1. FINAL CLINICAL STUDY PROTOCOL AMENDMENT 2

UNION therapeutics A/S

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2b Dose-Ranging Study to Evaluate the Efficacy and Safety of Orismilast in Adults with Moderate-to-Severe Plaque-Type Psoriasis

Protocol Number: UNI50001-203

IND Number:	129386
EudraCT Number:	2021-003209-22
Name of Investigational Product:	Orismilast
Phase of Development:	2b
Indication:	Treatment of moderate-to-severe plaque-type psoriasis
Sponsor Representative(s):	[redacted] Dermatology Tel: [redacted] Email: [redacted]
Sponsor:	UNION therapeutics A/S Tuborg Havnevej 18 DK-2900 Hellerup, Denmark Tel: +45 61 77 74 35
Protocol Version:	3.0
Protocol Date:	20 May 2022

PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2b Dose-Ranging Study to Evaluate the Efficacy and Safety of Orismilast in Adults with Moderate-to-Severe Plaque-Type Psoriasis

Protocol Number: UNI50001-203

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

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Consultant, [redacted]

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Date (DD-Mmm-YYYY)

Coordinating Investigator

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Consultant Dermatologist, [redacted]

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Biostatistician

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UNION therapeutics A/S

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Signature

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INVESTIGATOR SIGNATURE PAGE

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Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol (and any amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and any amendments), GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by UNION therapeutics A/S including, but not limited to, the current Investigator's Brochure.
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of UNION therapeutics A/S and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to UNION therapeutics A/S and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the UNION therapeutics A/S study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial patients will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.
- Information developed in this clinical study may be disclosed by UNION therapeutics A/S to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Name:

Title:

Institution:

Investigator Signature

Date (DD-Mmm-YYYY)

2. SYNOPSIS

Title of Study:	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2b Dose-Ranging Study to Evaluate the Efficacy and Safety of Orismilast in Adults with Moderate-to-Severe Plaque-Type Psoriasis
Protocol Number:	UNI50001-203
Investigators/Study Sites:	Approximately 40 centers in Europe and North America
Phase of Development:	Phase 2b
Objectives:	**Primary objective:** • The primary objective is to evaluate the efficacy and safety of a modified-release orismilast tablet versus placebo in adults with moderate-to-severe plaque-type psoriasis. **Secondary objectives:** • Evaluate the dose response of orismilast and identify the dose with the best benefit/risk ratio to be evaluated in a Phase 3 program. **Exploratory objectives:** • [redacted] • Evaluate the change in cardiovascular risk factors under orismilast treatment. • [redacted] • Evaluate the change in skin psoriasis at "difficult to treat" anatomical areas such as the scalp. • Evaluate the change in psoriasis at "difficult to treat" anatomical areas such as nails.
Study Endpoints:	**Primary endpoint:** • The primary endpoint in this study is the percentage change in Psoriasis Activity and Severity Index (PASI) score from Baseline at Week 16. **Key secondary endpoints:** • Patients achieving 75% reduction in PASI (PASI75) response at Week 16. • Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in Investigator Global Assessment (IGA) at Week 16. **Other secondary endpoints:** • Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in IGA at Weeks 4, 8, 12, and 20. • Patients achieving PASI75 response at Weeks 4, 8, 12, and 20. • Patients achieving 50% reduction in PASI (PASI50) and 90% reduction in PASI (PASI90) response at Weeks 4, 8, 12, 16, and 20. • Change from Baseline in PASI at Weeks 4, 8, 12, and 20. • Change from Baseline in total Psoriasis Symptoms Scale (PSS) score at Weeks 4, 8, 12, 16, and 20.

	• Change from Baseline in each individual item of the PSS at Weeks 4, 8, 12, 16, and 20. • Change from Baseline in the affected body surface area (BSA) at Weeks 4, 8, 12, 16, and 20. • Change from Baseline in Dermatology Life Quality Index (DLQI) score at Weeks 16 and 20. • Patients experiencing psoriasis rebound by Week 20, defined as PASI ≥125% of Baseline or new generalized pustular, erythrodermic, or more inflammatory psoriasis. **Safety endpoints:** • The occurrence, severity, and seriousness of treatment-emergent adverse events (TEAEs) reported over the 16-week Treatment Period and the 4-week Follow-up Period. • Changes from Baseline in physical examination; vital sign measurements (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements); and body weight over the 16-week Treatment Period and the 4-week Follow-up Period. • Changes from Baseline in electrocardiogram (ECG) findings over the 16-week Treatment Period and the 4-week Follow-up Period. • Changes from Baseline in safety laboratory values (hematology, serum chemistry, and urinalysis) over the 16-week Treatment Period and the 4-week Follow-up Period. • Hospital Anxiety and Depression Scale at each visit except Week 2. • Columbia-Suicide Severity Rating Scale (C-SSRS) at each visit except Weeks 1 and 2. **Exploratory endpoints:** • Change from Baseline in Physician's Global Assessment of Fingernails (PGA-F) at Week 16. • Change in Scalp-Specific Investigator Global Assessment (ss-IGA) from Baseline at Week 16 in the subgroup of patients with Baseline score of at least 2 (mild scalp psoriasis). • Change from Baseline of scalp itch Numeric Rating Scale (NRS) at Week 16 in the subgroup of patients with Baseline score of at least 4 on the 11-point NRS. • [redacted] • Change in cardiovascular risk factors at Week 16. The following parameters will be collected: weight, body mass index, waist and hip circumferences, blood pressure, fasting serum glucose, triglycerides, cholesterol (total and high-density lipoprotein / low-density lipoprotein fractions), and C-reactive protein. • [redacted] • Plasma levels of the drug and its metabolites at scheduled visits.
Study Design:	This multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2b dose-ranging study is designed to assess the efficacy and safety of modified-release orismilast compared with placebo in adult patients with moderate-to-severe plaque-type psoriasis. Efficacy and safety outcomes will be evaluated to select an appropriate orismilast dose for subsequent Phase 3 studies.

