Cover Page

Study title: A Phase 3, Randomised, Investigator-blind, Active-controlled, Parallel Group, Multicentre Trial Comparing the Efficacy and Safety of 4-weeks Treatment With LEO 90100 and Daivobet® Ointment in Adult Chinese Subjects With Stable Plaque Psoriasis
LEO Pharma number: LP0053-2277
NCT number: NCT05919082
Date: 09-Nov-2022

Title Page

Protocol Title:	A phase 3, randomised, investigator-blind, active-controlled, parallel group, multicentre trial comparing the efficacy and safety of 4 weeks treatment with LEO 90100 and Daivobet® ointment in adult Chinese subjects with stable plaque psoriasis
Brief Title:	A study to investigate efficacy and safety with LEO 90100 compared with Daivobet® ointment in adult Chinese subjects with stable plaque psoriasis
Compound:	LEO 90100
Trade Name:	Enstilar®
Indication:	Stable plaque psoriasis
Sponsor:	LEO Pharma A/S Industriparken 55, DK-2750 Ballerup, Denmark
Protocol Number:	LP0053-2277
Study Phase:	Phase 3
Version:	Version 3.0
Approval Date:	Final, 09 Nov 2022

Sponsor Signatory: For information about the sponsor signatory refer to Appendix 6: Protocol Elements for Redaction, Section 10.7.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY			
Document	**Amendment Scope; Region/Country Identifier (if applicable)**	**Protocol Version**	**Date**
Amendment 2	Global	Version 3.0	09 Nov 2022
Amendment 1	Global	Version 2.0	27 Jun 2022
Original Protocol	Not Applicable	Version 1.0	07 Apr 2022

Amendment 2 (09 Nov 2022)

Overall Rationale for the Amendment:

The protocol was updated to revise the indication to align the approved indication of Daivobet® ointment in China based on the clinical trial authorization's comments, clarify the rescue treatment or discontinuation and the rationale for the non-inferiority margin. The changes neither significantly impacted the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold and underline** and deleted text has a ~~line through it~~).

Section # and Name	Description of Change	Brief Rationale
Throughout	Indication changed from psoriasis vulgaris to stable plaque psoriasis (if is about the active ingredients for the trial) or plaque psoriasis (if is about the disease).	Revised the indication to align the approved indication of Daivobet® ointment in China based on the clinical trial authorization's comments.
Section 1.1 Synopsis Section 2.1 Trial Rationale	This trial is conducted to assess the efficacy and safety of LEO 90100 when used **on the body** for the treatment of stable plaque psoriasis in adult Chinese subjects, compared to Daivobet® ointment, which is approved **in China**	Revised the indication to align the approved indication of Daivobet® ointment in China based on the clinical trial authorization's comments.

Section # and Name	Description of Change	Brief Rationale
	for the **treatment of stable plaque psoriasis on the body**~~same indication in China~~.	
Section 2.3 Ethical Considerations	Trial subjects will be under careful supervision of dermatologists and physicians experienced in GCP clinical trials and in the handling of plaque psoriasis. During the entire course of the trial, subjects will be required to attend planned trial visits every 2 weeks. At either their own or the physician's discretion, subjects may be withdrawn from the trial at any time. **In case of lack of efficacy of the investigational medicinal product (IMP), it will be at the discretion of the trial site physician whether the subject needs rescue treatment or discontinuation from the trial. This is further described in Section 6.9.2 and Section 7.**	Added rescue treatment or discontinuation based on the clinical trial authorization's comments.
Section 6.9.2 Rescue Treatment	**Section 6.9.2 Rescue Treatment** **If medically necessary (i.e., to control intolerable psoriatic symptoms), rescue treatment for stable plaque psoriasis can be initiated to trial subjects at the discretion of the investigator. If possible, investigators should attempt to limit the first step of rescue treatment to topical treatments. Before the initiation of rescue treatment, investigators should make every attempt to conduct efficacy and safety assessments (for example, disease severity scores [PASI and sPGA] and safety labs). Unscheduled visit(s) may be used for this purpose, if necessary.** **The investigator is responsible for the rescue treatment oversight and duration as well as switching and escalating to another rescue therapy, when appropriate. The investigator should consider if discontinuation of IMP is necessary depending on the type of rescue medication and the**	Added rescue treatment based on the clinical trial authorization's comments.

Section # and Name	Description of Change	Brief Rationale
	severity of the subject's symptoms (see Section 7, discontinuation criteria). **The use of any rescue treatment must be recorded in the eCRF (refer to Section 7).**	
Section 7.1 Discontinuation of Trial Treatment	• **Lack of efficacy defined as at least a CCI in mPASI score from baseline until Week 2 or unscheduled visits thereafter and where the investigator sees a need for rescue therapy.**	Added rescue treatment based on the clinical trial authorization's comments.
Section 7.2 Subject Discontinuation/Withdrawal from the Study	**In order to ensure appropriate treatment of the subjects after they have discontinued IMP or withdrawn from the trial, the subjects will be treated at the investigator's discretion.**	Added discontinuation based on the clinical trial authorization's comments.
Section 9.1.1 Multiplicity Adjustment	**Justification for non-inferiority margin of CCI on the odds-ratio scale.** **There is no guidelines nor meta-analysis that suggest non-inferiority margins when assessing PGA 0/1 or mPASI in the population to be studied in this trial. Therefore, the non-inferiority margin has been set based on the following general principles:** • **The non-inferiority margin should be on the same scale as the primary analysis (Odds-ratio).** • **The non-inferiority margin should not be too large. Here CCI is chosen as a conservative margin. The justification for CCI being conservative is that** o **For bioequivalence trials margins of 0.8-1.25 is usually applied.** o **Reaching the non-inferiority margin of CCI in example means: for LEO 90100 having 170 responders in 300**	Clarified the rationale for the non-inferiority margin.

Section # and Name	Description of Change	Brief Rationale
	subjects =56.7% and 154 in 300 subjects =51.3% for Daivobet ointment gives a crude odds-ratio of 1.23 with 95% CI of [CCI];1.7]. Therefore, on a population basis the difference in proportion of responders is in the neighborhood of 56.7% - 51.3% =5.3%, so approximately 10% relative to Daivobet ointment – but still with an odds-ratio of 1.23 in favor of LEO 90100.	
Section 10.5 Appendix 5: COVID 19 Pandemic Contingency Plan	• [CCI] [CCI]. ~~The subjects will receive a link to complete the assessments in a web browser from their own device.~~	Electronic clinical outcome assessment will not be set up for phone visit. Subject may receive the paper version of the [CCI] via courier.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

Table of Contents

List of Tables

List of Figures

Abbreviations and Definitions

Abbreviation	Description
AE	adverse event
ANCOVA	analysis of covariance
CCI	CCI
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CI	Confidence interval
CMO	contract manufacturing organisation
COVID-19	coronavirus disease 2019
CRO	contract research organisation
CCI	CCI
(e)CRF	(electronic) case report form
EDC	electronic data collection
FAS	full analysis set
FCS	fully conditional specification
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IB	investigator's brochure
IE	intercurrent event
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IWRS	interactive web response system
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
(m)PASI	(modified) Psoriasis Area and Severity Index
OR	odds ratio
CCI	CCI
PGA	Physician's Global Assessment of disease severity
CCI	CCI
CCI	CCI
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
CCI	CCI
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	system organ class
US	United States
WOCBP	woman of childbearing potential
WONCBP	woman of nonchildbearing potential

1 Protocol Summary

1.1 Synopsis

Protocol Title: A phase 3, randomised, investigator-blind, active controlled, parallel group, multi-centre trial comparing the efficacy and safety of 4 weeks treatment with LEO 90100 and Daivobet® ointment in adult Chinese subjects with stable plaque psoriasis

Brief Title: A study to investigate efficacy and safety with LEO 90100 compared with Daivobet® ointment in adult Chinese subjects with stable plaque psoriasis

Sponsor Protocol No.: LP0053-2277

Study Phase: Phase 3

Sponsor: LEO Pharma A/S

Rationale:

LEO 90100 (Enstilar® Foam) is a fixed combination product containing calcipotriol monohydrate, a vitamin D analogue, and betamethasone dipropionate, a potent steroid that is approved for topical treatment of stable plaque psoriasis in many countries. This trial is conducted to assess the efficacy and safety of LEO 90100 when used on the body for the treatment of stable plaque psoriasis in adult Chinese subjects, compared to Daivobet® ointment, which is approved in China for the treatment of stable plaque psoriasis on the body.

Primary Objective, Related Endpoints and Primary Estimands:

Primary Objective	Endpoints	Primary Estimands
To evaluate the efficacy of LEO 90100 compared with Daivobet® ointment on severity and extent of stable plaque psoriasis.	*Primary endpoint* • Having PGA score of 0 (clear) or 1 (almost clear) at Day 29, with at least a 2-point reduction from baseline.	• Composite strategy will be used to address permanent discontinuation of IMP not due to pandemic restrictions.[1] • Hypothetical strategy will be used to address permanent discontinuation of IMP due to pandemic restrictions.[2]
	Key secondary endpoint • Having a decrease in mPASI of at least 75% (mPASI-75) from baseline to Day 29. *Secondary endpoint* • Having a decrease in mPASI of at least 90% (mPASI-90) from baseline to Day 29.	
	CCI CCI CCI CCI CCI CCI	• CCI CCI CCI CCI CCI CCI CCI CCI

Abbreviations: AE=adverse event; CCI; COVID-19=coronavirus disease 2019; IMP=investigational medicinal product; mPASI=modified Psoriasis Area and Severity Index; mPASI-75=a decrease in mPASI of at least 75%; mPASI-90=a decrease in mPASI of at least 90%; PGA=Physician's Global Assessment of disease severity; SAP=statistical analysis plan.

[1] **Permanent discontinuation of IMP not due to pandemic restrictions**: This event occurs when a subject permanently discontinues IMP for reasons not related to pandemic restrictions. This event can occur either at the subject's own initiative or at the investigator's or sponsor's discretion. The timing of the event will be defined in the SAP. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will be interpreted as permanent discontinuation of IMP not due to pandemic restrictions.

[2] **Permanent discontinuation of IMP due to pandemic restrictions**: This event occurs when a subject permanently discontinues IMP for reasons related to pandemic restrictions. Examples of permanent discontinuation of IMP due to pandemic restrictions are quarantines (i.e., subjects who have or have a suspicion they have COVID-19 and are not allowed on to site for visits due to quarantine measures imposed), travel limitations, subject being unable or unwilling to travel to site due to personal pandemic-related reasons, site closures, reduced availability of site staff and interruptions to the supply chain of IMP. The timing of the event will be defined in the SAP. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will not be interpreted as permanent discontinuation of IMP due to pandemic restrictions, unless caused by quarantine measures.

Secondary and CCI Objectives and Endpoints:

Objectives	Endpoints
Secondary	
To evaluate the safety of LEO 90100 compared with Daivobet® ointment treating stable plaque psoriasis.	*Secondary endpoint* • Number of TEAEs from baseline to Day 43 per subject.
CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI

Abbreviations: CCI
CCI TEAEs=treatment-emergent adverse events.

Overall Design Summary:

- This phase 3, randomised, prospective, investigator-blinded, active-controlled, parallel group, multicentre trial will evaluate the efficacy and safety of 4 weeks treatment with LEO 90100 compared with Daivobet® ointment.
- Native Chinese subjects (aged ≥ 18 years) with at least mild stable plaque psoriasis.
- Trial subjects will be randomised in a 1:1 ratio to either LEO 90100 or Daivobet® ointment treatment, stratified by Physician's Global Assessment of disease severity (PGA) at baseline (mild [PGA=2], moderate [PGA=3] or severe [PGA=4]).
- As LEO 90100 and Daivobet® ointment are provided in different containers (LEO 90100 is in a can and Daivobet® ointment is in a tube), the subject will know which investigational medicinal product (IMP) he/she is receiving. To ensure that the investigator's assessment of efficacy and safety is not influenced or biased, the investigator will stay blinded throughout the trial.

Brief Summary:

The purpose of this trial is to evaluate the efficacy and safety of LEO 90100 compared with Daivobet® ointment in native Chinese subjects (aged ≥ 18 years) with at least mild stable plaque

psoriasis. For each subject, the trial duration will be up to 10 weeks. The treatment duration will be up to 4 weeks. The visit frequency will be bi-weekly from the treatment period to the end of the follow-up period.

Number of Subjects:

Approximately 600 trial subjects will be randomised in a 1:1 ratio to either LEO 90100 or Daivobet® ointment treatment, with 300 evaluable subjects per treatment group.

Trial Arms and Duration:

For each subject, the trial will last 6 weeks to 10 weeks, including:

- A washout/screening period of up to 4 weeks (at least 1 visit).
- A treatment period up to 4 weeks (3 visits).
- A safety follow-up period of 2 weeks (1 visit for all subjects 2 weeks after the last IMP administration).

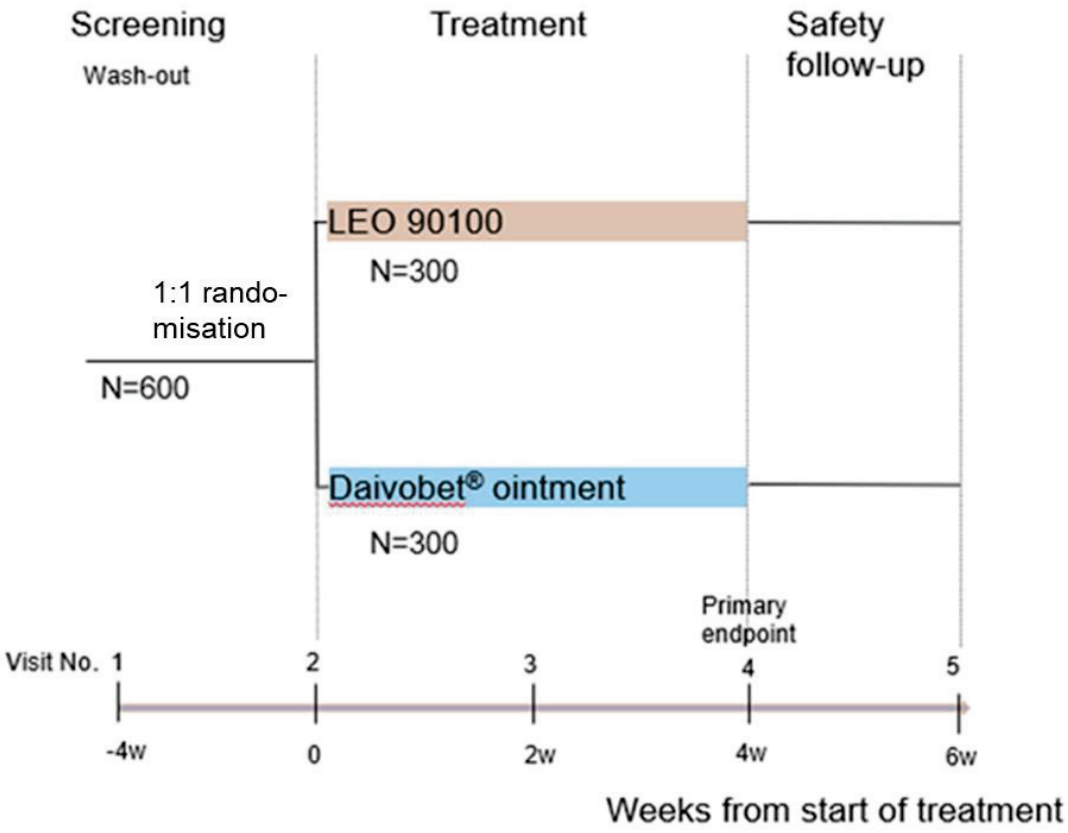
Eligible subjects will be randomised in a 1:1 ratio to receive 1 of the following treatments:

- Topical administration of LEO 90100 once daily (up to 15 g per day) until Week 4.
- Topical administration of Daivobet® ointment once daily (up to 15 g per day) until Week 4.

