripts and/or presentations. LEO Pharma shall have rights to review and comment. The investigator shall consider comments provided by LEO Pharma but is not required to modify the manuscript and/or presentation based on such comments, provided, however, that the investigator upon the request of LEO Pharma remove any confidential information (other than results generated by the investigator) prior to submitting or presenting the manuscripts. The investigator shall, upon the request of LEO Pharma withhold the publication or presentation to allow LEO Pharma to protect its inventions and other intellectual property rights described in any such manuscripts.

In case no multi-centre publication has been made public at the time of investigator's notification of an independent publication to LEO Pharma, LEO Pharma and the writing group may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-centre publication.

In case of publications made by the investigator after the first multi-centre publication has been published, the above-mentioned requirements must still be followed.

Any publication must comply with Good Publication Practice (GPP3) standards.

LEO Pharma complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO Pharma complies with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan

Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results and authorship. LEO Pharma also follows the CONSORT reporting guidelines (33).

Appendix 5F: Insurance

LEO Pharma has taken out relevant insurances covering the subjects in the present clinical trial in accordance with applicable laws and regulations.

Appendix 5G: Financial disclosure

Investigators will provide LEO Pharma with sufficient, accurate financial information as requested to allow LEO Pharma to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the clinical trial and for 1 year after completion of the clinical trial, or for a longer period of time if required by local legislation.

Appendix 5H: Committee structure

Not applicable. A Data Monitoring Committee will not be set up for this trial with the following reasons.

Dovobet® ointment is marketed in Japan, and its use in this trial will be in keeping with the licensed conditions for use in Japan. Therefore, its use in this trial is not expected to reveal any new safety findings. LEO 90100 foam is a different formulation of Dovobet® ointment, having the same active ingredients at the same concentration. In a phase 1 trial of LEO 90100 foam, it was shown to have no safety concern in healthy Japanese subjects. LEO 90100 foam was approved in the US in 2015 as the first country for the topical treatment of plaque psoriasis in patients 18 years of age and older. The product has subsequently been approved in 34 countries, hereof the majority in EU. Its use in Japanese subjects in this trial is not expected to reveal any new safety findings.

Appendix 5I: Trial and site closure

Premature termination of trial or trial site

LEO Pharma, the investigator, the IRBs or competent authorities may decide to stop the clinical trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a clinical trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. As specified by applicable regulatory requirements, the investigator or LEO Pharma K.K. must promptly inform IRBs and provide a detailed written explanation. Relevant competent authorities must be informed.

The trial must be terminated if the perception of the benefit/risk ratio (judged from clinical signs and symptoms, (S)AEs and/or remarkable safety laboratory changes) becomes unfavourable for the continuation of the trial.

Reasons for the early closure of a trial site by LEO Pharma or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, LEO procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.

Due to the design of this trial, there are no statistical criteria for trial termination.

Completion of trial

Investigators will be informed when subject recruitment is to cease. Screening activities will be stopped at a trial site when the total requested number of subjects for the clinical trial has been obtained, irrespective of the specific site's planned inclusion number.

Trial sites will be closed upon trial completion. LEO Pharma will undertake arrangements for the collection and disposal of any unused trial material that the investigator is not required to keep in his/her files. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

Appendix 5J: Responsibilities

The signatory investigator is responsible for the approval of the clinical trial protocol and the clinical trial report on behalf of all clinical trial investigators and as agreed to in a Signatory Investigator Agreement.

The national coordinating investigators are responsible for national issues relating to the clinical trial as agreed to in a National Coordinating Investigator Agreement.

Each participating investigator is responsible for all aspects of the clinical trial conduct at his/her trial site as agreed to in a Clinical Trial Agreement.

18 Appendix 6: Contact list of LEO Pharma A/S, LEO Pharma K.K., protocol authors, vendors, international coordinating investigator and medical expert (Japan)

Contact details for the clinical project manager (CPM), medical expert (LEO) and safety scientist/safety physician are provided to participating trial sites outside the protocol on a list of LEO Pharma representatives.

Sponsor

The Sponsor of the clinical trial is LEO Pharma A/S:

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

LEO Pharma K.K. is the Sponsor of the clinical trial in Japan on behalf of LEO Pharma A/S:

LEO Pharma K.K.
3-11-6 Iwamotocho
Chiyoda-ku
Tokyo 101-0032
Japan

In this clinical trial protocol, LEO Pharma A/S and LEO Pharma K.K. are collectively called as 'LEO Pharma'.