	After a Screening visit up to 28 days before Baseline, approximately 200 patients will be assigned randomly in a 1:1:1:1 ratio to receive 1 of the 3 orismilast doses (20 mg, 30 mg, or 40 mg) or placebo twice daily (BID) for 16 weeks, with a 4-week Follow-up visit. Administration will begin at Baseline with a dose titration period. The maximum duration of study participation is approximately 24 weeks. Patients will be seen at the site on Screening, Baseline (Day 1), and Weeks 1, 2, 4, 8, 12, 16 (End-of-Treatment visit), and 20 (Follow-up visit, 4 weeks after treatment completion or discontinuation). Visits at Weeks 1 and 2 could be conducted via a telemedicine procedure at Investigator's discretion. At Baseline and each visit from Week 4 onwards, PASI, BSA, IGA, and PSS will be assessed. Quality of life will be assessed by administration of DLQI at Baseline and at Weeks 16 and 20 visits. Additional efficacy parameters include: an ss-IGA, a Physician Global Assessment of fingernail psoriasis (PGA-F), and [redacted]. These parameters will be assessed at Baseline and Weeks 16 and 20. Safety evaluations include adverse events (AEs), laboratory and vital sign assessments, physical examinations, as well as mood change evaluation by patient (Hospital Anxiety and Depression Scale) and suicidal ideation evaluation by Investigator (C-SSRS). A panel of cardiovascular risk factors will be assessed at Baseline and Week 16. Before administration of the study drug at Baseline and on Weeks 4, 8, and 16, blood will be collected for orismilast concentration determination. [redacted]
Selection of Patients:	Main Inclusion Criteria: 1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in the protocol. 2. Male and female patients ≥18 years of age at the time of signing the ICF. 3. Body weight of >40 kg at the time of signing the ICF. 4. Diagnosis of chronic, stable plaque-type psoriasis at least 2 months before the Screening visit. If the patient is diagnosed with psoriasis arthritis, the arthritis should be stable. 5. Moderate-to-severe plaque-type psoriasis as defined by PASI ≥12, BSA ≥10%, and IGA ≥3 at the screening and baseline visits. 6. Candidate for systemic antipsoriatic treatment or phototherapy. 7. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at the Baseline visit. In addition, sexually active WOCBP must agree to use a highly effective method of contraception until at least 4 weeks after the end of study treatment. Highly effective methods of contraception are those that have a failure rate of <1% (when implemented consistently and correctly) and include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implantable); progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable); intrauterine devices or systems; self or partner vasectomy; or bilateral tubal ligation. Patients must have been on a stable dose of hormonal contraceptives for at least 4 weeks before

	the Baseline visit. Abstinence from heterosexual intercourse is an accepted method of contraception if it is the patient's lifestyle and is practiced for the entire duration of the study. Note: A woman of nonchildbearing potential is defined as a woman with surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or a woman in a postmenopausal status defined as cessation of menses for at least 12 months without an alternative medical cause and a confirmatory follicle-stimulating hormone (FSH) test or as cessation of menses for at least 24 months without an alternative medical cause. Main Exclusion Criteria: 1. Therapy-resistant psoriasis defined as ≥2 treatment failures due to inadequate efficacy within the past 5 years of any biologic therapies (including but not limited to etanercept, adalimumab, infliximab, certolizumab pegol, guselkumab, secukinumab, risankizumab, ixekizumab, tildrakizumab, or ustekinumab) administered in adequate dose and duration according to the label or local/national guidelines (patients who stopped systemic treatment for reasons not related to lack of efficacy are not excluded). 2. Unstable psoriasis or PsA with acute deterioration within 4 weeks of the Screening visit. 3. History of allergy or hypersensitivity to any component of the study treatment. 4. Active infection (eg, bacteria, viral, fungal) requiring treatment with systemic antibiotics within 4 weeks of the Screening visit. 5. Malignancy or history of malignancy except for treated (ie, cured) basal cell skin carcinomas. 6. Current diagnosis of predominant guttate, erythrodermic, exfoliative, or pustular psoriasis, or of drug-induced psoriasis, or other skin conditions that might confound the evaluation of psoriasis vulgaris, as judged by the Investigator (eg, atopic dermatitis, lupus). 7. Any recurrent medical condition associated with serious gastrointestinal diseases, such as inflammatory bowel disease. 8. Any medical or psychiatric condition (eg, current major depression with a score for depressive symptoms ≥15 of Hospital Anxiety and Depression Scale at Baseline, schizophrenia, suicidal behavior, psychiatric hospitalization within the prior year) which, in the Investigator's opinion, would preclude the patient from adhering to the protocol, completing the study per protocol, and/or would place the patient at unacceptable risk for receiving the investigational therapy. 9. Any therapies and systemic treatments as described in Table 3 which do not comply with the indicated washout interval. 10. Any previous treatment with orismilast or failure of treatment with apremilast or any other systemic phosphodiesterase-4 inhibitor as described in Table 3. 11. Any condition, including laboratory or ECG abnormalities, that places the patient at unacceptable risk to participate in the study or confounds the ability to interpret data from the study. 12. Severe hepatic impairment based upon medical history and laboratory abnormalities (eg, low albumin and abnormal bilirubin). 13. Any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary: a. Absolute neutrophil count of $<3.0 \times 10^9$/L ($<3000/mm^3$)