Data Monitoring/Other Committee: No

1.2 Schema

Figure 1–1 Trial Design



Abbreviations: N=number of subjects; No.=number; w=weeks.

1.3 Schedule of Activities (SoA)

Table 1–1 Schedule of Activities (SoA)

Procedure	Washout/ screening	Treatment period			Follow-up	Unscheduled visit[2]	Early termination[3]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**			
Day	**-28 to 1**	**1**	**15**	**29**	**43**			
Week	**-4 to 0**	**0**	**2**	**4**	**6**			
Visit window (days)[1]	**NA**	**0**	**±3**	**±3**	**±3**			
Trial population and eligibility								
Informed consent[4]	X							10.1.3
Subject eligibility	X	X						5.1; 5.2
Investigator assessments at screening/baseline only								
Demographics	X							8.1
Fitzpatrick skin type	X							8.1
Medical history[5]	X	X						8.1
Height and weight		X						8.1
Treatments								
Randomisation		X						6.3
Subject treatment instructions		X						6.1.1
Dispensing of IMP		X	X					6.2
Dispensing of subject diary		X						6.5
IMP administration		X	X			X		6.1.1
Diary recording by subjects[6]		X	X	X				6.5
Treatment compliance[7]			X	X		X	X	6.5
Return of IMP			X	X	X	X	X	6.2
Concomitant medication and concurrent procedures	X	X	X	X	X	X	X	6.9.1

Procedure	Washout/ screening	Treatment period			Follow-up	Unscheduled visit[2]	Early termination[3]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**			
Day	**-28 to 1**	**1**	**15**	**29**	**43**			
Week	**-4 to 0**	**0**	**2**	**4**	**6**			
Visit window (days)[1]	**NA**	**0**	**±3**	**±3**	**±3**			
Investigator assessments of efficacy								
PGA[8]	X	X	X	X			X	8.2.1.1
CCI	X	X	X	X			X	8.2.1.2
mPASI		X	X	X			X	8.2.1.3
CCI								
CCI		X	X	X			X	8.2.2.1
CCI		X	X	X			X	8.2.2.2
CCI		X	X	X			X	8.2.2.3
Assessments of safety								
Physical examination	X			X		X	X	8.3.1
Chemistry (vitamin D)	X	X		X	X	X	X	8.3.2; 10.2
Serum and urine calcium and creatinine (central laboratory)	X	X		X	X	X	X	8.3.2; 10.2
Serum cortisol		X		X			X	8.3.2; 10.2
Serum pregnancy test	X							8.3.3; 8.4.5; 10.2
Chemistry (albumin, potassium, sodium and urea)	X	X		X	X	X	X	8.3.2 10.2
Urine pregnancy test (at site)	X	X		X	X	X	X	8.3.3; 8.4.5; 10.2
AEs	X	X	X	X	X	X	X	8.4
End of treatment/trial								
End-of-treatment form[9]				X			X	7.1
End-of-trial form[9]					X		X	4.4

Abbreviations: AEs=adverse events; CCI; eCRF=electronic case report form; ICF=informed consent form; IMP=investigational medicinal product; mPASI=modified Psoriasis Area and Severity Index; NA=not applicable; PGA=Physician's Global Assessment; CCI CCI

1 If the date of a trial visit does not fall in the visit window, subsequent visits should be planned to maintain the original visit schedule as outlined in the SoA above.

2 Assessments to be performed at unscheduled visits will be at the discretion of the investigator. The subject will be asked about AEs by the investigator.

3 Subjects who permanently discontinue IMP or withdraw from the trial will be asked to come for the primary endpoint visit and will be followed up (Section 7.1).

4 The ICF must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and washout of prohibited medications. Screening evaluations can be either on the same date the ICF was signed or at a later date.

5 In case medical history is incomplete at screening visit, missing data will be retrieved at Day 1 (baseline).

6 To supplement the compliance check made at Visits 3 and 4, a subject diary should be completed daily during the treatment period.

7 Treatment compliance includes recording the number of applications missed by each subject (Section 6.5).

8 The body areas to be assessed are the trunk (including the neck) and the limbs, i.e., arms (including hands) and legs (including feet and buttocks). The face, scalp, genitals and skin folds (i.e., the axillae, the inguinal folds, the inter-gluteal folds and the infra-mammary folds) are not to be treated with the IMP or assessed as part of the efficacy analysis.

9 An end-of-treatment form (Section 7.1) and end-of-trial form (Section 4.4) must be completed in the eCRF for all subjects assigned to treatment.

2 Introduction

LEO 90100 (Enstilar® Foam) is a fixed combination product containing calcipotriol monohydrate, a vitamin D analogue, and betamethasone dipropionate, a potent steroid that is approved for topical treatment of stable plaque psoriasis in many countries.

2.1 Trial Rationale

This trial is conducted to assess efficacy and safety of LEO 90100 when used on the body for the treatment of stable plaque psoriasis in adult Chinese subjects, compared to Daivobet® ointment, which is approved in China for the treatment of stable plaque psoriasis on the body.

2.2 Background

2.2.1 Plaque Psoriasis

Plaque psoriasis is a chronic, immune-mediated, inflammatory skin disease affecting up to 3% of the global population[1, 2, 3]. In China, the prevalence of psoriasis is 0.47%[4]. In addition to skin manifestations, psoriasis is associated with multiple co-morbidities such as arthritis and cardiovascular disease[5, 6]. The hallmark of psoriasis is inflammation of the skin. In the majority of subjects, psoriasis manifests as plaque type psoriasis, clinically seen as sharply demarcated, elevated, scaling and erythematous plaques located predominantly on the scalp, extensor sides of elbows and knees and the sacral region[6, 7, 8]. Skin lesions can be painful and pruritic and may cause significant emotional and physical discomfort[9, 10].

The majority of affected subjects have mild-to-moderate disease and can be treated with topical therapies[11]. In the group of subjects with moderate-to-severe psoriasis, topical therapies are also appropriate as an adjunct to either phototherapy or systemic therapy, including biological agents[11,12]. One of the advantages of topical therapies is a reduced risk of systemic toxicity compared with other treatment modalities.

2.2.2 LEO 90100

LEO 90100 (Enstilar® Foam) is a fixed combination product containing calcipotriol monohydrate, a vitamin D analogue, and betamethasone dipropionate, a potent steroid.
LEO 90100 is approved for topical treatment of stable plaque psoriasis in many countries. The first authorisation was received in the United States (US) in 2015, where LEO 90100 was approved for topical treatment of stable plaque psoriasis (plaque psoriasis) in subjects 18 years of age and older. The indication was extended to subjects 12 years of age and older with stable plaque psoriasis in July 2019. The marketing authorisation in Europe was achieved in 2016, where LEO 90100 was approved for topical treatment of stable plaque psoriasis in subjects 18

years and older. To date, LEO 90100 is approved in more than 40 markets worldwide, including Hong Kong (China). LEO 90100 is launched under the trademarks Enstilar®, Enstilum® and Dovobet® Foam. The recommended treatment duration is once daily for up to 4 weeks, and long-term maintenance is also approved in several countries.

Daivobet® ointment and Xamiol® gel contain the same 2 active pharmaceutical ingredients (calcipotriol monohydrate and betamethasone dipropionate), at the same concentration as LEO 90100, and are approved for topical treatment of stable plaque psoriasis in China since 2008 and 2013 respectively. LEO 90100 therefore represents a new formulation of a well-established combination with which Chinese physicians have gained much experience. Based on data from global trials, it is hypothesised that LEO90100 will have an advantage over Daivobet® ointment in terms of improved efficacy in the Chinese population.

Up until 30-Nov-2021, 797,227 treatment courses of Daivobet® ointment and 171,316 treatment courses of Xamiol® gel have been prescribed in China.

A detailed description of the chemistry, pharmacology, efficacy and safety of LEO 90100 is provided in the investigator's brochure (IB) and Summary of Product Characteristics (SmPC)[13, 14].

2.3 Ethical Considerations

This trial will be conducted in accordance with the ethical principles that have their origins in International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and in compliance with the approved protocol and applicable regulatory requirements.

Trial subjects will be under careful supervision of dermatologists and physicians experienced in GCP clinical trials and in the handling of plaque psoriasis. During the entire course of the trial, subjects will be required to attend planned trial visits every 2 weeks. At either their own or the physician's discretion, subjects may be withdrawn from the trial at any time. In case of lack of efficacy of the investigational medicinal product (IMP), it will be at the discretion of the trial site physician whether the subject needs rescue treatment or discontinuation from the trial. This is further described in Section 6.9.2 and Section 7.

No children or other vulnerable subjects incapable of giving informed consent will be included in this clinical trial. Pregnant or breastfeeding women and women trying to conceive will not be included in the trial. Woman of childbearing potential (WOCBP) must agree to use an adequate method of contraception to prevent pregnancy during the clinical trial and until end-of-treatment of IMP and for at least 8 weeks after last administration of the IMP. In addition, all WOCBP will

have a pregnancy test performed before and after study treatment to minimise the risk of foetuses being exposed to the IMP.

The trial design chosen for this efficacy and safety trial is regarded as ethically justified and adherent with ethical requirements. All subjects will receive active treatment for their plaque psoriasis during the treatment period.

2.4 Benefit/Risk Assessment

To date, 16 clinical trials with LEO 90100 have been completed. These trials included in total over 2000 subjects with stable plaque psoriasis and approximately 334 healthy subjects. Available clinical data do not indicate any specific safety or tolerability concerns with LEO 90100 formulation in adult subjects. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LEO 90100 and Daivobet® ointment may be found in the IB and SmPC of Enstilar® Foam and the SmPC of Daivobet® ointment[13, 14, 15].

In this trial, all subjects will be treated with LEO 90100 or Daivobet® ointment. Both IMPs will be applied to psoriasis lesions on the following body areas: the trunk (including the neck) and the limbs (such as arms [including hands] and legs [including feet and buttocks]). The face, scalp, genitals and skin folds (i.e., the axillae, the inguinal folds, the inter-gluteal folds and the infra-mammary folds) are not to be treated with the IMPs or assessed as part of the efficacy analysis. Permitted concomitant anti-psoriatic treatment for the scalp, trunk and limbs and face and sensitive areas (i.e., armpits, groin, under the breasts and in other skin folds around the genitals and buttocks) are specified in Section 6.9.1.

Overdose with calcipotriol may be associated with hypercalcaemia (although unlikely to occur if used within the limits of 105 g of LEO 90100 or Daivobet® ointment per week). Clinically important hypercalcaemia will be managed at the investigator's discretion with rehydration, bisphosphonate administration or according to local standard of care. Hypercalcaemia should rapidly subside when treatment is discontinued.

Overdose with corticosteroid containing products (although unlikely to occur if used within the limits of 105 g of LEO 90100 or Daivobet® ointment per week) may result in suppression of adrenal function which is usually reversible. In such cases, symptomatic treatment is indicated. In case of chronic toxicity, corticosteroid treatment must be discontinued gradually.

Subjects may face discomfort and might have to discontinue ongoing treatment during the washout phase. However, once the subjects enter the trial, they will be under close supervision of a dermatologist and will be provided with LEO 90100 or Daivobet® ointment for treatment of

psoriasis. LEO 90100 and Daivobet® ointment have been shown to be effective and safe when used for up to 4 weeks and for long-term maintenance (trial LP0052-1004).

Participation in clinical trials may currently be associated with increased risk and added challenges due to the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The proposed trial is not believed to put subjects with plaque psoriasis at an increased risk for viral infections including SARS-CoV-2. However, a risk of exposure to infected people cannot be excluded as the trial subjects may enter public areas (e.g., commute to the trial site) and have additional human contact (e.g., with trial site staff). Appropriate risk assessments and mitigation measures must be considered to protect the subjects and trial site staff and to ensure the integrity of the trial data. If on-site visits are not possible, the affected site will postpone screening and randomisation of new subjects until on-site visits can be conducted. For already randomised subjects, post-baseline visits can be done remotely via phone or video (see Section 10.5 for details). During the trial, safety monitoring will ensure that all AEs are continuously monitored. COVID-19 vaccines are allowed during the trial and should be recorded as a concomitant medication.

Details regarding justification of exclusion criteria for safety reasons can be referenced from Section 4.2.

Taking into account the measures taken to minimise risk for the trial subjects, the potential risks identified in association with LEO 90100 and Daivobet® ointment are justified by the anticipated benefits that may be afforded to adult Chinese subjects with stable plaque psoriasis.

3 Objectives, Endpoints and Estimands

Table 3–1 Primary Objective, Related Endpoints and Primary Estimands

Primary Objective	Endpoints	Primary Estimands
To evaluate the efficacy of LEO 90100 compared with Daivobet® ointment on severity and extent of stable plaque psoriasis.	*Primary endpoint* • Having PGA score of 0 (clear) or 1 (almost clear) at Day 29, with at least a 2-point reduction from baseline.	• Composite strategy will be used to address permanent discontinuation of IMP not due to pandemic restrictions.[1] • Hypothetical strategy will be used to address permanent discontinuation of IMP due to pandemic restrictions.[2]
	Key secondary endpoint • Having a decrease in mPASI of at least 75% (mPASI-75) from baseline to Day 29. *Secondary endpoint* • Having a decrease in mPASI of at least 90% (mPASI-90) from baseline to Day 29.	
	CCI	• CCI

Abbreviations: AE=adverse events; CCI; COVID-19=coronavirus disease 2019; IMP=investigational medicinal product; mPASI=modified Psoriasis Area and Severity Index; mPASI-75=a decrease in mPASI of at least 75%; mPASI-90=a decrease in mPASI of at least 90%; PGA=Physician's Global Assessment of disease severity; SAP=statistical analysis plan.

[1] **Permanent discontinuation of IMP not due to pandemic restrictions**: This event occurs when a subject permanently discontinues IMP for reasons not related to pandemic restrictions. This event can occur either at the subject's own initiative or at the investigator's or sponsor's discretion. The timing of the event will be defined in the SAP. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will be interpreted as permanent discontinuation of IMP not due to pandemic restrictions.

[2] **Permanent discontinuation of IMP due to pandemic restrictions**: This event occurs when a subject permanently discontinues IMP for reasons related to pandemic restrictions. Examples of permanent discontinuation of IMP due to pandemic restrictions are quarantines (i.e., subjects who have or have a suspicion they have COVID-19 and are not allowed on to site for visits due to quarantine measures imposed), travel limitations, subject being unable or unwilling to travel to site due to personal pandemic-related reasons, site closures, reduced availability of site staff and interruptions to the supply chain of IMP. The timing of the event will be defined in the SAP. Permanent discontinuation

of IMP due to sickness with COVID-19 (an AE) will not be interpreted as permanent discontinuation of IMP due to pandemic restrictions, unless caused by quarantine measures.

Table 3–2 Secondary and CCI Objectives and Endpoints

Objectives	Endpoints
Secondary	
To evaluate the safety of LEO 90100 compared with Daivobet® ointment treating stable plaque psoriasis.	*Secondary endpoint* • Number of TEAEs from baseline to Day 43 per subject.
CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI

Abbreviations: CCI; CCI; CCI
CCI TEAEs=treatment-emergent adverse events.

4 Trial Design

4.1 Overall Design

This phase 3, randomised, prospective, investigator-blinded, active-controlled, parallel group, multicentre trial will evaluate the efficacy and safety of 4 weeks treatment with LEO 90100 compared with Daivobet® ointment in native Chinese subjects (aged ≥ 18 years) with at least mild stable plaque psoriasis.

600 trial subjects are planned to be randomised in a 1:1 ratio to either LEO 90100 or Daivobet® ointment treatment. Randomisation will be stratified by Physician's Global Assessment of disease severity (PGA) at baseline (mild [PGA=2], moderate [PGA=3] or severe [PGA=4]).

For each subject, the trial will last 6 weeks to 10 weeks, including:

- A washout/screening period up to 4 weeks (at least 1 visit);
- A treatment period up to 4 weeks (3 visits);
- A safety follow-up period of 2 weeks (1 visit for all subjects 2 weeks after the last IMP administration).