Protocol Authors

Name	Role	Address
Hidemi Nakagawa, MD, PhD	International Coordinating Investigator	
PPD, MD	Medical Expert	
PPD	Clinical Project Manager	LEO Pharma K.K., Japan
PPD, MD	Principal Medical Adviser	LEO Pharma A/S, Denmark
PPD	Biostatistician	LEO Pharma A/S, Denmark

PPD	Pharmacovigilance	LEO Pharma A/S, Denmark
PPD	Medical Writer	LEO Pharma A/S, Denmark
PPD	Senior Clinical Project Manager (responsible for monitoring)	LEO Pharma K.K., Japan

CRO/vendors

Service	Name and address
Data management, SDTM programming, Biostatistics, Medical writing	CMIC Co., Ltd. East Japan, Hamamatsucho Bldg, 1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan
CMO	Klifo A/S, Smedeland 36, DK 2600 Glostrup, Denmark
Central lab	Covance Central Laboratory Services LP 8211 SciCor Drive Indianapolis, IN 46214 USA

19 Appendix 7: WHO Classification of Topical Corticosteroids

WHO CLASSIFICATION OF TOPICAL CORTICOSTEROIDS
Based on the Anatomical Therapeutic Chemical (ATC) classification system

Group I: weak
Hydrocortisone
Methylprednisolone
Prednisolone

Group II: moderately potent
Alclometasone
Clobetasone
Desonide
Flumetasone
Fluocortin butyl
Fluprednidene
Hydrocortisone butyrate
Triamcinolone

Group III: potent
Amcinonide
Beclometasone
Betamethasone
Betamethasone dipropionate
Budesonide
Desoximetasone
Diflorasone
Diflucortolone
Fluclorolone acetonide
Fludroxycortide
Fluocinolone acetonide
Fluocinonide
Fluocortolone
Fluticasone
Halometasone
Mometasone

Prednicarbate
Ulobetasol

Group IV: very potent
Clobetasol
Halcinonide

20 Appendix 8: WHO Classification of Topical Corticosteroids compared to the Japanese Classification

WHO Classification of Topical Corticosteroids	
Group I : Weak	Hydrocortisone Methylprednisolone Prednisolone
Group II : Moderately Potent	Alcometasone Clobetasone Desonide Flumetasone Fluocortin butyl Fluprednidene Hydrocortisone butyrate Triamcinolone

Japanese Classification of Topical Corticosteroids	
Group V : Weak	Dexamethasone Fludroxycortide Hydrocortisone acetate Prednisolone
Group IV : Medium	Alclometasone dipropionate Clobetasone butylate Flumetasone pivalate Hydrocortisone butyrate Triamcinolone acetate
Group III : Strong	Betamethasone valerate Beclometasone dipropionate Deprodone propionate Dexamethasone propionate Dexamethasone valerate Fluocinolone acetate Prednisolone valerate acetate

WHO Classification of Topical Corticosteroids	
Group III : Potent	Amcinonide Beclometasone Betamethasone Betamethasone dipropionate Budesonide Desoximetasone Diflorasone Diflucortolone Fluclorolone acetonide Fludroxycortide Fluocinolone acetonide Fluocinonide Fluocortolone Fluticasone Halometasone Mometasone Prednicarbate Ulobetasol
Group IV : Very Potent	Clobetasol Halcinonide

Japanese Classification of Topical Corticosteroids	
Group II : Very Strong	Amcinonide Betamethasone butyrate propionate Betamethasone dipropionate Diflucortolone valerate Difluprednate Fluocinonide Hydrocortisone butyrate propionate Halcinonide Mometasone fluorate
Group I : Strongest	Clobetasol propionate Diflorasone diacetate

21 Appendix 9: Descriptors for intermediate intervals in severity score of clinical signs of target lesion

In the Investigator's assessment of the severity of clinical signs of the target leson, intermediate intervals (0.5, 1.5, 2.5, 3.5) serve as mid-points between the defined grades (0, 1, 2, 3, 4). For the purposes of data coding, these intermediate levels are defined as:

0.5 = mid-point between 'none' and 'slight'
1.5 = mid-point between 'slight' and 'mild'
2.5 = mid-point between 'mild' and 'moderate'
3.5 = mid-point between 'moderate' and 'severe'

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