	b. Hemoglobin of <10.0 g/dL or hematocrit <30% c. Platelet count of $<100 \times 10^3$ cells/mm^3 (SI: $<100 \times 10^9$ cells/L). d. Absolute lymphocyte count of $<1.0 \times 10^9$/L (<1000/mm^3) e. Total bilirubin >1.5 × the upper limit of normal (ULN); patients with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ULN; f. Alanine aminotransferase or aspartate aminotransferase >2.5 × the ULN; g. Serum creatinine ≥1.5 mg/dL. For a patient with a value of ≥1.5 mg/dL, a creatinine clearance of ≥60 mL/min (calculated using the CKD-EPI Creatinine Equation) is allowed. 14. History or evidence of hepatitis B virus (HBV) infection at Screening. Patients with positive hepatitis B surface antigen (HBsAg) are excluded. For patients with isolated positive antihepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb) result must also be positive to be considered for this study. 15. History or positive test result for hepatitis C virus (HCV) antibody, indicating ongoing infection, at Screening. Confirmatory testing for HCV RNA will be conducted for patients who have a positive test result. Patients who have a negative result for HCV RNA will be eligible to participate in the study. 16. History of positive HIV, or have congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease). Patients who are positive for HIV antibodies (HIV-1 or HIV-2) at Screening are excluded from the study. 17. Suicidal ideation or behavior in the past 12 months as indicated by a positive response (yes) to questions 4 or 5 on the C-SSRS completed at the Screening visit or the C-SSRS completed at the Baseline visit. 18. Pregnant or breastfeeding. 19. History of alcohol or substance abuse within 6 months before Baseline that, in the opinion of the Investigator, will preclude participation in the study. 20. Institutionalized by court order or by local authority.
Planned Sample Size:	Approximately 200 patients will be enrolled to ensure approximately 50 patients per arm. This sample size is based on assumptions that the percentage change from Baseline in PASI is -32.2% and -50.9% for placebo and each orismilast dose group, respectively, and the standard deviation is 33%. Using a 2-sided 2-sample *t*-test, 50 patients in each treatment arm can achieve a power of 80% at the significance level of 5%.
Investigational Therapy:	Name: orismilast Unit doses strength and dose formulation: 20 mg (2 × 10 mg tablets), 30 mg (1 × 30 mg tablet), and 40 mg (1 × 10 mg tablet and 1 × 30 mg tablet) Route and frequency of administration: oral, twice daily Use: experimental Sourcing: provided centrally by the Sponsor Packaging and labeling: provided in individually labeled wallet cards with blistered tablets. Each card will be labeled as required per country requirement

Reference Therapy:	Matching placebo tablets
Treatment Duration:	The Treatment Period for this study is 16 weeks, with a 4-week Follow-up visit. Refer to Table 2 for the dose titration schedule.
Pharmacokinetics	The plasma levels of the drug and its metabolites will be summarized descriptively by visit in this study. Patients will be offered optional participation in specific blood sampling for calculation of pharmacokinetic profiles.
Statistical Methods and Planned Analyses:	For inferential analyses of primary and secondary efficacy endpoints, each active treatment group will be compared with the placebo group. Primary and secondary efficacy endpoints are to be assessed in the Intention-to-Treat (ITT) Analysis Population. Missing data for primary and key secondary endpoints will be handled with multiple imputation method. For categorical efficacy endpoint based on a continuous variable, the multiple imputation will be first done for the continuous variable, then determine the category using the imputed values. Analyses will be repeated on the Per-Protocol Population for primary and secondary endpoints. When appropriate, the raw parameter, its change from Baseline, and percentage change from Baseline will be summarized. The primary endpoint, percentage change from Baseline to Week 16 in PASI, will be analyzed using analysis of covariance with treatment group as factor and Baseline PASI as covariate. The mixed model for repeated measures (MMRM) will be used as a supportive analysis. Each active treatment dose will be compared with placebo. No adjustment for multiplicity will be made and the 0.05 level of significance will be used to claim efficacy compared with placebo. Least square means and the 95% confidence interval of the difference between each active treatment and placebo will be calculated. The primary analysis set will be the ITT Analysis Population with multiple imputation approach to handle missing values. The same analyses will be repeated for Weeks 20, 12, 8 and 4. The key secondary and other binary endpoints (IGA success, PASI50, PASI75, PASI90) will be analyzed using the Mantel-Haenszel (MH) test, comparing each active treatment group to placebo in the ITT Analysis set. For categorical variables, the MH procedure, with ridit scores, will be used; this test is the same as the nonparametric Wilcoxon test and enhances the analysis when the parameter is not normally distributed. Graphics will be added to facilitate interpretation. IGA scores/full scale will be analyzed using the MH test and the row mean score statistics and the ridit transformation. The other continuous secondary endpoints will be analyzed using MMRM. The above endpoints (PASI changes and percentage changes, IGA success, PASI50, PASI75, PASI90) and the percentage change of BSA will be presented graphically over time from Baseline to Week 20. In addition, shift tables will be provided between Baseline and each visit for the IGA distribution. The PASI percentage changes from Baseline will be plotted to identify where the best separation between treatments occurs. All safety analyses will be conducted using the Safety Analysis Population. AE data will be presented and tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) classification. Reported AEs will be summarized by the number of patients reporting the events, as well as by

	System Organ Class (SOC) and Preferred Term (PT), SOC, PT, and severity, and SOC, PT, and relationship to study product. Laboratory (chemistry and hematology) parameters and vital signs will be tabulated by visit using descriptive statistics and shift tables. The value at each visit, as well as the change from Baseline, will be presented. No interim analysis is planned in this study.