The subjects will provide written consent according to national laws and regulations before any trial-related activities are carried out.

Washout/Screening Period

For subjects who have been receiving prohibited medications (see Section 6.9) prior to screening, the screening period may be extended up to 4 weeks to ensure they complete the required washout period before they start receiving the IMP. On completion of the washout period, confirmation of the subject's ongoing eligibility for the trial will be made at Day 1 (baseline). However, if no washout is needed the subject will enter Day 1 (baseline) directly.

Treatment Period

The treatment period will last for up to 4 weeks and includes 3 visits: Visit 2 (Day 1), Visit 3 (Week 2) and Visit 4 (Week 4). The start of IMP treatment will be at Day 1 and this visit will be considered as baseline. The first application of the IMP will be made at site under supervision and instruction of an un-blinded member of the trial staff (not the investigator, as this is an investigator-blinded trial) at the Day 1 visit. The subjects also have the option to apply the first IMP at home after the instruction has been given at the site. Refer to Section 6.1 for further details on the treatment principles applied.

Follow-up Period

The follow-up visit (Visit 5) will be performed at Week 6, which is 2 weeks after the last visit in the treatment period.

The trial design is illustrated in Figure 1–1 and visit schedule is provided in Table 1–1.

Refer to Section 10.5 for the COVID-19 pandemic contingency plan.

4.2 Scientific Rationale for Study Design

Treatment Duration and Comparator

As part of the registration process for LEO 90100 in China, this trial is being conducted to provide efficacy and safety data in the Chinese population. The treatment regimen of once daily for a duration of 4 weeks is consistent with the current approved label in Europe and the US. The comparator, Daivobet® ointment, is a well-established treatment of stable plaque psoriasis in China.

Trial Population

The current indication of LEO 90100 in Europe is topical treatment of stable plaque psoriasis in adults. The inclusion and exclusion criteria are set to include the target population for LEO 90100 in China, namely native Chinese subjects aged ≥ 18 years with stable plaque psoriasis.

Inclusion criteria 2 to 4 are set to ensure that subjects have a stable and correct diagnosis of stable plaque psoriasis, and to comply with the reference safety information:

Exclusion criteria 1, 2, 3 and 14 to 16 are set to exclude subject conditions that may interfere with safety endpoint assessment.

Exclusion criterion 4 is set to minimise the risk of serious allergic reactions.

Exclusion criteria 5 to 12 are set to exclude subject conditions that may interfere with clinical and safety endpoint assessment.

Exclusion criterion 17 is set to ensure that subjects can tolerate the washout period.

Exclusion criteria 13 and 18 are set to exclude subject conditions that may interfere with clinical endpoint assessment.

Exclusion criterion 19 is set to ensure subjects are mentally stable, able to comprehend the consent process, follow the protocol and maximise safety of patients.

Exclusion criterion 20 is set to avoid biases.

Exclusion criterion 21 is set as there is currently no (adequate) safety data on the use of IMPs during pregnancy or lactation.

Trial Endpoints

The PGA scale, the modified Psoriasis Area and Severity Index (mPASI) and CCI [redacted] CCI [redacted] measurements will be used to determine the severity of psoriasis among subjects entering the trial. The trial will be investigator-blinded to avoid bias from knowing the type of IMP on efficacy assessments.

The PGA is an instrument used in clinical trials to rate the severity of psoriasis. It is a 5-point scale measurement ranging from 0 (clear) to 4 (severe) based on degree of plaque thickening, scaling and erythema (Section 8.2.1). The PGA score will be assessed by the investigator according to the Schedule of Activities (SoA, Table 1–1). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit.

The mPASI score will be assessed according to the SoA (Table 1–1). The investigator will make assessments of the extent and severity of clinical signs of the subject's psoriasis (Section 8.2.1.3). Assessment is not made for the face, scalp, genitals and skin folds (i.e., the axillae, the inguinal folds, the inter-gluteal folds and the infra-mammary folds). Hence, this PASI assessment is modified to exclude the aforementioned areas.

The investigator will assess the total psoriatic involvement on the trunk (including the neck) and the limbs (such as arms [including hands] and legs [including feet and buttocks]) as a percentage of the CCI [redacted]; any involvement on face, scalp, skin folds and genitals will be excluded. The purpose of this assessment is to obtain an estimate of the total area to be treated with the IMP. As a guidance for this estimate, CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

Trial-specific Laboratory Measurements

Laboratory evidence of adrenal insufficiency due to the use of topical corticosteroid treatment has been reported[17]. Any systemic absorption of betamethasone and potential effect on the adrenal function will be evaluated by measuring the serum cortisol concentration at baseline and at the end-of-treatment at Week 4.

Overdosage with topical calcipotriol, a vitamin D analogue, may cause hypercalcaemia due to the systemic absorption of calcipotriol[18]. Any systemic absorption of calcipotriol will be evaluated by measurement of serum calcium, urinary calcium excretion and the urinary calcium/creatinine ratio. Albumin-corrected serum calcium concentration is the most clinically relevant assessment for assessing calcium metabolism, but urinary assessment of calcium concentrations is more sensitive to identify small changes; therefore, both assessments will be included in this trial.

4.3 Justification for Dose

The strengths of LEO 90100 and Daivobet® ointment planned for the trial (up to 15 g per day, once daily for up to 4 weeks) follow the current approved label in Europe and the US.

4.4 End-of-Trial Definition

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

A subject is considered to have completed the trial if he/she has completed all periods of the trial including the last follow-up visit.

End-of-trial Form

An end-of-trial form must be completed in the electronic case report form (eCRF) for all subjects assigned to treatment when they have had their last visit (that is, the follow-up visit at Week 6 or early termination visit). The following data will be collected:

- Date of last contact.
- Did the subject complete the trial?
- Primary reason for not completing the trial based on the following categories: death, AE, lack of efficacy, lost to follow-up, withdrawal by subject, screen failure (failure to meet eligibility criteria) or other.
- Whether the reason for not completing the trial was related to COVID-19.

If 'AE' is selected, the AE in question will be linked to the non-completion of the trial. If 'other' is selected as a reason, a specification must be provided in the eCRF. If 'withdrawal by subject is selected, it will be recorded whether the subject withdrew informed consent or not.

For end-of-treatment form, please referred to Section 7.1.

5 Trial Population

Prospective approval of protocol deviations to eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

The trial population will consist of subjects who are native Chinese subjects aged ≥ 18 years with stable plaque psoriasis. Subjects must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

It will be recorded in the eCRF if the subject has met all the inclusion criteria and none of the exclusion criteria.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

Age

1. Subject of either gender aged 18 years or above.

Type of Subject and Disease Characteristics

2. A clinical diagnosis of stable plaque psoriasis for at least 6 months, which can be controlled by treatment with a maximum of 105 g of LEO 90100 per week, in the investigator's opinion.
3. Stable plaque psoriasis on the trunk and/or limbs (excluding psoriasis on the face, scalp, genitals, and skin folds) involving 2-30% of the CCI at Day 1 (Visit 2).
4. A PGA of at least 'mild' at Day 1 (Visit 2).
5. An mPASI score of at least 2 on the trunk and/or limbs at Day 1 (Visit 2).

Contraceptive/Barrier Requirements

6. Female subjects of childbearing potential* must use an adequate form of birth control throughout the trial and for at least 8 weeks after last administration of IMP.

   * A woman is defined as not being of childbearing potential if she is postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening) or surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy).
7. Male subjects with a female partner of childbearing potential must use adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).

Informed Consent

8. Signed and dated informed consent has been obtained prior to any protocol-related procedures.

Others

9. Subject is native Chinese.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Known or suspected renal insufficiency, hepatic disorders or severe heart disease.
2. Clinical signs or symptoms of Cushing's disease or Addison's disease.
3. Hypercalcaemia or abnormal calcium metabolism.
4. Known or suspected hypersensitivity to any component(s) of the IMP.

Prior/Concomitant Therapy

5. Systemic treatment with biological therapies, whether marketed or not, with a possible effect on plaque psoriasis within the following time periods:
    a. Etanercept (Yisaipu®), within 4 weeks prior to treatment assignment;
    b. Adalimumab (Humira®), Infliximab (Remicade®) or Brodalumab (Kyntheum®), within 8 weeks prior to treatment assignment;
    c. Ustekinumab (Stelara®), within 16 weeks prior to treatment assignment;
    d. Secukinumab (Cosentyx®), within 12 weeks prior to treatment assignment;
    e. Other products, within 4 weeks/5 half-lives (whichever is longer) prior to treatment assignment.
6. Systemic treatment with a possible effect on plaque psoriasis (e.g., corticosteroids, retinoids, methotrexate, ciclosporin and other immunosuppressants, traditional Chinese medicine) within 4 weeks prior to treatment assignment.
7. Systemic treatment with Apremilast within 4 weeks prior to treatment assignment.
8. Psoralen combined with ultraviolet A therapy (PUVA) within 4 weeks prior to treatment assignment.
9. Ultraviolet B (UVB) therapy within 2 weeks prior to treatment assignment.
10. Topical treatment of psoriasis with very potent (World Health Organization [WHO] classes IV and stronger) corticosteroids within 2 weeks prior to treatment assignment.
11. Topical treatment of psoriasis with traditional Chinese medicine within 2 weeks prior to treatment assignment.
12. Treatment with any non-marketed drug substance (that is, an agent which has not yet been made available for clinical use following registration) within 4 weeks/5 half-lives (whichever is longer) prior to treatment assignment.
13. Any topical treatment that could affect plaque psoriasis within 2 weeks prior to treatment assignment.

Prior/Concurrent Clinical Study Experience

14. Current participation in any other interventional clinical trial.
15. Previously screened in this clinical trial.
16. Previously participated in a clinical trial within 4 weeks prior to treatment assignment.

Diagnostic Assessments

17. Current diagnosis of guttate, erythrodermic, exfoliative, pustular or unstable (psoriasis is getting worse quickly and may become erythrodermic) psoriasis.
18. Subjects with any of the following conditions present on any skin area: viral lesions, fungal and bacterial skin infections, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, rosacea, acne vulgaris, acne rosacea, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, ulcers and wounds.

Other Exclusion Criteria

19. 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.
20. 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.
21. Women who are pregnant, lactating, or of childbearing potential and wish to become pregnant during the trial.

5.3 Lifestyle Considerations

Detailed instructions on permitted concomitant anti-psoriatic treatment, prohibited medication and procedures and contraception are provided in Section 6.9.1, Section 6.9.3 and Appendix 4: Contraceptive and Barrier Guidance, respectively.

5.4 Screen Failures

A screen failure occurs when a subject who has consented to participate in the clinical study is not subsequently randomly assigned to treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (i.e., eligibility requirements failed) and documentation of any medical occurrences that qualify as serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this trial (screen failure) may not be rescreened. However, if the reason for screen failure is not due to the subject failing to meet the eligibility criteria but is administrative (e.g., delayed test results or temporary site closure due to the COVID-19 pandemic), re-screening may be permitted. This will require approval by the medical monitor of the designated contract research organisation (CRO), after confirmation with

LEO Pharma A/S. Rescreened subjects should be assigned a new subject number for every screening/rescreening event.

5.4.1 Screening and Enrollment Log and Subject Identification Numbers

The investigator will maintain a log of all subjects considered for screening, whether they have provided written informed consent or not (pre-screening log). This log will be anonymous and will include the reason(s) for not entering the trial, if applicable, or the allocated subject identification number. For subjects not willing to consent, the main reason will be collected on the pre-screening log (e.g., time constraint, other safety concerns, number of blood samples).

Upon enrollment, each subject will receive a unique subject identification number. Subject numbers must not be re-used for different subjects.

The investigator will maintain a log of all consented subjects at the trial site (subject identification list). This log will include each subject's identity, date of consent and corresponding subject identification number, so that any subject may be identified if required for any reason. The log must not be copied or retained by LEO Pharma A/S and the designated CRO.

6 Trial Treatment(s) and Concomitant Therapy

Trial treatments are all pre-specified, investigational and non-IMPs, intended to be administered to the study subjects during the trial conduct.

6.1 Trial Treatment(s) Administered

Table 6–1 Trial Treatment(s) Administered

Treatment Name	LEO 90100	Daivobet® ointment
Active Ingredient and Concentration	Calcipotriol 50 mcg/g (as monohydrate) and betamethasone 0.5 mg/g (as dipropionate)	Calcipotriol 50 mcg/g (as monohydrate) and betamethasone 0.5 mg/g (as dipropionate)
Type	Drug	Drug
Dosage Formulation	Foam	Ointment
Dosage Level(s)	Once daily for 4 weeks; up to 15 g per day (or 105 g per week)	Once daily for 4 weeks; up to 15 g per day (or 105 g per week)
Route of Administration	Topical	Topical
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by LEO Pharma A/S.	Provided centrally by LEO Pharma A/S.
Packaging and Labelling	LEO 90100 will be provided in an aluminum can, which is pre-filled and subsequently administered through a continuous valve. 240 g of IMP will be dispensed every second week to subjects. Each can will be labelled as required per China requirement.	Daivobet® will be provided in a tube. 240 g of IMP will be dispensed every second week to subjects. Each tube will be labelled as required per China requirement.

Abbreviations: IMP= investigational medicinal product; NIMP=non-investigational medicinal product.

6.1.1 Administration of Trial Treatment

Dosing visits are shown in the SoA (Table 1–1). Subjects will be asked to use the assigned IMP once daily (up to 15 g per day) on skin affected by psoriasis on trunk and limbs, at no specific time of the day, for the duration of the 4 weeks treatment period, starting on Day 1.

At Visit 2 (Day 1) the subject will be given a treatment instruction sheet, and the subject will receive verbal instruction about how to apply the IMP. The first application of the IMP should be made either under supervision and instruction of an un-blinded member of the trial staff (not the investigator) or at home the same day the subject attended the Day 1 visit. The IMP will be dispensed by a designated un-blinded person (different from the investigator). The dispenser should ensure that the subject is familiar with the procedures for IMP administration, including instructions to return all dispensed cans/tubes, whether used or not, at the following visit. All returned IMP should be stored in the kit outer box.

Dispensing of IMP is described in Section 6.2.

6.2 Preparation, Handling, Storage and Accountability

Dispensation of IMP

All kits will contain 240 g of IMP.

IMP will be supplied at the dispensing visits listed in the SoA (Table 1–1). Each kit will contain the necessary amount of IMP to treat a subject between 2 visits in the treatment period.

The subject may use up to a maximum of 15 g per day (or 105 g per week), and 240 g of IMP will be dispensed every second week.

Storage of IMP

All LEO Pharma A/S supplied IMP must be stored in a secure, environmentally controlled and monitored (manual or automated) area under the conditions specified on the label and remain in the original container until dispensed, with access limited to the authorised site staff (different from the investigator).

The investigator or designee (e.g., hospital pharmacy) must maintain a log to confirm appropriate conditions (e.g., temperature) have been maintained during transit for all IMP received, and any discrepancies are reported and resolved before use of the IMP. Damaged IMP should be documented and may not be used. Storage facilities should be checked at least every working day.

The following storage conditions and handling precautions should be observed for LEO 90100:

- Store below 30°C. Do not freeze.
- Extremely flammable aerosol.
- Pressurised container: May burst if heated.
- Protect from sunlight.
- Do not expose to temperatures exceeding 50°C.
- Do not pierce or burn, even after use.
- Do not spray on an open flame or other ignition source.
- Keep away from sparks, open flames and other ignition sources.
- No smoking.
- Keep out of the reach of children.

The following storage conditions and handling precautions should be observed for Daivobet® ointment:

- Do not store above 25°C. Do not refrigerate.
- Keep the tube in the outer carton and way from sunlight.
- Keep out of the reach of children.

Only subjects randomised in the study may receive IMP, and only authorised site staff (different from the investigator) may supply, prepare or administer IMP.