3. TABLE OF CONTENTS

3.1. List of In-text Tables

3.2. List of In-text Figures

4. LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	atopic dermatitis
ADL	Activities of Daily Living
AE	adverse event
AESI	Adverse Event of Special Interest
AUC	area under the curve
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
AUC_{0-t}	area under the curve from time 0 to the last measurable concentration
BID	twice daily
BMI	body mass index
BSA	body surface area
cAMP	cyclic adenosine monophosphate
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
cGMP	cyclic guanosine monophosphate
COPD	chronic obstructive pulmonary disease
C_{max}	maximum plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
eCRF	electronic case report form
ECG	electrocardiogram
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EOT	End of Treatment
GCP	good clinical practice
GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN-γ	interferon gamma
IGA	Investigator Global Assessment
IL	interleukin
IND	Investigational New Drug

Abbreviation	Definition
IRB	institutional review board
ITT	intent-to-treat
IWRS	Interactive Web Response System
MH	Mantel-Haenszel
MHRA	Medicines and Healthcare Products Regulatory Agency
MIP-1α	macrophage inflammatory protein-1 alpha
MMRM	mixed model for repeated measure
NRS	Numeric Rating Scale
PASI	Psoriasis Activity and Severity Index
PASI50	50% reduction in PASI
PASI75	75% reduction in PASI
PASI90	90% reduction in PASI
PD	pharmacodynamics
PDE	phosphodiesterase
PGA	Physician's Global Assessment of disease severity
PGA-F	Physician Global Assessment of Fingernail/ Physician Global Assessment of Fingernail psoriasis
PK	Pharmacokinetic(s)
PP	Per-protocol
PRO	patient-reported outcome
PsA	psoriatic arthritis
PSS	Psoriasis Symptoms Scale
PT	preferred term
QoL	quality of life
SAE	serious adverse event
SOC	system organ class
ss-IGA	scalp-specific Investigator Global Assessment
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

5. INTRODUCTION

5.1. Background on Plaque-Type Psoriasis

Psoriasis is a multisystem disease with predominantly skin and joint manifestations characterized by well-demarcated, erythematous, scaly plaques which are often itchy. Psoriasis is considered a systemic disease; it is associated with psychological, metabolic, arthritic, and cardiovascular comorbidities. Epidemiological data on the incidence of psoriasis are limited, with studies conducted mainly in Europe and North America (Parisi 2020). Reported prevalence of psoriasis in adults varies from about 1.4% in the United States (US) to 2.5% in Western or Eastern Europe (https://www.globalpsoriasisatlas.org/statistics/statistics).

The most common clinical type of psoriasis, affecting 80% to 90% of patients, is psoriasis vulgaris (plaque-type psoriasis). For patients with moderate-to-severe plaque-type psoriasis who comprise about one-third of all psoriasis patients, systemic agents (biological or nonbiological) or phototherapy is the regimen of choice (Menter 2009, 2010). However, the long-term treatment of psoriasis with biological therapies may be limited by safety and tolerability issues, reduced efficacy over time, and poor adherence due to an inconvenient route of administration (eg, injection) (Ravindran 2008). Therefore, despite a large number of biologic agents being available, there is still an unmet need for safe, effective, and convenient long-term oral treatments for patients with moderate-to-severe psoriasis.

The involvement of inflammatory cells, such as T cells and myeloid dendritic cells, and proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), and interleukin (IL)-12 and IL- 17 in the pathogenesis of psoriasis is well established (Quaglino 2011). Phosphodiesterases (PDEs) constitute a superfamily of enzymes catalyzing the hydrolysis of the intracellular second messengers cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP) that play key roles in mediating biological responses generated by a variety of extracellular signals. PDE4 is a cAMP-specific PDE expressed by immune and inflammatory cells, including neutrophils, T-lymphocytes, macrophages, and eosinophils. High cAMP levels decrease proliferation and cytokine production whereas low concentrations have the opposite effect. Specific inhibition of PDE4 thus has the potential to have beneficial effects in a wide variety of inflammatory disorders including rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, airway disease, skin disease, and neuro inflammation.

Currently marketed PDE4 inhibitors include roflumilast approved for chronic obstructive pulmonary disease (COPD), crisaborole for atopic dermatitis, and apremilast approved for psoriasis, psoriatic arthritis (PsA), and oral ulcers associated with Behcet's disease.

One of the key challenges for an effective PDE4 therapy has been the narrow therapeutic window. Most of the programs investigating PDE4 inhibitors failed because of safety issues, up until the approval of roflumilast for COPD, and apremilast for psoriasis and PsA some years later. Both therapies had tolerability issues affecting, primarily, but not exclusively, the

gastrointestinal (GI) tract, characterized by nausea, vomiting, and diarrhea/loose stools. These undesired GI effects were consistently observed from the beginning of treatment, and this led to the titration of those drugs (apremilast over 1 week, roflumilast 1 month) to reduce side effects.

5.2. Background on Orismilast

Orismilast is a PDE4 inhibitor currently in Phase 2 of clinical development for oral treatment of various inflammatory skin diseases including hidradenitis suppurativa, plaque-type psoriasis and atopic dermatitis. During initial development Phase 1/2a, different oral formulations have been tested in the clinic. Because the immediate-release tablet appeared to be less well tolerated compared with the drug in capsule formulation, newly developed oral Orismilast formulation concepts were tested, and a modified-release formulation selected for further development. This new formulation was shown to improve the GI tolerability without a significant loss in systemic exposure.

5.2.1. Nonclinical Studies

Both oral and topical administration of orismilast exhibited anti-inflammatory effects in the chronic oxazolone mouse model, an animal model that shares some similarities with human atopic dermatitis (AD) and chronic skin inflammation. Oral administration of orismilast to mice also reduced levels of TNF-α in this model.

The selectivity of orismilast has been investigated using a panel of 76 G protein coupled receptors, 40 kinase assays, and patch-clamp tests with 8 cardiac ion channels, and no effects were seen except some inhibition of hERG ion channel current amplitudes at 10 μM.

The pharmacokinetics (PK) of orismilast has been investigated in mice, rats, rabbits and minipigs after administration by oral gavage. In rats, area under the curve (AUC) and maximum plasma concentration (C_{max}) generally increased in proportion to dose in the tested range (0.5–1.75 mg/kg), with female rats having AUC and C_{max} values 1.5 to 3 times higher than male rats. In mice, rabbits, and minipigs, AUC and C_{max} increased less than, or proportional to, the investigated doses (5–500 mg/kg, twice daily dosing, and 1.0–30 mg/kg, respectively), and AUC and C_{max} values were generally comparable in females and males. In a minipig telemetry study, mean concentrations increased less than proportionally to the investigated doses (1.0–10 mg/kg) and were lower in females than in males. There was little or no accumulation in mice, rats, rabbits, or minipigs. Orismilast was excreted mainly via the faces in rats and minipigs.

The in vitro plasma protein binding of orismilast was low to moderate (35–67%) in a variety of species tested (mouse, rat, rabbit, minipig, and human). The in vitro metabolism of orismilast has been investigated using hepatocytes from mouse, rat, hamster, rabbit, minipig, dog, marmoset, cynomolgus monkey, and human. The extent of metabolism was generally low.

In safety pharmacology assessments, the in vitro assessment of the effect on hERG tail current recorded from human embryonic kidney (HEK-293) cells gave an IC50 value of 11.4 μM. In

conscious telemetered minipigs, oral administration of orismilast produced no treatment- related effects on heart rate, body temperature, QRS, QT or QTcR intervals or electrocardiogram (ECG) morphology. An increase in systolic blood pressure was observed in minipigs at the highest dose level only (10 mg/kg). No effect was observed on the central nervous system in a modified Irwin test or on respiratory parameters in rats.

Orismilast was not genotoxic when tested in the standard International Council for Harmonisation (ICH) battery of 2 in vitro and 1 in vivo genotoxicity tests.

The outcome and assessment of nonclinical data showed that neither orismilast (LEO 32731) nor its major metabolite LEO 40815 have been found to be genotoxic in the standard battery of genotoxicity testing that included in vitro Ames and mouse lymphoma assay testing and in vivo micronucleus testing (LEO 32731). In addition, reproductive toxicity studies on fertility and early embryonic development, as well as embryo fetal development, have been conducted across a range of time courses, dose, and exposure levels in rats, mice, minipigs, and rabbits. The weight of evidence from these nonclinical studies indicates that neither orismilast nor its major metabolite LEO 40815 are teratogenic or have adverse effects on male and female fertility or the female reproductive system. The no-observed-adverse-effect levels, as well as safety margins, are based on AUC from these studies for the highest proposed clinical dosing regimen of 40 mg twice daily (BID; 80 mg/kg/day).

Overall, treatment was well tolerated at 1 mg/kg. Refer to the Investigator's Brochure for further details on orismilast nonclinical studies.

5.2.2. Clinical Studies

As of 01 Dec 2020, the orismilast clinical development program in psoriasis consists of 8 completed trials including 7 Phase 1 trials in healthy subjects and 1 Phase 2a trial in subjects with moderate-to-severe psoriasis vulgaris.

The completed trials include 2 dose-finding and PK trials using a solution and a capsule formulation (drug in capsule; trials LP0058-S01 and LP0058-1114), a PK trial using a capsule (drug in capsule) and modified-release tablets (3 different release profiles; trial LP0058-1005), a PK trial in healthy Japanese men using a tablet formulation (immediate release; LP0058- 1362), a PK trial evaluating the PK and safety/tolerability profiles of several new formulations (LP0058-1442), 2 drug-drug interaction trials using a orismilast immediate-release tablet formulation and midazolam (trial LP0058-1267 and LP0058-1324), and a proof of concept Phase 2a trial using an immediate-release tablet formulation (trial LP0058-1072).

5.2.2.1. Clinical Pharmacology

After single and multiple dosing of up to 60 mg twice daily of the initial capsule formulation, in the fasted state or after a standard breakfast, orismilast was steadily absorbed with a median time to maximum plasma concentration (t_{max}) of 2–4 hours. Systemic exposure to orismilast increased in an approximately dose proportional manner. Estimates of elimination half-lives varied across

studies, from 4–6 hours (for dose levels up to 30 mg 3 times a day) and up to 10 hours (for 60 mg twice daily dose level). After multiple dosing of up to 30 mg 3 times a day, steady state was attained within 2 days. Minimal accumulation of orismilast was observed. Dosing after a high-fat meal delayed t_{max} by 2 hours and increased area under the curve from time 0 to infinity ($AUC_{0-\infty}$) by 40%, compared with dosing in the fasted state.