Accountability of IMP

The investigator is fully responsible for the IMP accountability, reconciliation and record maintenance (e.g., receipt, reconciliation and final disposition records). However, the aforementioned tasks will be delegated to an un-blinded person as the investigator needs to stay blinded from the IMP type.

Management of IMP may be delegated (e.g., to a hospital pharmacy) as locally applicable.

Documentation of drug accountability must be kept of the IMP administered to each individual subject in the trial. This documentation must be available during monitoring visits and will be checked by the monitor to verify correct dispensing of the IMP.

The subject will return used, partly used and unused IMP (including packaging material) at the visits specified in the SoA (Table 1–1).

Returned IMP (used, partly used and unused [including packaging material]) can be stored under condition as described above and must be stored separately from non-allocated IMP.

All unused IMP (including packaging material) supplied by the contract manufacturing organisation (CMO) on behalf of LEO Pharma A/S will be returned to the CMO or local depot. Prior to their return, the IMP must be fully accounted for by the monitor with the help of site staff responsible for dispensing the IMP.

IMP Destruction

Used and unused IMP will be destroyed by the CMO or local depot according to approved procedures and/or local requirements.

6.3 Treatment Assignment

Subjects will be randomly assigned to one of the following IMP, via a central interactive web response system (IWRS) in accordance with a computer-generated randomisation schedule in a 1:1 ratio:

- LEO 90100
- Daivobet® ointment

Randomisation will be stratified by baseline disease severity determined by the PGA (mild [PGA=2], moderate [PGA=3] or severe [PGA=4]).

At Visit 2, after confirmation of eligibility, the subject randomisation number will be generated by the IWRS. The IWRS will assign treatment for each subject and will provide a kit number. Likewise, at the subsequent dispensing visits, the site personnel (different from the investigator) will access the IWRS to be informed of the kits to assign to the subject.

IMP will be administered/dispensed at the study visits as summarised in the SoA (Table 1–1).

Returned IMP should not be re-dispensed to the subjects.

6.3.1 Randomisation Code List

The randomisation code lists will be generated by the IWRS of the designated CRO. These files will be stored securely by the CRO, inaccessible to staff involved with the conduct and administration of the clinical trial until the clinical trial data base is declared clean and released to the trial statistician.

These files are only shared with un-blinded LEO Pharma A/S representatives Clinical Trial Supplies (CTS), Global Safety or the CMO as required.

6.4 Blinding

The trial is investigator-blinded.

As LEO 90100 and Daivobet® ointment are provided in different containers (LEO 90100 is in a can and Daivobet® ointment is in a tube), the subject will know which IMP he/she is receiving. To ensure that the investigator's assessment of efficacy and safety is not influenced or biased, the investigator will stay blinded throughout the trial. It is important that the investigator does not see or get information about which IMP the subject is receiving. The IMP will be handed out to the subjects by a designated person so the investigator will not know which IMP the subject has

received. Subjects will be instructed/reminded not to reveal the form of the IMP that they are dispensed to the investigator each time product is dispensed.

In addition, to minimise the risk of potential bias, a measure of artificial blinding will be implemented to preserve the integrity of the trial data. Detailed strategies on artificial blinding and a study team list specifying blinded and unblinded functions will be described in a blinding plan.

6.4.1 Breaking the Randomisation Code

Un-blinding of Individual Subject Treatment

Un-blinding of individual subject treatment is not considered necessary as the ingredients in the 2 IMPs are the same.

Un-blinding of the Clinical Trial

The clinical trial will be un-blinded when a final validated database has been produced, the statistical analysis specified in this protocol has been reviewed in relation to the blinded data actually obtained and the Statistical Analysis Plan (SAP) Update has been approved.

6.5 Treatment Compliance

Subjects will be provided with a paper diary to record adherence to the once daily treatment regimen during the treatment period. The diary should be returned to the site staff at the subsequent trial visit.

The investigator (or designee) should review the compliance data recorded by subjects in the paper diary before each visit. In case of non-compliance, the investigator should remind the subject of the importance of following the instructions given. Compliance/non-compliance and the reason for it must be recorded in the eCRF.

6.6 Dose Modification

Not applicable

6.7 Continued Access to Trial Treatment After the End of the Trial

After the end of the trial, subjects will be treated at the investigator’s discretion or referred to other physician(s) according to standard practice.

6.8 Treatment of Overdose

For this study, any dose of LEO 90100 and Daivobet® ointment greater than 105 g within one week will be considered an overdose.

Overdose with calcipotriol may be associated with hypercalcaemia. Clinically important hypercalcaemia will be managed at the investigator's discretion with rehydration, bisphosphonate administration or according to local standard of care. Hypercalcaemia should rapidly subside when treatment is discontinued.

Overdose with corticosteroid containing products may result in suppression of adrenal function, which is usually reversible. In such cases, symptomatic treatment is indicated. In case of chronic toxicity, corticosteroid treatment must be discontinued gradually.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the trial must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.
- The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Prior and Concomitant Medications Review

The investigator or qualified designee will review and record prior medication use taken by the subject within at least 16 weeks prior to treatment assignment or longer if required to washout other products per exclusion criterion 5.

The investigator or qualified designee will record medication, if any, taken by the subject during the study through the last visit. Concomitant medications will be recorded for 14 days after the last IMP administration (or longer if related to an SAE).

6.9.1 Concomitant Medication and Concurrent Procedures

Concomitant anti-psoriatic treatments allowed during the trial are listed in Table 6–2.

Table 6–2 Permitted Concomitant Anti-psoriatic Treatment

Location	Permitted concomitant anti-psoriatic treatment
Scalp	Non-medicated and medicated shampoos/products except those that contain corticosteroids or vitamin D analogues (e.g., tar, salicylic acid, tazaroten, anthraline) are allowed.
Trunk/limbs	Bath oils and moisturising soaps are allowed. Unlimited use of emollients (except within 6 hours of clinic visits) is allowed. Emollients used should not contain alpha-hydroxy acids, beta-hydroxy acids or acetylic acid; emollients containing urea acid (≤ 5%) are allowed.
Face and sensitive areas	Any topical treatments other than class 1-5* corticosteroids or vitamin D analogues (calcipotriol, calcitriol or tacalcitol) are allowed (e.g., topical calcineurin inhibitors). Topical use of mild corticosteroids (class 6-7)* is allowed, but should be for short term use and be minimised to the largest possible extent. Unlimited use of emollients is allowed. Bath oils and moisturising soaps are allowed.

* Corticosteroid classified by World Health Organization (WHO) model prescribing information: drugs used in skin diseases, 1997[19].

Note: Sensitive areas refer to armpits, groin, under the breasts and in other skin folds around the genitals and buttocks.

Any medication or vaccine that the subject receives and any medical procedure the subject undergoes, from screening through follow-up, must be recorded in the subject's medical record and the eCRF.

6.9.2 Rescue Treatment

If medically necessary (i.e., to control intolerable psoriatic symptoms), rescue treatment for stable plaque psoriasis can be initiated to trial subjects at the discretion of the investigator. If possible, investigators should attempt to limit the first step of rescue treatment to topical treatments. Before the initiation of rescue treatment, investigators should make every attempt to conduct efficacy and safety assessments (for example, disease severity scores [PASI and sPGA] and safety labs). Unscheduled visit(s) may be used for this purpose, if necessary.

The investigator is responsible for the rescue treatment oversight and duration as well as switching and escalating to another rescue therapy, when appropriate. The investigator should consider if discontinuation of IMP is necessary depending on the type of rescue medication and the severity of the subject's symptoms (see Section 7, discontinuation criteria).

The use of any rescue treatment must be recorded in the eCRF (refer to Section 7).

6.9.3 Prohibited Medication and Procedures

Prohibited medications and procedures during the trial are listed in Table 6–3. Details regarding prohibited medications and procedures prior to screening and during washout are also described in Section 5.3.

In case any prohibited medication is used during the trial, they must be recorded as concomitant medication.

Table 6–3 Prohibited Medications and Procedures

Medication or procedure	Prohibited from	Prohibited to
Systemic treatment with biological therapies (marketed and not marketed), with a possible effect on plaque psoriasis	Etanercept: 4 weeks prior to treatment assignment.	End-of-trial (Week 6)
	Adalimumab, Infliximab or Brodalumab: 8 weeks prior to treatment assignment.	End-of-trial (Week 6)
	Ustekinumab: 16 weeks prior to treatment assignment.	End-of-trial (Week 6)
	Secukinumab: 12 weeks prior to treatment assignment.	End-of-trial (Week 6)
	Other products: within 4 weeks/5 half-lives prior to treatment assignment (whichever is longer).	End-of-trial (Week 6)
Systemic treatment with therapies other than biologicals with a possible effect on plaque psoriasis (e.g., corticosteroids, retinoids, methotrexate, ciclosporin, other immunosuppressants and traditional Chinese medicine)	4 weeks prior to treatment assignment.	End-of-trial (Week 6)
Systemic treatment with Apremilast	4 weeks prior to treatment assignment.	End-of-trial (Week 6)
Use of non-marketed/other IMPs	4 weeks or 5 half-lives (whichever is longer) prior to treatment assignment.	End-of-trial (Week 6)
PUVA therapy	4 weeks prior to treatment assignment.	End-of-trial (Week 6)
UVB therapy	2 weeks prior to treatment assignment.	End-of-trial (Week 6)

Medication or procedure	Prohibited from	Prohibited to
Any topical treatment including corticosteroids (except for emollients, non-steroid medicated shampoos and low potency corticosteroids on sensitive areas)	2 weeks prior to treatment assignment. On areas treated with the IMP, emollients should not be used within 6 hours of clinic visits.	End-of-trial (Week 6)
Initiation of or changes to concomitant medication that could affect plaque psoriasis (e.g., beta-blockers, lithium, anti-malaria drugs, ACE inhibitors)	Treatment assignment.	End-of-trial (Week 6)
Vitamin D supplements > 400 IU/day, (note: stable dose of vitamin D supplements ≤ 400 IU/day is permitted)	Treatment assignment.	End-of-trial (Week 6)

Abbreviations: ACE=angiotensin-converting-enzyme; IMP=investigational medicinal product; PUVA=psoralen combined with ultraviolet A therapy; UVB=ultraviolet B.

7 Discontinuation of Trial Treatment and Subject Discontinuation

A subject may withdraw from the trial (prior to first dose or during the treatment period) or permanently discontinue IMP at any time if the subject, the investigator or the medical monitor of the designated CRO considers that it is not in the subject's best interest to continue. The decision made by the designated CRO will need to be confirmed by LEO Pharma A/S.

Subjects who withdraw from the trial and subjects who permanently discontinue IMP will not be replaced.

Discontinuation of specific sites or of the study as a whole are handled as part of the appendix on Governance, Appendix 1, Section 10.1.8.

7.1 Discontinuation of Trial Treatment

It may be necessary for a subject to permanently discontinue IMP. If IMP is permanently discontinued, the subject should, if at all possible, remain in the study and attend an early termination visit and a follow-up visit 2 weeks after the last IMP administration. See the SoA (Table 1–1) for data to be collected at the time of IMP discontinuation and follow-up and for any further evaluations that need to be completed.

IMP must be discontinued permanently in case of the following:

- An AE that, in the opinion of the investigator or medical monitor of the designated CRO, contraindicates further dosing. The decision made by the designated CRO will need to be confirmed by LEO Pharma A/S;
- Evidence of pregnancy;
- Subject decides to discontinue voluntarily;
- Lack of efficacy defined as at least a [redacted] in mPASI score from baseline until Week 2 or unscheduled visits thereafter and where the investigator sees a need for rescue therapy.

End-of-treatment Form

An end-of-treatment form will be completed in the eCRF for all subjects exposed to IMP when they have had their last IMP administration. This form will also be completed for subjects who permanently discontinue IMP prior to Week 4 and subjects who withdraw from the trial, unless they were never exposed to IMP (see Table 1–1 for early termination assessments).

The date and time of last IMP administration and time of permanent discontinuation of IMP will be recorded on the end-of-treatment form. It will also be recorded if the subject completed the IMP treatment (i.e., did not discontinue IMP prior to Week 4). If not, the primary reason for permanent IMP discontinuation must be recorded in the medical records and on the end-of-treatment form in the eCRF where the following options are available:

- AE;
- Death;
- Lost to follow-up;
- Pregnancy;
- Withdrawal by subject;
- Lack of efficacy;
- Pandemic restrictions as defined in Section 9.3.5.1;
- Other.

If ‘AE’ is selected, the AE in question will be linked to the IMP discontinuation. If ‘other’ is selected as a reason, a specification must be provided in the eCRF.

It will also be recorded whether the IMP discontinuation was related to the COVID-19 pandemic to support the statistical analysis.

7.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at their own request or for any reason (or without providing any reason). A subject may be withdrawn at any time at the discretion of the investigator for safety, behavioral or compliance reasons. The subject will be permanently discontinued from the IMP and the trial at that time.

If the subject withdraws consent for disclosure of future information, the investigator must document this in the site study records; data collected before a withdrawal of consent may be retained and used.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1–1). Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

In order to ensure appropriate treatment of the subjects after they have discontinued IMP or withdrawn from the trial, the subjects will be treated at the investigator's discretion.

7.3 Loss to Follow-Up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and are unable to be contacted by the trial site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible (and within the visit window, where one is defined), counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether the subject wishes to and/or should continue in the trial.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record/eCRF.
- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

Study procedures and their timing are summarised in the SoA (Table 1–1). Protocol waivers or exemptions are not allowed. The IMP will be administered after subject and investigator assessments.

Trial subjects will be under careful supervision by the principal investigator who must be a dermatologist. Investigators must be physicians who are experienced in treating psoriasis, have documented experience and have received the training for the use of the assessments required by the protocol.

AEs must be assessed by a physician (Section 8.4).

Immediate safety concerns should be discussed with LEO Pharma A/S immediately upon occurrence or awareness to determine if the subject should continue or discontinue the IMP.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for subject visits, assessments, medication distribution and monitoring may be implemented by LEO Pharma A/S or the investigator, as per local health authority/ethics requirements.

Blood and urine samples will be drawn for biochemistry assessments and pregnancy tests (for WOCBP only). The maximum amount of blood collected from each subject over the duration of the trial, including any extra assessments that may be required, will not exceed 100 mL, which is less than the volume of blood taken during a blood donation (which is approximately 500 mL). The total volume of urine needed is approximately 300 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Subject Identification Card

All subjects will be given a subject identification card identifying them as subjects in a research study. The card will contain trial site contact information (including direct telephone numbers) to

be used in the event of an emergency. The investigator or qualified designee will provide the subject with a subject identification card immediately after the subject provides written informed consent. At the time of treatment allocation/randomisation, site personnel will add the treatment/randomisation number to the subject identification card.

The subject identification card also contains information about the IMP.

8.1 Administrative and Baseline Procedures

Demographics

The following demographic data will be recorded:

- Date of birth. If full date of birth is not allowed to be recorded, the month and/or year (as allowed by local legislation) of birth should be collected, together with the subject's age.
- Sex: Female or male.

Fitzpatrick Skin Type

The subject's skin type will be recorded using the Fitzpatrick skin classification (Table 8–1).

Table 8–1 Fitzpatrick Skin Classification

Skin type	Description
I	Individuals who never tan and always sunburn if exposed to any appreciable amount of sunlight, primarily red-headed individuals and lightly complected blondes.
II	Individuals who frequently burn but are able to tan to a small degree after extended sun exposure.
III	Individuals who burn infrequently and tan readily.
IV	Individuals who rarely burn and tan heavily with moderate sun exposure, especially individuals of Asian, American Indian, Mediterranean and Latin American descent.
V	Individuals who have dark constitutive pigmentation but become noticeably darker with sun exposure, especially lightly complected Black individuals, those of Indian descent.
VI	Individuals who have the heaviest constitutive pigmentation, especially dark-skinned Black individuals.