Formation of the human-specific metabolite LEO 40815 was rapid, with median t_{max} occurring approximately 1 hour after that of orismilast. The disposition of the metabolite mirrored that of orismilast, suggesting formation rate-limited elimination of LEO 40815. The ratio of metabolite to parent compound was relatively constant across doses and upon repeated dosing, indicating that systemic exposure to LEO 40815 was approximately 53–75% lower than to orismilast. PDE4 enzymatic activity was measured in a scintillation proximity assay using purified human recombinant PDE4D protein. Orismilast is a potent inhibitor of PDE4D activity. LEO 40815 was approximately 100 times less potent than orismilast.

The PK profile for the orismilast immediate-release tablet formulation, used in trial LP0058-1267, appeared similar to the PK profile for the immediate-release capsule formulation used in the first 3 clinical trials. Furthermore, there has not been identified any differences in the PK profile of orismilast between races (LP0058-1362) or gender (LP0058-1114).

Data from the LP0058-1324 trial showed that the exposure of midazolam was more than 30% higher when midazolam was administered at steady state (Day 17) after administration of 30 mg orismilast twice daily compared with midazolam alone (geometric means of 132% for area under the curve from time 0 to the last measurable concentration [AUC_{0-t}] $_{and}$ 137% for C_{max}). These results classify orismilast as a weak inhibitor of CYP3A4.

Pharmacodynamic evaluation from trial LP0058-S01 using an ex vivo cytokine release assay indicated that orismilast inhibited the secretion of TNF-α and interferon gamma (IFN-γ). Maximum inhibition generally occurred between 4–6 hours postdose. There was no clear dose-relationship in the maximal response or duration of inhibitory response. Mean decreases from Baseline to Day 7 ranged from approximately 67–70% for TNF-α and 52–77% for INF-γ levels across dose groups receiving 10, 20 and 30 mg 3 times a day orismilast. In accordance, reduced levels of TNF-α, IFN-γ, macrophage inflammatory protein-1 alpha (MIP-1α), and MIP-1β were observed in lipopolysaccharide- stimulated blood from subjects treated with orismilast in the LP0058-1072 trial, suggesting that pharmacologically relevant levels of orismilast were present.

5.2.2.2. Efficacy

So far one efficacy trial (LP0058-1072) with orismilast immediate-release tablets has been completed. A total of 36 subjects with moderate-to-severe psoriasis vulgaris were randomized in the trial in a 1:1 ratio to treatment with either 30 mg orismilast or placebo, administered orally as 3 tablets twice daily for 16 weeks (1-week dose escalation followed by 15-week full dose treatment).

After 16 weeks of treatment, the mean psoriasis area and severity index (PASI) score (primary endpoint) was statistically significantly lower in subjects treated with orismilast tablets (least squares mean: 7.1) compared with subjects in the placebo group (least squares mean: 13.1). Mean PASI at entry was 14.9. A higher proportion of patients achieved a 75% improvement in PASI (PASI75) in the orismilast group (44.4%) vs placebo (5.6%; P =.019). In addition, treatment success (defined as clear or almost clear) according to Physician's Global Assessment of disease severity (PGA) at Week 16 was higher in the orismilast group (7 of 18 subjects, 38.9%) than in the placebo group (1 of 18 subjects, 5.6%). The estimated itch score was numerically lower at Week 16 in the orismilast group (least squares mean: 3.4) compared with the placebo group (least squares mean: 5.7).

Approximately half of the subjects in both treatment groups were withdrawn from the LP0058-1072 trial, mainly owing to tolerability issues in the orismilast group and lack of efficacy in the placebo group, respectively. Although the bias introduced by this attrition had an impact on the estimated efficacy, it was not considered to disqualify the clear difference observed between the 2 treatments.

5.2.2.3. Safety

Orismilast administered as capsules was safe and well tolerated in single doses up to 45 mg, and in multiple doses up to 30 mg 3 times a day after an up-titration period of 7 days. Orismilast was moderately well tolerated in multiple doses up to 50 mg twice daily, after gradual up-titration to the 50 mg twice daily level over 8 days. Poor tolerability at the 60 mg dose level was due to an increased incidence and severity of GI adverse events (AEs). This was most likely related to high local concentrations of orismilast in the GI tract, as the symptoms at the 60 mg dose level generally started before t_{max} and were markedly greater than at lower doses, despite mean systemic exposure being comparable to that seen at 45 mg.

Orismilast administered as immediate-release tablets was relatively well tolerated at the 20 mg twice daily level but was poorly tolerated when up-titrated to the 40 and 50 mg twice daily levels in trial LP0058-1267. Six subjects were withdrawn from the trial by the Investigator because of AEs. Likewise, in the LP0058-1072 trial, orismilast tablets (30 mg twice daily) were poorly tolerated in subjects with moderate-to-severe psoriasis vulgaris. AEs leading to withdrawal from the trial were reported for 50% of the subjects in the orismilast group compared with 16.7% in the placebo group. In the orismilast group, the majority of withdrawals were due to GI disorders.

A total of 5 serious adverse events (SAEs) were reported across all trials; 3 SAEs in 3 subjects in the LP0058-1072 trial in subjects with moderate-to-severe psoriasis vulgaris and 2 SAEs in 1 subject in the LP0058-1324 trial. In the LP0058-1072 trial, 2 subjects in the orismilast group had 1 SAE each (ureterolithiasis, considered not related to the treatment, and erysipelas on the arm, considered possibly related to the treatment), and 1 subject in the placebo group had 1 SAE ('condition aggravated', relating to preexisting Scheuermann's disease and considered not related to the treatment). In the LP0058-1324 trial, 1 subject reported SAEs (abdominal pain and abdominal cramps, considered possibly related to the treatment).

The majority of nonserious AEs were of mild intensity and considered possibly or probably related to orismilast. Generally, the incidence, frequency, and severity of AEs increased with increasing dose of orismilast. The most frequently reported orismilast -related AEs were GI disorders (particularly nausea and diarrhea), nervous system disorders (particularly headache and dizziness), and musculoskeletal and connective tissue disorders (particularly back pain).

5.3. Clinical Risks/Benefits

Despite the positive and encouraging efficacy results of the Phase 2a study of the immediate-release tablets of orismilast, this formulation presented an undesirable safety profile with 50% of patients prematurely discontinuing because of GI effects. To improve the GI tolerance, several formulations were tested in an extensive Phase 1 clinical program, leading to the selection of a modified-release formulation with notably better GI tolerance in healthy volunteers. The modified-release formula is expected to mitigate potential GI effects previously observed in psoriasis patients with the immediate-release tablets while maintaining the efficacy previously observed. The titration dosing schedule at the initiation of study treatment will help to reduce the incidence and severity of GI side effects that tend to occur primarily when starting therapy. The improved safety profile of the modified-release formulation is expected to make the therapeutic window of orismilast wider this allowing to achieve dosing levels with adequate efficacy and good tolerability.

Occurrence and severity of GI disorders will be promptly identified by monitoring the subjects for any signs of abdominal discomfort, abdominal distension, abdominal pain, nausea, vomiting, loss of appetite, and diarrhea. Depending on their severity, these AEs may qualify as an adverse event of special interest (AESI). Based on the occurrence of GI or other AEs considered having a causal relationship with study treatment, the Investigator might consider decreasing the daily dosing regimen or stopping the treatment for a few days, until recovery. Besides the above, all subjects will be monitored for any cardiovascular manifestations using vital signs and 12-lead ECG at each visit. Drug class potential effects such as weight loss and major depression will be monitored during the study. Subjects with major depression, presenting major psychiatric disorders or at risk for suicide will be excluded from enrollment, and suicidal ideation and depressive symptoms will be assessed in the course of the study by Columbia-Suicide Severity Rating Scale (C-SSRS) and Hospital Anxiety and Depression Scale (HADS), respectively. Patients will be informed of the potential increased risk of depression or suicidal thoughts of this class of drugs; and recommended to promptly contact their study doctor in case of such event.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of orismilast may be found in the Investigator’s Brochure.

5.4. Study Rationale

PDE4 inhibitors have demonstrated efficacy in psoriasis and AD with 2 drugs having reached the market: apremilast, an oral agent for the treatment of plaque-type psoriasis and crisaborole, a

topical agent, for the treatment of AD. Orismilast is a novel PDE4 inhibitor being developed for the oral treatment of psoriasis. After an extensive Phase I program in healthy subjects and a Phase 2a study in patients with moderate-to-severe psoriasis, the clinical development program is progressing into a Phase 2b dose-finding clinical study using a modified-release oral formulation that is expected to present a more favorable safety profile.

The purpose of this study is to assess the efficacy and safety of 3 different dose levels (20 mg, 30 mg, or 40 mg) of orismilast administered orally BID over a period of 16 weeks in patients with moderate-to-severe plaque psoriasis. Efficacy and patient's outcome will be assessed through a set of validated measures for psoriasis. In addition, PK and pharmacodynamic (PD) evaluations will be conducted. The results of the study will inform the design and the dose level(s) of the subsequent Phase 3 program.

5.4.1. Dose Rationale

The modified-release formulation was studied in 1 clinical trial (LP0058-1442) and administered in a total of 36 healthy volunteers: 18 in part 1, 9 in part 2, and 9 in part 3. Twenty-seven (27) healthy volunteers received a single administration of 30 mg orismilast, and 9 subjects received multiple administrations over a period of 17 days with an up-titration up to a maximum of 60 mg BID.

Part 1 of this study was to evaluate the key PK parameters of the new modified-release formulation compared to the reference capsule formulation with immediate release. Orismilast was rapidly absorbed from both formulations with median t_{max} values of 3.00 hours postdose for the immediate-release capsule and 2.52 hours postdose for the modified-release tablet. The individual t_{max} ranges were approximately 1 to 6 hours postdose for the immediate-release capsule and 1 to 4 hours postdose for the modified-release tablet. Following t_{max}, the plasma concentrations of orismilast declined in a generally biphasic manner for both formulations with geometric mean terminal half-life ($t_{1/2}$) values of 6.48 and 6.67 hours for the modified-release tablet and immediate-release capsule, respectively. With a geometric mean value of 507 ng.h/mL for $AUC_{0-\infty}$, systemic exposure to orismilast following administration of the modified-release tablet was comparable to the one of the immediate-release capsules (506 ng.h/mL). Statistical analyses comparing key PK parameters of orismilast for both formulations did not show any significant difference. Exposure to LEO 40815 and LEO 32731, the main metabolites, appeared generally similar for the modified-release tablet and the immediate-release formulation.

It can thus be concluded that the systemic exposure following administration of the modified-release formulation is not different from the one following the administration of the immediate-release formulation. It can therefore be reasonably assumed that the safety profile resulting from systemic effects can be extrapolated from studies having investigated the immediate-release formulation and in particular, study LP0058-1072, a Phase 2a study including 36 patients with moderate to severe psoriasis vulgaris.