Medical History

All relevant medical and surgical history, including concurrent/ongoing diagnoses, must be recorded. In addition, all relevant medical history including all past and current skin diseases

(i.e., other locations of psoriasis, previous anti-psoriatic therapy, last anti-psoriatic therapy) will be collected from the subject's date of birth. For each condition, diagnosis or surgical procedure, the start date and stop date or whether it is ongoing will be recorded.

- Other locations of psoriasis: The presence of psoriasis affecting regions of the body not considered to be part of the treatment area (i.e., face, scalp, skin folds and genitals) will be recorded.
- Previous anti-psoriatic therapy: All previous anti-psoriatic treatment (systemic and topical medications and light therapy) used by the subject to treat their plaque psoriasis will be recorded by pre-defined category.
- Last anti-psoriatic therapy: Last anti-psoriatic treatment (systemic and topical medications and light therapy) used by the subject to treat their plaque psoriasis will be recorded.

Height and Weight

The subject's height (without shoes) in 'cm' will be measured; the subject's weight (in indoor clothing and without shoes) in 'kg' will be measured.

8.2 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Table 1–1).

8.2.1 Investigator Assessments

The body areas to be assessed are the trunk (including the neck) and the limbs, i.e., arms (including hands) and legs (including feet and buttocks). The face, scalp, genitals and skin folds (i.e., the axillae, the inguinal folds, the inter-gluteal folds and the infra-mammary folds) are not to be treated with the IMP or assessed as part of the efficacy analysis.

8.2.1.1 PGA

The PGA is an instrument used in clinical trials to rate the severity of psoriasis. It is a 5-point scale measurement ranging from 0 (clear) to 4 (severe) based on degree of plaque thickening, scaling and erythema (Table 8–2). The PGA score will be assessed according to the SoA (Table 1–1). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit.

Table 8–2 Physician's Global Assessment of Disease Severity

Score	Disease severity	PGA morphological descriptors
0	Clear	Plaque thickening: No elevation or thickening over normal skin. Scaling: No evidence of scaling. Erythema: None (no residual red colouration but post-inflammatory hyperpigmentation may be present).
1	Almost clear	Plaque thickening: None or possible thickening but difficult to ascertain whether there is slight elevation above normal skin level. Scaling: None or residual surface dryness and scaling. Erythema: Light pink colouration.
2	Mild	Plaque thickening: Slight but definite elevation. Scaling: Fine scales partially or mostly covering lesions. Erythema: Light red colouration.
3	Moderate	Plaque thickening: Moderate elevation with rounded or sloped edges. Scaling: Most lesions are at least partially covered. Erythema: Definite red colouration.
4	Severe	Plaque thickening: Marked elevation typically with hard or sharp edges. Scaling: Non-tenacious scale predominates, covering most or all of the lesions. Erythema: Very bright colouration.

Abbreviations: PGA=Physician's Global Assessment of disease severity.

8.2.1.2 CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

8.2.1.3 mPASI

The mPASI score will be assessed according to the SoA (Table 1–1). The investigator will make assessments of the extent and severity of clinical signs of the subject's psoriasis. Assessment is not made for the face and hence, this PASI assessment is modified to exclude the face.

The **extent** of psoriatic involvement will be recorded for each of the areas (trunk [including the neck] and the limbs [such as arms and legs]; excluding any involvement on face, scalp, genitals and skin folds) using the following scale:

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

This assessment of extent is the percentage of that body area that is affected, and **not** the percentage CCI [redacted] (see Section 8.2.1.2). For example, if one arm was totally affected, and the other arm was totally unaffected, the extent assessment for the arms would be 50% (half of the arms affected).

The **severity** of the psoriatic lesions in each of the areas will be recorded for each of the clinical signs of redness, thickness and scaliness. For each clinical sign, a single score, reflecting the average severity of all psoriatic lesions on the given body region, will be determined according to Table 8–3.

Table 8–3 Scale for Disease Severity

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

The following formula will be used to calculate the mPASI:

- Arms 0.2 (R + T + S) E = X
- Trunk 0.3 (R + T + S) E = Y
- Legs 0.4 (R + T + S) E = Z

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

The sum of X + Y + Z gives the mPASI which can range from 0 to 64.8.

8.2.2 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

CCI

8.2.2.1 CCI

CCI

CCI

CCI

CCI

CCI

CCI

8.2.2.2 CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

8.2.2.3 CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

Site staff will train the subject on the proper reporting at Day 1 (baseline) visit.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1–1).

8.3.1 Physical Examinations

An abbreviated physical examination of the subject, including assessment of the skin, lungs, cardiovascular system and abdomen (liver and spleen), must be performed according to the SoA (Table 1–1). Abnormal findings may preclude subject eligibility for the trial or where the subject remains eligible despite the finding, they may be documented as concurrent diagnoses.

8.3.2 Clinical Safety Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and the SoA (Table 1–1) for the timing and frequency. All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the laboratory manual.

Central Laboratory

Chemistry and urinalysis will be analysed by a central laboratory which will provide results to the trial sites. Laboratory parameters will be classified as ‘low’, ‘normal’ or ‘high’, depending on whether the value is below, within or above the reference range, respectively. The investigator must evaluate all results outside the reference range (‘clinically significant’ or ‘not clinically significant’) and sign and date the evaluation. The signed and dated version will be filed with the investigator’s trial documentation. In case of clinically significant abnormal results, appropriate action, as judged by the investigator, must be taken and the results must be reported as an (S)AE as defined in Appendix 3.

A laboratory manual will be provided to the trial sites specifying the procedures for collection, processing, storage and shipment of samples, as well as laboratory contact information specific to this trial.

Tests Performed at the Trial Site

Urine pregnancy test will be performed according to the SoA (Table 1–1).

At each visit, the site staff will record in the eCRF if a blood and/or urine sample was taken. If not, a reason should be provided. The investigator’s assessment of the results (‘normal’,

'abnormal, not clinically significant', 'abnormal, clinically significant') will be recorded in the eCRF.

Clinically significant abnormal laboratory results at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition will be reported as an AE. Any new clinically significant sign, symptom or illness occurring after randomisation will be reported as an AE (see Section 8.4).

8.3.3 Pregnancy Testing

For WOCBP, serum and/or urine pregnancy tests will be performed as shown in the SoA (Table 1–1). Negative pregnancy test results must be obtained at screening and at baseline prior to randomisation.

If the subject becomes pregnant during the trial, IMP must be discontinued immediately.

It will be recorded in the eCRF if the subject is a WOCBP and if a serum and/or urine pregnancy test was performed. If not, a reason should be provided. Also, the date and the outcome of the pregnancy test will be recorded in the eCRF ('positive', 'negative').

8.4 AEs, SAEs and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

AEs reported by the subjects or observed by the investigator must be recorded on the AE form of the eCRF (see Section 8.4.2).

The investigator and any qualified designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE and remain responsible for following up of AEs and SAEs as described in Section 8.4.3.

The method of recording, evaluating and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of informed consent form (ICF) until the end-of-trial (defined as attending the last visit in the trial [the early termination visit or the last follow-up visit (Visit 5), whichever comes last]), at the timepoints specified in the SoA (Table 1–1).

It will be recorded in the eCRF if the AE started prior to first IMP administration.

All SAEs will be recorded and reported to LEO Pharma A/S immediately without undue delay but no later than within 24 hours of awareness, as indicated in Appendix 3. The investigator will submit any updated SAE data to LEO Pharma A/S within 24 hours of it being available.

Investigators are not obliged to actively seek information on AEs or SAEs after the conclusion of trial participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the trial, and the investigator considers the event to be reasonably related to the IMP or trial participation, the investigator must promptly notify LEO Pharma A/S.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

At all visits, subjects will be asked a non-leading question by the investigator about AEs, e.g., 'How have you felt since I saw you last?'.

If the AE qualifies as an SAE, expedited reporting is required (see Appendix 3). It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts.

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 possibly or probably related to the IMP for 2 weeks or until the final outcome is determined, whichever comes first.

SAEs must be followed up until a final outcome has been established, that is, the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, for example chronic or stabilised conditions, the final outcome should be reported as 'not recovered'. In addition, a statement that the SAE has stabilised or is chronic should be added to the narrative description of the SAE on the SAE form.

Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours, see Appendix 3) by the investigator to LEO Pharma A/S of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a trial treatment under clinical investigation are met.

LEO Pharma A/S has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial treatment under clinical investigation. LEO Pharma A/S will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from LEO Pharma A/S will review and then file it along with the IB and SmPC of LEO 90100 and the SmPC of Daivobet® ointment, and will notify the IRB/IEC, if appropriate according to local requirements.

All SAEs that occur during the trial, and all SAEs occurring until the safety follow-up visit, whether considered to be associated with the IMP or not, must be reported to LEO Pharma A/S on the (paper) SAE form immediately, without undue delay and no later than within 24 hours of obtaining knowledge. The completed SAE forms must be faxed or scanned and e-mailed to Global Safety at LEO Pharma A/S. Contact details are given as described in Appendix 3.

Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

8.4.5 Pregnancy

Details of all pregnancies in female subjects and partners of male subjects will be collected after the start of IMP and until 7 days after the last dose of IMP (or longer if appropriate according to local requirements) for partners of male subjects and 8 weeks after the last dose of IMP for female subjects.

Any pregnancy occurring after first exposure to IMP and until the subject has completed the trial must be reported to LEO Pharma A/S within 24 hours of first knowledge using the (paper) pregnancy form (part I). All pregnancies must be followed up until delivery or termination, and 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 Global Safety at LEO Pharma A/S. Contact details are given in Appendix 3.

Pregnant subjects must immediately discontinue IMP permanently (see Section 7.1).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., maternal serious complications, therapeutic abortion, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered to be SAEs and will be reported as such.

The subject/pregnant partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject/pregnant partner and the neonate and the information will be forwarded to LEO Pharma A/S.

Any post-trial pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to LEO Pharma A/S as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former trial subjects/pregnant partners, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will discontinue IMP.

8.4.6 Other Events

8.4.6.1 Medication Errors

Medication error refers to any unintentional error in the dispensing or administration of an IMP.

Medication errors include accidental overdose or underdose, inappropriate schedule of product administration, incorrect route of product administration, wrong product administered and expired product administered.

Accidental overdose or underdose where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement.

Inappropriate schedule of product administration where a clinical consequence occurred or could have occurred should be recorded based on investigator judgement.

Treatment non-compliance (including missed doses) where no clinical consequence occurred or could have occurred should not be recorded as medication errors. See Section 6.5 for recording of treatment compliance.

Medication error must be recorded on the other event involving IMP form in the eCRF. In addition, any clinical consequences of the medication error must be recorded as separate AEs on

the AE form. If the AE originating from the medication error qualifies as an SAE, expedited reporting is required (see Appendix 3).

8.4.6.2 Misuse or Abuse

The terms misuse and abuse are similar in that they both represent the intentional use of a drug in a way other than defined in the protocol.

Misuse refers to situations where the IMP is intentionally and inappropriately used for therapeutic purposes not in accordance with the protocol.

Abuse refers to intentional use of an IMP for what could be considered desirable non-therapeutic effects (e.g., sedative, stimulant, euphoric effects).

Misuse and abuse must be recorded on the other event involving IMP form in the eCRF. In addition, any clinical consequences of misuse or abuse must be recorded as separate AEs on the AE form. If the AE originating from the misuse or abuse qualifies as an SAE, expedited reporting is required (see Appendix 3).

8.4.7 Handling of Urgent Safety Measures

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined as "…the occurrence of any new event relating to the conduct of the trial or the development of the IMP where that new event is likely to affect the safety of the subjects, LEO Pharma A/S and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard." [21].

If the investigator becomes aware of information that requires an immediate change in a clinical trial procedure or a temporary halt of the clinical trial 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 A/S, regulatory authorities or IRBs/IECs.

The investigator must immediately inform the clinical project manager or medical monitor of the designated CRO of this change in a clinical trial procedure or of the temporary halt; the investigator will provide full details of the information and the decision-making process leading to the implementation of the urgent safety measure.

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

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this trial.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this trial.

8.7 Genetics

Genetics are not evaluated in this trial.

8.8 Biomarkers

Biomarkers are not evaluated in this trial.

8.9 Immunogenicity Assessments

Immunogenicity is not evaluated in this trial.

8.10 Storage and Future Use of Biological Samples

Blood and urine samples are collected only for clinical laboratory tests in the trial (chemistry and urinalysis). The storage and destruction of these biological samples will therefore follow the standard operating procedures at the sites and laboratories where the tests are conducted.

8.11 Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics parameters are not evaluated in this trial.

9 Statistical Considerations

The SAP will be finalised as per ICH E9 requirements[22]. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section describes the planned statistical analyses of the most important endpoints including primary, key secondary, secondary and CCI [redacted] endpoints.

Any changes from the statistical analyses planned in this clinical trial protocol will be described and justified in a protocol amendment, the SAP, and/or in the clinical trial report, depend on the type of change.

9.1 Statistical Hypotheses

For the primary, key secondary and one secondary endpoints, superiority 2-sided hypotheses will be tested for LEO 90100 versus Daivobet® ointment, except for the primary endpoint "having PGA score of 0 (clear) or 1 (almost clear) at Day 29, with at least a 2-point reduction from baseline", that will first be evaluated for non-inferiority (at threshold T= CCI) and subsequently for superiority.

Let the treatment effect defined as odds ratio (OR), then:

- For binary endpoints (non-inferiority): H_0:OR $\leq$ T against H_a:OR $>$ T.
- For binary endpoints (superiority): H_0:OR ≤ 1 against H_a:OR > 1.

9.1.1 Multiplicity Adjustment

The primary endpoint, the key secondary endpoint and the other secondary endpoint are included in a closing testing procedure with hierarchical tests will be used to control the overall type I error at nominal 2-sided 5% level. The hypothesis relating to a specific endpoint cannot be rejected unless all hypotheses earlier in the hierarchy are also rejected.

The confirmatory conclusions from the confirmatory testing strategy will be based on the results from the primary analyses of the primary estimands. The primary endpoint will first be evaluated for non-inferiority and if the 95% confidence interval (CI) for the treatment effect (on the OR scale) not only lies entirely above the non-inferiority threshold (T=CCI) but also above 1 then there is evidence of superiority in terms of statistical significance at the 2-sided 5% level.

In this case, it is acceptable to calculate the p-value associated with a test of superiority and evaluate whether this is sufficiently small (two-sided p-value<0.05) to reject the hypothesis of no difference. In the switch from non-inferiority to superiority there is no multiplicity argument that affects the interpretation because, in statistical terms, it corresponds to a simple closed test procedure.

The complete superiority testing scheme is described below and illustrated in Figure 9–1. If non-inferiority is confirmed the following 3 hypotheses will be tested sequentially:

- No difference in the proportion of subjects with at least a 2-point PGA reduction from baseline having PGA score of 0 (clear) or 1 (almost clear) at Day 29 between LEO 90100 and Daivobet® ointment treatment.
- No difference in the proportion of subjects having mPASI-75 at Day 29 between LEO 90100 and Daivobet® ointment treatment.

- No difference in the proportion of subjects having mPASI-90 at Day 29 between LEO 90100 and Daivobet® ointment treatment.

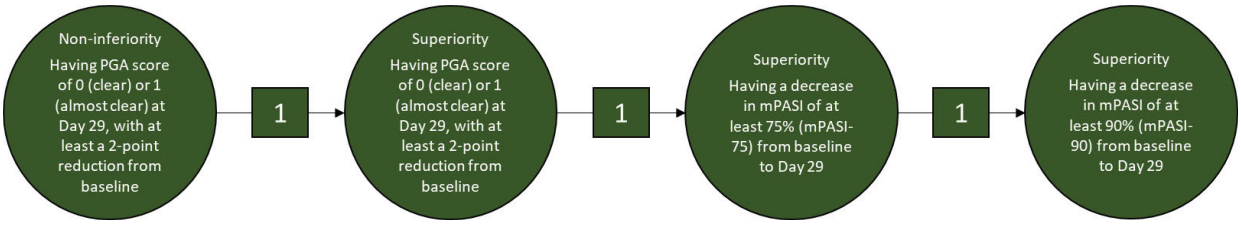
The trial is considered a success if non-inferiority is confirmed for the primary endpoint. The non-inferiority margin of 10% on the OR scale, is equivalent to a non-inferiority threshold of T=CCI.

Justification for non-inferiority margin of CCI on the odds-ratio scale.

There is no guidelines nor meta-analysis that suggest non-inferiority margins when assessing PGA 0/1 or mPASI in the population to be studied in this trial. Therefore, the non-inferiority margin has been set based on the following general principles:

- The non-inferiority margin should be on the same scale as the primary analysis (Odds-ratio).
- The non-inferiority margin should not be too large. Here CCI is chosen as a conservative margin. The justification for CCI being conservative is that
    - For bioequivalence trials margins of 0.8-1.25 is usually applied.
    - Reaching the non-inferiority margin of CCI in example means: for LEO 90100 having 170 responders in 300 subjects =56.7% and 154 in 300 subjects =51.3% for Daivobet ointment gives a crude odds-ratio of 1.23 with 95% CI of [CCI;1.7]. Therefore, on a population basis the difference in proportion of responders is in the neighborhood of 56.7% - 51.3% =5.3%, so approximately 10% relative to Daivobet ointment – but still with an odds-ratio of 1.23 in favor of LEO 90100.

Figure 9–1 Graphical Display of Closed Testing Procedure for Primary, Key Secondary and Secondary Endpoints



Abbreviations: mPASI=modified Psoriasis Area and Severity Index; PG=Physician's Global Assessment.

9.2 Analysis Sets

For purposes of analyses, the following analysis sets are defined:

Table 9–1 Subject Analysis Sets

Subject Analysis Set	Description
FAS	All randomised subjects. Subjects will be included in the analyses according to randomised treatment allocation. Exclusions from the FAS can be considered in special cases, as described in Section 5.2.1 (Full Analysis Set) of ICH E9 guidelines[22]. If a subject is excluded from the FAS, a justification per ICH E9 guidelines[22] will be given.
Safety analysis set	All subjects who are exposed to the IMP. Subjects will be analysed according to the treatment they actually received.

Abbreviations: FAS=full analysis set; IMP=investigational medicinal product.

The full analysis set (FAS) will be used for the analysis of efficacy data and the safety analysis set will be used for the analysis of safety data.

The decisions regarding inclusion/exclusion of subjects or subject data from the analysis sets will be taken by during a blinded data review meeting and will be documented with reasons for exclusions, before unblinding of the trial.

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

9.3 Statistical Analyses

9.3.1 General Considerations

Significance tests will be 2-sided using the 5% significance level. All CIs will be presented with 95% degree of confidence, unless otherwise specified.

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

Categorical data will be summarised using the number and percentage of subjects in each category. Continuous data will be summarised using the mean, median, standard deviation, 1st quartile, 3rd quartile, minimum and maximum values.

Baseline measurements will be defined as the latest available observation at or prior to the date of randomisation.

The statistical analyses were performed using SAS software (SAS Institute, Cary NC), version 9.3 or later.

9.3.2 Disposition of Subjects

The reasons for permanent IMP discontinuation and for not completing the trial will be presented for all randomised subjects and by treatment group.

An overall summary of subject disposition will be presented for all randomised subjects. The disposition summary will include information on the number of randomised, exposed, included in the FAS, permanently discontinuing IMP and not completing the trial by treatment group and overall.

9.3.3 Demographic 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, body mass index, Fitzpatrick skin type, washout period, past and current medical history and prior and concomitant medication. In addition, the baseline scores, utilised to derive efficacy variables for the primary, key secondary and secondary endpoints will be summarised.

9.3.4 Exposure and Treatment Compliance

The duration of exposure to IMP in a specific week interval will be calculated as the number of days from date of first IMP administration in that period to the date of last IMP administration in that period, both days included.

Exposure to IMP will be presented for the safety analysis set as days of exposure per treatment group.

The average weekly and total amount of IMP used will be presented for the safety analysis set for each visit interval and for the total treatment period.

Treatment compliance will be presented for the safety analysis set for each treatment group.

9.3.5 Estimand Strategy

9.3.5.1 General Considerations

The analysis of endpoints related to efficacy will be based on the FAS.

An intercurrent event (IE) refers to a post-randomisation event that affects either the interpretation or the existence of the measurements of an endpoint. For the purposes of this trial, the following 2 IEs are defined:

- **Permanent discontinuation of IMP not due to pandemic restrictions:** This IE occurs when a subject permanently discontinues IMP for reasons not related to pandemic restrictions. This event can occur either at the subject's own initiative or at the investigator or sponsor's discretion. The timing of the event will be defined in the SAP. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will be interpreted as permanent discontinuation of IMP not due to pandemic restrictions.
- **Permanent discontinuation of IMP due to pandemic restrictions:** This IE occurs when a subject permanently discontinues IMP for reasons related to pandemic restrictions. Examples of permanent discontinuation of IMP due to pandemic restrictions are quarantines (i.e., subjects who have or have a suspicion they have COVID-19 and are not allowed on to site for visits due to quarantine measures imposed), travel limitations, subject being unable or unwilling to travel to site due to personal pandemic-related reasons, site closures, reduced availability of site staff and interruptions to the supply chain of IMP. The timing of the event will be defined in the SAP. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will not be interpreted as permanent discontinuation of IMP due to pandemic restrictions, unless caused by quarantine measures.

Note, there is a distinction between permanent discontinuation of IMP (an IE) and withdrawal from trial and/or lost to follow-up. Withdrawal from trial and lost to follow-up, which are not IEs, will be addressed when specifying methods and/or assumptions for handling missing data. If the withdrawal from trial is related to the pandemic restrictions, missing data will be handled as missing data related to the pandemic restrictions.

The death of a subject has not been described above as an IE since occurrences of this event is considered unlikely in the setting of this trial. Should it happen that a subject dies, then analyses will handle this using the same strategy as described below for addressing permanent discontinuation of IMP due to pandemic restrictions.

The following strategies will be implemented for handling the IEs (ICH E9 [R1] guidelines[23]):

- The 'hypothetical' strategy attempts to quantify the effect of treatment in the hypothetical situation where IEs do not occur.
- The 'treatment policy' strategy attempts to quantify the effect of the decision to treat subjects with the randomised treatment, thus ignoring the occurrence of IEs.
- The 'composite' strategy accounts for the occurrence of IEs, through the definition of a suitable composite endpoint, whose components include the aforementioned IEs, as well as the endpoint of interest.

Depending on the strategy selected, the occurrence of an IE may lead to the exclusion of data observed after the occurrence of the event, be ignored, be accounted for in the definition of a composite endpoint or restrict the relevant observation window to the time prior to the occurrence of the IE.

For each efficacy endpoint associated with a trial objective, a primary estimand will be pre-specified. For the binary endpoints a secondary estimand will be used to further aid in the interpretation of the results (see Section 9.3.5.2 and Section 9.3.5.3).

The following primary and secondary estimands will be defined:

- The primary estimand for binary endpoints will use a 'composite' strategy to handle IEs for subjects who have permanently discontinued IMP independently of pandemic restrictions prior to the Week 4 visit (Visit 4). Subjects will be imputed as non-responders, reflecting an assumption that permanent discontinuation of IMP independent of pandemic restrictions indicates failure of the randomised treatment to achieve response. A 'hypothetical' strategy, in the form of a multiple imputation method, will be used to address permanent discontinuation of IMP due to pandemic restrictions. For subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4 (Visit 4) data collected after permanent discontinuation of IMP will be replaced by model-based predictions.
- Differently from the primary estimand for the binary endpoints, the secondary estimand for binary endpoints will use "treatment policy" strategy to handle IEs for subjects who have permanently discontinued treatment independently of pandemic restrictions prior to the Week 4 visit (Visit 4). Data will be used as observed.
- The primary estimand for continuous endpoints will use the same strategies applied for the secondary estimand for binary variables.

The occurrence of IEs will be listed and summarised by treatment group. Table 9–2 presents an overview of how observed and missing data will be handled according to the IEs for the primary analysis for estimands.

Table 9–2 Handling of Observed and Missing Data According to the IEs for the Primary Analysis for Estimands

IE	Data observed or missing	Estimands for binary endpoints		Estimand for continuous endpoints
		Primary	Secondary	Primary
Permanent discontinuation of IMP **not due to pandemic** restrictions	Observed	**Composite:** N/A, value of the endpoint is determined by the IE (non-response)	**Treatment policy:** Used as observed	**Treatment policy:** Used as observed
	Missing	N/A, value of the endpoint is determined by the IE (non-response)	MI (MAR within treatment arms)	MI (MAR within treatment arms)
Permanent discontinuation of IMP **due to pandemic** restrictions	Observed	**Hypothetical:** Treated as missing, MI (MAR within treatment arms)	**Hypothetical:** Treated as missing, MI (MAR within treatment arms)	**Hypothetical:** Treated as missing, MI (MAR within treatment arms)
	Missing	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)
No IE	Observed	Used as observed	Used as observed	Used as observed
	Missing **not due to pandemic** restrictions	NRI	MI (MAR within treatment arms)	MI (MAR within treatment arms)
	Missing **due to pandemic** restrictions	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)

Abbreviations: IE=intercurrent event; IMP=investigational medicinal product; MAR=missing at random; MI=multiple imputation, N/A=not applicable; NRI=non-responder imputation.

9.3.5.2 Estimand Strategy for Binary Endpoints

Evaluation of non-inferiority as well as test of the null hypothesis that the response rate for the LEO 90100 arm is less than or equal to the rate for the Daivobet® ointment arm, against the alternative that LEO 90100 is superior to Daivobet® ointment, will be based on the Wald-type test statistic for the estimated treatment effect from a logistic regression model, adjusted for baseline PGA.

The main analysis is based on the following assumptions:

1. Missing data will be handled according to Table 9–2.
2. Use of prohibited medication and procedures will be assumed to have no influence on the endpoint of interest among subjects not discontinuing IMP.

For each of the imputed datasets, estimates of the treatment effect along with the associated standard errors will be kept on the log-scale. The pooled estimate of risk difference and OR at Week 4, along with the associated 95% CIs and nominal p-values will be presented based on applying Rubin's rules to the estimates and standard errors from the logistic regression of the imputed data sets and transforming to the odds-scale. Details for multiple imputation and pooling methods will be described in the SAP.

Primary Analysis of the Primary Estimand

The purpose of 'hypothetical' strategy is to predict what value the estimands variable would take if the given subject would not permanently discontinue IMP due to pandemic restrictions, assuming a similar course of events as experienced by subjects from the same treatment arm who have not permanently discontinued IMP due to pandemic restrictions. With this purpose in mind 2 questions naturally arise because of the composite strategy used to address permanent discontinuation of IMP independent of pandemic restrictions:

1. Would the subject still have been on treatment at Week 4 as opposed to having permanently discontinued IMP independently of pandemic restrictions beforehand?
2. If yes, would the subject have had binary response (0/1) with a 2-point reduction from baseline at Week 4?

In practice, both of these hypothetical questions will be addressed, although in reverse order, by carrying out the following steps:

1. Under missing at random (MAR) assumption within treatment arm, binary response at Week 4 (or Week 2) will be imputed for subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4 (or Week 2) and for subjects who have not permanently discontinued IMP prior to Week 4 (or Week 2) and whose score at Week 4 (or Week 2) is missing due to pandemic restrictions. Fully conditional specification (FCS) method will be implemented to impute missing binary responses by implementing logistic or regression methods (number of imputed datasets = 1000; seed = 2)[24]. FCS logistic regression will be implemented for the binary PGA and CCI [redacted]. FCS linear regression will be utilised to impute the mPASI score. Binary mPASI-75 and mPASI-90 will be derived from the imputed score. Response at Week 4 (or Week 2) will be imputed using the stratification PGA, the value baseline score value (not for PGA as it coincides with the randomisation strata) and response at the Week 2 visit (not applicable when imputing data for Week 2) as covariates.
2. Non-responder imputation will be applied for subjects who have not permanently discontinued IMP prior to Week 4 (or Week 2) and whose binary response at Week 4 (or Week 2) is missing for reasons other than pandemic restrictions.
3. A logistic regression model will be implemented to estimate each subject's probability of permanent discontinuation of IMP not due to pandemic restrictions up until Week 4 (Day 29) among subjects who permanently discontinued IMP due to pandemic restrictions. Stratification PGA, sex and age will be utilised as covariates. Using the subject predicted probability (p_i) of discontinuation, the following steps will be followed to derive the treatment adherence variable:
    a. For each imputed dataset, a value from the exponential distribution with rate p_i will be drawn and multiplied with 29 to obtain days (starting seed = 3)
    b. Person-days already spent in the trial will be added to the drawn number
    c. Derive the treatment adherence variable with the following categorisation:
        - Days <15: subject discontinued before Week 2
        - 15 ≤ Days < 29: subject discontinued after Week 2 and before Week 4
        - Days ≥ 29: the subject did not discontinue.

Table 9–3 Hypothetical Strategy for Addressing Permanent Discontinuation of IMP Due to Pandemic Restrictions and Handling of Missing Data in the Primary Analysis of the Primary Estimand

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute binary (0/1) response at Week 4 under MAR assumptions within treatment arm	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4.	Hypothetical strategy
		Subjects who have not permanently discontinued IMP prior to Week 4 and whose score at Week 4 is missing due to pandemic restrictions.	Handling of missing data
2	Impute binary (0/1) response at Week 4 based on NRI	Subjects who have not permanently discontinued IMP prior to Week 4 and whose score at Week 4 is missing for reasons other than pandemic restrictions.	Handling of missing data
3	Impute treatment adherence status at Week 4 within treatment arm	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4.	Hypothetical strategy

Abbreviations: IMP=investigational medicinal product; MAR=missing at random; NRI=non-responder imputation.

Sensitivity Analysis of the Primary Estimand

For the sensitivity analysis, which is rather conservative against the LEO 90100 group, 'treatment policy' will be applied for Daivobet® ointment instead of the 'composite strategy' for those subjects who permanently discontinued the IMP not due to pandemic restrictions with observed response at Week 4. In addition, missing data for subjects in the Daivobet® ointment group will be imputed, as described in Point 1 of hypothetical strategy summarised in Table 9–3.

Primary Analysis of the Secondary Estimand

For the primary analysis of the secondary estimand, under MAR assumption within treatment arm, binary response at Week 4 will be imputed for subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4 and for subjects who have not permanently discontinued IMP prior to Week 4 and whose score at Week 4 is missing due to pandemic restrictions. FCS method will be applied, as described for the primary analysis of the primary estimand.

9.3.5.3 Estimand Strategy for Continuous Endpoints

With the treatment policy strategy, subjects who have permanently discontinued IMP independently of pandemic restrictions prior to the endpoint Visit 4 (Week 4) will be included in the analysis with the actually observed score at this Visit.

Permanent discontinuation of IMP due to pandemic restrictions will be addressed by a hypothetical strategy. Data collected after such an event will not be applied in the analysis. The hypothetical scenario envisaged is that permanent discontinuation of IMP due to pandemic restrictions would not occur, assuming subjects who have experienced this event would respond like subjects from the same treatment arm who have not experienced it. The hypothetical strategy and the handling of missing data in the primary analysis are outlined in Table 9–4.

Table 9–4 Hypothetical Strategy for Addressing Permanent Discontinuation of IMP Due to Pandemic Restrictions and Handling of Missing Data in the Primary Analysis of the Primary Estimand for Continuous Secondary Endpoints

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute score at the endpoint visit under MAR assumptions within treatment arm	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit.	Hypothetical strategy
		Subjects who have not permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit and whose score at the endpoint visit is missing.	Handling of missing data

Abbreviations: IMP=investigational medicinal product; MAR=missing at random.

The imputation of scores will be carried out like the imputation of mPASI scores for the primary estimand of the primary endpoint (FCS linear regression with stratification PGA, value of the continuous variable at baseline and Week 2 as covariates). Data collected from subjects who have permanently discontinued IMP independently of pandemic restrictions will be included when applying this multiple imputation method, in alignment with the treatment policy strategy used for addressing occurrences of that IE.

Each of the imputed data sets will be analysed based on an analysis of covariance (ANCOVA) model, including treatment arm, and adjusting for the baseline score as a covariate. The pooled estimate of the difference in the least-saure (LS)-mean change from baseline at Week 4, along with the associated 95% CIs and nominal p-values will be presented based on applying Rubin's

rules to the estimates and standard errors from the ANCOVA analyses of the imputed data sets. Details for multiple imputation and pooling methods will be described in the SAP.

9.3.6 Primary Endpoint Analysis

The primary endpoint will be analysed following the estimand strategy for binary endpoints described in Section 9.3.5.2. The non-inferiority and superiority 2-sided hypothesis, described in Section 9.3.1, will be tested for LEO 90100 vs Daivobet® ointment based on the primary analysis for the primary estimand.

9.3.7 Secondary Endpoints Analysis

The binary key secondary and secondary endpoint will be analysed following the estimand strategy for binary endpoints described in Section 9.3.5.2. The superiority 2-sided hypothesis, described in Section 9.3.1, will be tested for LEO 90100 vs Daivobet® ointment based on the primary analysis for the primary estimand. Continuous secondary endpoints will be analysed following the estimand strategy for the continuous endpoints, as per Section 9.3.5.3.

9.3.8 CCI [redacted]

The binary CCI [redacted] (binary) will be analysed following the primary estimand strategy for binary endpoints described in Section 9.3.5.2. Continuous secondary endpoints will be analysed following the estimand strategy for the continuous endpoints, as per Section 9.3.5.3.

9.3.9 Safety Analyses

All safety analyses will be made on the safety analysis set.

9.3.9.1 AEs

AEs will be coded during the course of the trial according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term and primary system organ class (SOC).

Treatment-emergent AEs will be summarised; however, all AEs recorded during the course of the trial will be included in subject data listings. An event will be considered treatment-emergent if it started after the first IMP administration or if it started before the first IMP administration and worsened in severity after the first IMP administration. The tabulations described in the following will only include the treatment-emergent AEs. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary SOC.

AEs will be summarised in terms of the number of subjects with at least 1 event, the percentage of subjects with at least 1 event, the number of events and the event rate per 100 patient years of observation time.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to the IMP as 'not related'.

An overall summary presenting any treatment-emergent AEs, deaths, SAEs, permanent discontinuations from IMP and/or withdrawals from the trial due to AEs, treatment-related AEs and severe AEs will be presented.

Tabulations by SOC and preferred term will be presented for all AEs, SAEs, related AEs, AEs leading to withdrawal from trial and AEs leading to permanent IMP discontinuation. In addition, all AEs will be presented by severity and causal relationship to IMP, respectively. If an AE worsens in severity, the severity will be reported as the most severe recording for that AE.

SAEs will be evaluated separately, and a narrative will be given.

AEs leading to withdrawal from trial and AEs leading to permanent IMP discontinuation will be listed. The detailed listing will provide an overview of the individual cases and include the age and sex of the subject, treatment received at the time of AE onset, the AE preferred and reported terms, causality and severity of the AE, the action taken with the IMP, AE outcome, start and stop date of AE, duration of AE and number of days since first and last IMP administration. No narratives will be given.

The MedDRA search terms for AEs will be provided in the SAP.

Other events (medication error, misuse and abuse of IMP) will be tabulated and listed. No narratives will be given.

9.3.9.2 Physical Examination

For physical examination, abnormalities at baseline and end-of-treatment (or early termination) as well as the transition from baseline to end-of-treatment (or early termination) will be summarised for each treatment group.

9.3.9.3 Clinical Safety Laboratory Tests

For laboratory parameters, the absolute values as well as the changes from baseline will be summarised by visit for each treatment group.

A shift table will be produced for relevant parameters showing the categories at baseline against those at each post-baseline visit.

For subjects with post-baseline values, out of reference range events reported up to Week 6 will be summarised.

9.4 Interim Analyses

No interim analysis is planned during the trial.

9.5 Sample Size Determination

Data from the EU SmPC is used for the sample size calculation[14]. Table 9–5 shows results from a historical comparative trial on the "Percentage of subjects with 'treatment success' according to the PGA of the body at Week 4 (PGA 0/1)". These data from the SmPC give a relative risk of 1.27 and a crude OR of 1.59 in favour of LEO 90100.

Table 9–5 EU SmPC Trial Result

Data from SmPC	LEO 90100	Daivobet® ointment
Trial Three	(N=141) 54.6%	(N=135) 43.0%

Abbreviations: SmPC=Summary of Product Characteristics.

Table 9–6 illustrates the power with 600 subjects randomised 1:1. The probability of superiority and non-inferiority is found by running 10,000 simulations using the data from the EU SmPC. The responder probabilities are used in a binomial sampling of the number of subjects with treatment success. For each of the simulations, the OR with 95% CI limits is calculated using Fisher's exact test and the lower 95% boundary is used to evaluate superiority and non-inferiority at the thresholds 1 and CCI respectively.

Table 9–6 Simulated Power

Endpoint	Proportion responders for Daivobet® ointment	Proportion responders for LEO 90100	Probability of superiority	Probability of non-inferiority with a NI margin OR=CCI	Probability of point estimate for LEO 90100 exceeds Daivobet® ointment (OR > 1)
PGA 0/1 at Day 29	43.0%	54.6%	0.799	0.9198	0.9975

Abbreviations: NI=non-inferiority; OR=odds ratio; PGA=Physician's Global Assessment of disease severity.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable ICH GCP guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/EC.
- Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures.
- Overall conduct of the study at the site and adherence to requirements of the Code of Federal Regulations (CFR) Title 21, ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable) and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide LEO Pharma A/S with sufficient, accurate financial information in accordance with local regulations to allow LEO Pharma A/S 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 study and for 1 year after completion of the trial.

10.1.3 Informed Consent Process

The ICF(s) must be signed prior to performing any protocol related procedures, including but not limited to screening evaluations and initiation of washout for treatments listed as exclusion criteria.

The investigator or their representative will explain the nature of the trial, including the risks and benefits, to the subject and answer all questions regarding the trial.

Potential subjects must be informed that their participation is voluntary. Subject will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or trial site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the trial and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

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

Subjects who are rescreened are required to sign a new ICF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all subjects subsequently enrolled in the trial as well as those currently enrolled in the trial.

10.1.4 Data Protection

Subjects will be assigned a unique identifier by LEO Pharma A/S. Any subject records or datasets that are transferred to LEO Pharma A/S will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that their personal study-related data will be used by LEO Pharma A/S in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by LEO Pharma A/S, by appropriate IRB/IEC members and by inspectors from regulatory authorities.

10.1.5 Dissemination of Clinical Study Data

LEO Pharma A/S 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 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 leopharmatrials.com in accordance with LEO Pharma A/S Position on Public Access to Clinical Trial Information within approximately 12 months of 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.

10.1.6 Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to LEO Pharma A/S or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.

The investigator must permit trial-related monitoring, audits, IRB/IEC review and Regulatory Agency inspections and provide direct access to source documents.

Monitoring details describing strategies, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in the Monitoring Plan.

LEO Pharma A/S or designee is responsible for the data management of this trial including quality checking of the data.

LEO Pharma A/S assumes accountability for actions delegated to other individuals (e.g., CROs).

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of LEO Pharma A/S. No records may be transferred to another location or party without written notification to LEO Pharma A/S.

All data generated by the site personnel will be captured electronically at each trial site using eCRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the eCRF clinical data have been submitted to the central server at the independent data site, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data collection (EDC) application. The appropriate staff at the trial site will answer queries sent to the investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to trial sites in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

10.1.6.1 Quality Tolerance Limits

Quality Tolerance Limits will be pre-specified prior to first subject first visit.

10.1.7 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete and verifiable from source documents; that the safety and rights of subjects are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP and all applicable regulatory requirements.

10.1.8 Study and Site Start and Closure

The trial start date is the date of the first subject's first visit.

Trial/Site Termination

LEO Pharma A/S or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of LEO Pharma A/S. Trial sites will be closed upon trial completion. 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.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

For trial termination:

- Discontinuation of further IMP development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the procedures of LEO Pharma A/S or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator.
- Total number of subjects included earlier than expected.

If the trial is prematurely terminated or suspended, LEO Pharma A/S shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.9 Publication Policy

A publication can be a journal manuscript, an abstract, a poster/presentation for a congress or any openly accessible material.

A primary publication including the primary results of the trial (i.e., the results of the primary endpoint[s]) will be submitted for peer-reviewed publication within 12 months of database lock (DBL). LEO Pharma A/S is responsible for this publication. All authors (trial responsible employees and/or applicable investigators and advisers) must fulfil the criteria for authorship from the International Committee of Medical Journal Editors (ICMJE).

The investigators may reach out to LEO Pharma A/S to publish results that are not included in the primary publication. The investigator and LEO Pharma A/S should agree on terms for data sharing and collaboration on such publications, as well as timing for release of the publication(s). In all cases, LEO Pharma A/S retains the right to review and comment on the draft publication in due time before submission, but the investigator is not required to revise the draft accordingly, unless it discloses company confidential information or protected personal information, or may compromise intellectual property rights of LEO Pharma A/S.

LEO Pharma A/S may give researchers outside LEO Pharma A/S access to anonymised data from this trial for further research according to the principles outlined by the European Federation of Pharmaceutical Industries and Associations (EFPIA). In that case, the researchers are obliged to attempt publication of the results obtained from their analyses.

LEO Pharma A/S complies with Good Publication Practice (GPP3) standards and the recommendations from ICMJE.

10.1.10 Protocol Approval and Amendment

Before the start of the trial, the trial protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. LEO Pharma A/S must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the trial.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the subject benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.11 Liability and Insurance

LEO Pharma A/S will take out reasonable third party liability insurance cover in accordance with all legal requirements. The civil liability of the investigator, the persons instructed by him or her and the hospital, practice or institute in which they are employed and the liability of LEO Pharma A/S with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this trial are governed by the applicable law.

LEO Pharma A/S will arrange for patients participating in this trial to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the trial.

10.1.11.1 Access to Source Data

During the trial, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual subject's medical records, assess drug accountability and ensure that the trial is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the trial. Moreover, regulatory authorities of certain countries, IRBs, IECs and/or the Clinical Quality Assurance group of LEO Pharma A/S may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The investigator assures LEO

Pharma A/S, and Parexel if involved in monitoring/data management, of the necessary support at all times.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10–1 will be performed by a central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either IMP administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either an IMP decision or response evaluation, the results must be recorded.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 10–1 Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters	
Clinical chemistry	Albumin[1] Creatinine Calcium[1] Cortisol	Potassium Sodium Urea 25-hydroxy vitamin D
Urinalysis (spot urine)	Calcium[2]	Creatinine[2]
Pregnancy testing (WOCBP only)	Highly sensitive serum/urine hCG pregnancy test (as needed for WOCBP) at screening detailed in the SoA (Table 1–1).[3]	
NOTES: 1. The laboratory will report albumin-corrected serum calcium, which is calculated in mmol/L using the formula: serum calcium (total) in mmol/L + (0.02 × [40-serum albumin in g/L]). If the albumin-corrected serum calcium is outside the range of 2-2.9 mmol/L, additional visits or a follow-up visit with the subject should be performed (this may involve requesting repeat samples). 2. The calcium/creatinine ratio will be calculated. 3. Local urine testing (as needed for WOCBP) at timepoints detailed in the SoA (Table 1–1).		

Abbreviations: hCG= human chorionic gonadotropin; SoA=schedule of activities; WOCBP= woman of childbearing potential.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

10.3.1 Definition of AE

AE 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 E2A guidelines[25]).

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 8.3.2).

10.3.2 Definition of SAE

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening, that is at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).
- Requires in-patient hospitalisation or prolongation of existing hospitalisation*.
- Results in persistent or significant disability or incapacity.

- Is a congenital anomaly or birth defect.
- 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 treatment 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 bronchospasm, blood dyscrasias and convulsions that do not result in hospitalisation, development of drug dependency or drug abuse.

***Notes:**

- Hospitalisation for procedures or treatments planned prior to the subject consented to trial participation does not constitute an AE and should therefore not be reported as an AE or SAE.
- Hospitalisation for elective treatment of a pre-existing condition which did not worsen from the subject is not considered an AE and should therefore not be reported as an AE or SAE, even if not planned before consent to trial participation.
- Hospitalisation for routine scheduled treatment or monitoring of the studies indication not associated with any aggravation of the condition does not constitute an AE and should therefore not be reported as an AE or SAE.
- Hospitalisation for administrative, trial-related or social purpose does not constitute an AE and should therefore not be reported as an AE or SAE.
- Complications that occur during hospitalisation are (S)AEs. If a complication prolongs hospitalisation, the event is an SAE.
- When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.

Additionally, all malignancies, including skin malignancies, should be reported as SAEs.

10.3.3 Recording and Follow-up of AE and SAE

AE and SAE Recording

AEs must be assessed by a physician.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event.

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

The AE term must be in precise English medical terminology (that is, 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 may be described as (e.g., the face, scalp, back, chest, arm, leg, trunk or limb). Additionally, the location should be described using the following terminology:

- Lesional/perilesional (≤ 2 cm from the border of lesion [s] treated with the IMP).
- Distant (> 2 cm from the border of lesions [s] treatment with the IMP).

The duration of the AE must be reported by the start date and stop date of the event, unless the event is ongoing. If the event is ongoing, it will be marked as ongoing. In addition, it will be recorded if the AE started prior to first IMP administration.

AEs must be classified in terms of severity, causality and outcome according to the definitions provided below.

Action taken with IMP: Any action taken with IMP as a consequence of the AE must be recorded (dose not changed, drug withdrawn, not applicable, unknown).

Withdrawal from trial due to this AE: It must be recorded whether the AE led to withdrawal from the trial.

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

Assessment of Intensity

The severity of the AE should be described in terms of mild, moderate or severe according to the investigator's clinical judgement. If the AE worsens in severity, the new severity including date of worsening, should be recorded. However, if an AE with onset prior to IMP initiation worsens after IMP administration, a new AE should be recorded:

- **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.

  An event is defined as 'serious' when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship.

A *reasonable possibility* of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.

The investigator will also consult the IB and SmPC for LEO 90100 and the SmPC for Daivobet® ointment in their assessment[13, 14, 15].

For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report in the EDC tool. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the EDC tool.**

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The following decision choices will be used by the investigator to describe the causality assessment:

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.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of 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 an 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 investigator, e.g., subject lost to follow-up.

The definitions of LEO Pharma A/S versus Clinical Data Interchange Standards Consortium (CDISC) definitions: Note that as per the above definition, LEO Pharma A/S 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 definitions of LEO Pharma A/S 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 A/S 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 A/S with the outcome 'recovered/resolved with sequelae' could have been classified with the outcome 'recovered/resolved' according to the CDISC definition.

In summary, the definitions used by LEO Pharma A/S are more conservative than those used by CDISC.

Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by LEO Pharma A/S to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.

If a subject dies during participation in the trial or during a recognised follow-up period, the investigator will provide LEO Pharma A/S with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed form.

The investigator will submit any updated SAE data to LEO Pharma A/S within 24 hours of receipt of the information.

10.3.4 Reporting of SAE

Investigator Reporting Responsibilities

Any SAE must be reported to LEO Pharma A/S on the (paper) SAE form immediately, without undue delay but not later than within 24 hours of obtaining knowledge. This report should contain among others an assessment of available information on seriousness, severity, causal relationship to the IMP or trial procedure, the action taken, the outcome to date and a narrative description of the course of the event. For more details regarding reporting of any SAE, please see the guidance text on the SAE form.

By signing and dating the SAE form, the investigator acknowledges that he/she is aware of the SAE and has assessed the causal relationship of the IMP(s) and any of the other medications to the SAE.

The actual reporter, if not the investigator, should also sign and date the SAE form.

The completed SAE form must be faxed or scanned and e-mailed to Global Safety at LEO Pharma A/S using the e-mail address or fax number below:

Global Safety at LEO Pharma A/S

E-mail address: drug.safety@leo-pharma.com

Fax number: +45 7226 3287

If relevant, the investigator will enclose other information with the SAE form, such as anonymised reports of diagnostic procedures, hospital records, autopsy reports, etc.

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

The investigator must notify the local IRB(s)/IEC(s) of SAEs, as required by current applicable legislation for the concerned country.

SAEs occurring after the completion of the clinical trial should not be routinely sought or recorded. However, such events should be reported immediately without undue delay and no later than 24 hours of obtaining knowledge to Global Safety at LEO Pharma A/S (see contact details above) if the investigator becomes aware of them.

LEO Pharma A/S Reporting Responsibilities

Global Safety at LEO Pharma A/S is responsible for assessing whether an SAE is expected. The relevant reference safety information documents for this clinical trial are:

For LEO 90100, the latest version of the IB and SmPC must be used[13, 14].

For Daivobet® ointment, the latest version of the SmPC must be used[15].

Global Safety at LEO Pharma A/S will notify the regulatory authorities and concerned investigators of SAEs according to the current applicable legislation for the concerned countries.

The IRB(s)/IEC(s) will be notified of SAEs according to the current applicable legislation for the concerned countries.

The following reporting requirements apply: all SAEs which are assessed as causally related to the IMP(s) by either the investigator or LEO Pharma A/S, and which are unexpected (i.e., suspected unexpected serious adverse reactions [SUSARs]), are subject to expedited reporting to regulatory authorities, and IEC(s)/IRB(s) according to the current applicable legislation in the concerned countries. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

WOCBP

Women in the following categories are considered WOCBP (fertile):

1. Following menarche.
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below):

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilisation methods (for the purpose of this study) include:
    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy;
    - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination or medical history interview.

- If fertility is unclear (e.g., amenorrhea in athletes) and a menstrual cycle cannot be confirmed before first dose of IMP, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:
    a. Documented hysterectomy;
    b. Documented bilateral salpingectomy;
    c. Documented bilateral oophorectomy;
    d. For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining trial entry.

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination or medical history interview.

2. Postmenopausal female:
    a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        i. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
        ii. Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before randomisation.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency Failure rate of < 1% per year when used consistently and correctly.
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomised or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male subject can come from the site personnel's review of the subject's medical records, medical examination or medical history interview.
Highly Effective Methods[b] That Are User Dependent Failure rate of < 1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]: - oral - intravaginal - transdermal - injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c]: - oral - injectable
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Note: Periodic abstinence (e.g., calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: COVID-19 Pandemic Contingency Plan

Without compromising the safety of subjects and trial integrity, it is expected that efforts are made to secure attendance at sites for all visits, ensuring important efficacy and safety assessments for the trial.

If on-site visits are not possible due to local authority-issued preventive measures, the affected site will postpone screening and randomisation of new subjects until on-site visits can be conducted. For already randomised subjects, post-baseline visits can be done remotely via phone or video. At phone visits, no investigator assessments of efficacy can be done, but the following data will be collected remotely, according to the SoA (Table 1–1):

- AE reporting.
- Treatment compliance (daily completion in the paper diary).
- Concomitant medication and concurrent procedures.
- CCI
- Urine pregnancy test. WOCBP will receive 1 extra urine pregnancy test at the randomisation visit to keep at home in case on-site visits become impossible during the trial. The subject will perform the test at home and inform the investigator about the result via phone and to send a picture of the test to the site or show it via video. Additional urine pregnancy tests can be shipped to the subject's home together with IMP (see below) if needed.
- Serum cortisol and serum and urine calcium and creatinine should continue to be monitored by a local laboratory, at the timepoints outlined in the SoA (Table 1–1).

In the eCRF, it will be recorded whether a visit or a given assessment was done on site, remotely or not done. If remotely or not done, it will be recorded if this was due to pandemic restrictions as defined in Section 9.3.5.1.

It will be at the discretion of the investigator to decide whether clinical laboratory samples are considered necessary to ensure subject safety in periods when on-site visits are not possible.

Contingency plans due to COVID-19 must follow the authorities' COVID-19 guidelines and local requirements. Written procedures describing the contingency plan must be in place at site and depot. To ensure availability of IMP, the trial sites will dispense additional IMP if considered relevant (i.e., if local authority-issued preventive measures are to be expected at the given trial site). This will allow subjects to continue IMP although they are not able to go to the trial site. If a subject will not be able to attend on-site visits due to the COVID-19 pandemic before running out of IMP, the trial site will ensure shipping of IMP to the subject's home.

If a subject is tested positive for COVID-19, the investigator will evaluate whether this is an AE that contraindicates further dosing, in which case the subject will permanently discontinue IMP as described in Section 7.1.

10.6 Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

Amendment 1 (27 Jun 2022)

Overall Rationale for the Amendment:

The protocol was updated to clarify that the same amount of IMP will be dispensed at both visits and the kits of IMP will be packaged with detailed identifying information. The changes neither significantly impacted the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has a ~~line through it~~).

Section # and Name	Description of Change	Brief Rationale
Section 6.2 Preparation, handling, storage and accountability	~~IMP will be supplied in Visit Kits.~~ **All kits will contain 240 g of IMP.**	Clarification that same amount of IMP will be dispensed at both visits.
Section 6.2 Preparation, handling, storage and accountability	IMP will be supplied ~~in Visit Kits given to subjects~~ at the **dispensing** visits listed in the SoA (Table 1-1). Each **kit** ~~Visit Kit~~ will contain the necessary **amount of IMP** ~~supplies~~ to treat a subject **between 2 visits in the treatment period** ~~for 2 weeks~~.	Clarification that the kit with enough IMP will be dispended to the subject on Visit 2 and Visit 3.
Section 6.2 Preparation, handling, storage and accountability Table 6-1 Trial treatment(s) administered	~~A maximum of 210~~ 240 g of IMP will be dispensed every second week.	Clarification that same amount of IMP will be dispensed at both visits.

Section # and Name	Description of Change	Brief Rationale
Section 6.4 Blinding	~~IMP will be packaged in Visit Kits that will not display any information or details identifying the IMP contained in the kit.~~ ~~Consequently, it is expected that the investigator will remain unaware of the individual treatment assignment during the conduct of the clinical trial.~~	The kits will be packed open label.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

10.7 Appendix 6: Protocol Elements for Redaction

10.7.1 Information About Sponsor Signatory

Approval Statement for Sponsor Signatories:

Electronic signatures made within LEO Pharma A/S Clinical Vault are 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

Head of Medical Department

PPD

Biostatistics Lead

PPD

Medical Lead, Medical Department

Medical Monitor Name and Contact Information will be provided separately.

11 References

1 Hrehorow E, Salomon J, Matusiak L, Reich A, Szepietowski JC. Patients with psoriasis feel stigmatized. Acta Derm Venereol. 2012;92(1):67-72.

2 Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. Arch Dermatol. 2001;137(3):280-284.

3 Tan X, Feldman S, Balkrishnan R. Quality of life issues and measurement in patients with psoriasis. Targets and Therapy. 2012;2:13-23.

4 Committee on Psoriasis CSoD. Guideline for the diagnosis and treatment of psoriasis in China. Chin J Dermatol. 2019;52(4):223-230.

5 Gisondi P, Tessari G, Conti A, Piaserico S, Schianchi S, Peserico A, Giannetti A, Girolomoni G. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. Br J Dermatol. 2007;157(1):68-73.

6 Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007;370(9583):263-271.

7 Griffiths CE, Christophers E, Barker JN, Chalmers RJ, Chimenti S, Krueger GG, Leonardi C, Menter A, Ortonne JP, Fry L. A classification of psoriasis vulgaris according to phenotype. Br J Dermatol. 2007;156(2):258-262.

8 Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005;64 Suppl 2:ii18-23; discussion ii24-15.

9 Dubertret L, Mrowietz U, Ranki A, van de Kerkhof PC, Chimenti S, Lotti T, Schafer G. European patient perspectives on the impact of psoriasis: the EUROPSO patient membership survey. Br J Dermatol. 2006;155(4):729-736.

10 Rapp SR, Feldman SR, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol. 1999;41(3 Pt 1):401-407.

11 Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, Gottlieb A, Koo JY, Lebwohl M, Lim HW, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60(4):643-659.

12 Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, Rosenbach T, Sammain A, Schlaeger M, Sebastian M, et al. S3 - Guidelines on the treatment of psoriasis vulgaris (English version). Update. J Dtsch Dermatol Ges. 2012;10 Suppl 2:S1-95.

13 Investigator brochure for LEO90100, Edition no. 11, dated 18 Mar 2022.

14 Summary of Product Characteristics for Enstilar®. https://mri.cts-mrp.eu/Human/Downloads/DK_H_2478_001_FinalSPC.pdf

15 Summary of Product Characteristics for Daivobet®. https://www.ema.europa.eu/en/documents/referral/daivobet-article-30-referral-annexes-i-ii-iii_en.pdf

16 Bushnell DM, Martin ML, McCarrier K, Gordon K, Chiou CF, Huang X, Ortmeier B, Kricorian G. Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. J Dermatolog Treat. 2013;24(5):356-360.

17 Levin C, Maibach HI. Topical corticosteroid-induced adrenocortical insufficiency: clinical implications. Am J Clin Dermatol. 2002;3(3):141-147.

18 Bourke JF, Mumford R, Whittaker P, Iqbal SJ, Le Van LW, Trevellyan A, Hutchinson PE. The effects of topical calcipotriol on systemic calcium homeostasis in patients with chronic plaque psoriasis. J Am Acad Dermatol. 1997;37(6):929-934.

19 World Health Organization. (1997). WHO model prescribing information : drugs used in skin diseases. World Health Organization. https://apps.who.int/iris/handle/10665/41975. Published 2021. Accessed April 7, 2022.

20 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-216.

21 European Parliament Union, European CoT. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use, 2001. (Ema ed. 2001).

22 ICH. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Statistical Principles for Clinical Trials. E9, Step 4; 05 Feb 1998.

23 ICH. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Addendum on estimands and sensitivity analysis in clinical trials to the guidelines on statistical principles for clinical trials. E9 (R1), Step 4; 20 Nov 2019.

24 Berglund P and Heeringa SG. Multiple Imputation of Missing Data Using SAS. SAS Publishing; 2014.

25 ICH. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Clinical Safety Data Management. Definitions and Standards for Expected Reporting (E2A), Step 4; 27 Oct 1994.

Investigator Agreement Page

Declaration of the Principal or Global Coordinating Investigator

Title: A phase 3, randomised, investigator-blind, active-controlled, parallel group, multicentre trial comparing the efficacy and safety of 4 weeks treatment with LEO 90100 and Daivobet® ointment in adult Chinese subjects with stable plaque psoriasis

This trial protocol was subjected to critical review and has been approved by LEO Pharma A/S. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on GCP.

Principal Coordinating Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Declaration of the National Coordinating Investigator

Title: A phase 3, randomised, investigator-blind, active-controlled, parallel group, multicentre trial comparing the efficacy and safety of 4 weeks treatment with LEO 90100 and Daivobet® ointment in adult Chinese subjects with stable plaque psoriasis

This trial protocol was subjected to critical review and has been approved by LEO Pharma A/S. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on GCP.

National Coordinating Investigator

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Declaration of the Investigator

Title: A phase 3, randomised, investigator-blind, active-controlled, parallel group, multicentre trial comparing the efficacy and safety of 4 weeks treatment with LEO 90100 and Daivobet® ointment in adult Chinese subjects with stable plaque psoriasis

All documentation for this trial that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this trial protocol, eCRF, and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted IRB or IEC. No changes will be made to the study protocol without the prior written approval of LEO Pharma A/S and the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Responsible investigator of the Local Trial Site

_____ _____

Signature Date

_____

Name (block letters)

_____

Title (block letters)

_____

Institution (block letters)

_____

Phone number

Signature Page for TMF-000792251 v3.0

Reason for signing: Reviewed without Comments	Manag Name: PPD Capacity: Biostatistics Date of signature: 16-Nov-2022 13:16:23 GMT+0000
Reason for signing: Reviewed without Comments	Manag Name: PPD Capacity: Medical Date of signature: 16-Nov-2022 13:17:01 GMT+0000
Reason for signing: Reviewed without Comments	Manag Name: PPD Capacity: Medical Date of signature: 16-Nov-2022 13:28:49 GMT+0000
Reason for signing: Approved	Approv Name: PPD Capacity: Medical Date of signature: 16-Nov-2022 13:32:55 GMT+0000
Reason for signing: Approved	Approv Name: PPD Capacity: Biostatistics Date of signature: 16-Nov-2022 13:33:48 GMT+0000
Reason for signing: Approved	Approv Name: PPD Capacity: Medical Date of signature: 16-Nov-2022 14:52:15 GMT+0000

Electronic signatures made within Clinical Vault are considered to be a legally binding equivalent of traditional handwritten signatures.

10.7 Appendix 6: Protocol Elements for Redaction

10.7.1 Information About Sponsor Signatory

Approval Statement for Sponsor Signatories:

Electronic signatures made within LEO Pharma A/S Clinical Vault are 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 PPD PPD

Senior Director, Medical Department

PPD PPD PPD

Biostatistics Lead

PPD PPD PPD

Medical Lead, Medical Department

Medical Monitor Name and Contact Information will be provided separately.

澄 清

Clarification

LEO LP0053-2277 Protocol Version 3.0 Signature Page

研究标题 **Protocol Title**	一项在中国稳定性斑块状银屑病成人受试者中比较 LEO 90100 和得肤宝®软膏治疗 4 周的有效性和安全性的 III 期、随机、研究者设盲、活性药物对照、平行分组、多中心试验 A phase 3, randomised, investigator-blind, active-controlled, parallel group, multicentre trial comparing the efficacy and safety of 4 weeks treatment with LEO 90100 and Daivobet® ointment in adult Chinese subjects with stable plaque psoriasis
试验药品 **Compound**	LEO 90100
方案编号 **Protocol Number**	LP0053-2277
方案版本 **Version**	3.0
方案版本日期： **Version Date**	2022 年 11 月 9 日 9 Nov 2022

Protocol version 3.0 有 3 份方案签字页，分别是

There are 3 signature pages for protocol version 3.0 listed as below,

签字页类型 Signature Type	日期 Date Signed	原因 Cause provided
电子签名 Electronic Signature	2022 年 11 月 16 日 16 Nov 2022	通过电子系统签字产生 Generate on eTMF system
手写签名 Handwriting	2022 年 11 月 21 日 21 Nov 2022	根据递交要求，出具手写签字页 Raise signature page in handwriting per IRB submission requirement
手写签名 Handwriting	2023 年 2 月 9 日 9 Feb 2023	2022 年 11 月 21 日手写签字页不清晰，所以重新手写签名

		The handwritten signature page of 21Nov2022 is indistinct. Therefore, re-raise it on 9Feb2023.

三份签字页均为 Protocol version 3.0 的签字页，具有同等效力，特此声明。

Hereby make the declaration that all of 3 signature pages of protocol version 3.0 are equal authentic.

附件：电子签名签字页 -2022 年 11 月 16 日

手写签名签字页 -2022 年 11 月 21 日

手写签名签字页 -2023 年 2 月 9 日

Attachment: Electronic Signature Page – 16 Nov 2022

Handwriting Signature Page – 21 Nov 2022

Handwriting Signature Page – 9 Feb 2023

LEO PHARMA CONSULTANCY (SHANGHAI) COMPANY LIMITED 上海利奥医药咨询有限公司

LEO Pharma A/S

精鼎医药研究开发（上海）有限公司

Parexel International

PAREXEL CHINA CO., LTD. 精鼎医药研究开发(上海)有限公司