In that study, patients received orismilast 30 mg BID or placebo for 16 weeks. The efficacy in psoriasis was confirmed on each predefined endpoint. No significant safety concerns were identified during the trial, and no adverse reaction not already seen with PDE4 inhibitors was reported. However, there was a high level of intolerance in the orismilast group. Most patients treated with orismilast had treatment-induced AEs related to GI functions, predominantly nausea and diarrhea, throughout the treatment period. These tolerability issues resulted in half of the patients in the orismilast group being withdrawn from the trial.

The hypothesis was that this high incidence of GI side effects was related to high local concentration of orismilast in the stomach, thus the formulation work to identify a slow-release formulation that would reduce local concentration of active compound in the stomach while preserving a similar systemic exposure for maintaining efficacy.

Study LP0058-1442 in healthy volunteers has confirmed these characteristics by showing a similar PK profile and an improved safety profile. Following multiple dosing up to 60 mg BID, the orismilast modified-release tablet was safe and well-tolerated. There were no clinically relevant findings in the vital signs data, clinical laboratory evaluations, 12-lead ECG parameters, or physical examinations for any subject, and there were no deaths or SAEs during any part of the trial. A total of 113 AEs were reported: 12 AEs in 3 subjects randomized to placebo and 101 AEs in 9 subjects following administration of up to 60 mg orismilast BID modified-release tablet. Headache, nausea, dizziness, pain in extremity, and diarrhea were the most commonly reported AEs. Of the 14 AEs of headache reported in subjects receiving orismilast, 6 occurred at the 40-mg dose level. Dizziness was only reported following dosing of 30 mg orismilast or above. Nausea was reported in 5 subjects receiving LEO 32731, with the majority of events occurring at the 60-mg dose level. Only 2 participants experienced nausea at a dose equal or lower to 40 mg, and these side effects lasted approximately 1 day before spontaneously disappearing, despite dosing and up-titration being maintained.

It was thus concluded that 40 mg BID was the maximal tolerated dose with 30 mg BID being the target dose for further development.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Study Objectives

6.1.1. Primary Objective

The primary objective is to evaluate the efficacy and safety of a modified-release orismilast tablet versus placebo in adults with moderate-to-severe plaque-type psoriasis.

6.1.2. Secondary Objectives

Evaluate the dose response of orismilast and identify the dose with the best benefit/risk ratio to be evaluated in a Phase 3 program.

6.1.3. Exploratory Objectives

The exploratory objectives are to:

- [redacted]
- Evaluate the change in cardiovascular risk factors under orismilast treatment.
- [redacted]
- Evaluate the change in skin psoriasis at "difficult to treat" anatomical areas such as the scalp.
- Evaluate the change in psoriasis at "difficult to treat" anatomical areas such as nails.

6.2. Study Endpoints

6.2.1. Primary Endpoint

The primary endpoint in this study is the percentage change in Psoriasis Activity and Severity Index (PASI) score from Baseline at Week 16.

6.2.2. Secondary Endpoints

6.2.2.1. Key Secondary Endpoints

- Patients achieving 75% reduction in PASI (PASI75) response at Week 16.
- Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in Investigator Global Assessment (IGA) at Week 16.

6.2.2.2. Other Secondary Endpoints

- Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in IGA at Weeks 4, 8, 12, and 20.

- Patients achieving PASI75 response at Weeks 4, 8, 12, and 20.
- Patients achieving 50% reduction in PASI (PASI50) and 90% reduction in PASI (PASI90) response at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in PASI at Weeks 4, 8, 12, and 20.
- Change from Baseline in total Psoriasis Symptoms Scale (PSS) score at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in each individual item of the PSS at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in the affected body surface area (BSA) at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in Dermatology Life Quality Index (DLQI) score at Weeks 16 and 20.
- Patients experiencing psoriasis rebound by Week 20, defined as PASI ≥125% of Baseline or new generalized pustular, erythrodermic, or more inflammatory psoriasis.

6.2.2.3. Safety Endpoints

- The occurrence, severity, and seriousness of treatment-emergent adverse events (TEAEs) reported over the 16-week Treatment Period and the 4-week Follow-up Period.
- Changes from Baseline in physical examination; vital sign measurements (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements); and body weight over the 16-week Treatment Period and the 4-week Follow-up Period.
- Changes from Baseline in ECG findings over the 16-week Treatment Period and the 4-week Follow-up Period.
- Changes from Baseline in safety laboratory values (hematology, serum chemistry, and urinalysis) over the 16-week Treatment Period and the 4-week Follow-up Period.
- HADS at each visit except Screening, Week 1 and Week 2.
- C-SSRS at each visit except Weeks 1 and 2.

6.2.3. Exploratory Endpoints

- Change from Baseline in Physician's Global Assessment of Fingernails (PGA-F) at Week 16.
- Change in scalp-specific Investigator Global Assessment (ss-IGA) from Baseline at Week 16 in the subgroup of patients with Baseline score of at least 2 (mild scalp psoriasis).

- Change from Baseline of scalp itch Numeric Rating Scale (NRS) at Week 16 in the subgroup of patients with Baseline score of at least 4 on the 11-point NRS.
- [redacted]
- Change in cardiovascular risk factors at Week 16. The following parameters will be collected: weight, body mass index (BMI), waist and hip circumferences, blood pressure, fasting serum glucose, triglycerides, cholesterol (total and high-density lipoprotein / low-density lipoprotein fractions), and C-reactive protein.
- [redacted]
- Plasma levels of the drug and its metabolites at scheduled visits.

7. INVESTIGATIONAL PLAN

7.1. Description of Overall Study Design and Plan

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2b dose-ranging study is designed to assess the efficacy and safety of modified-release orismilast compared with placebo in adult patients with moderate-to-severe plaque-type psoriasis. Efficacy and safety outcomes will be evaluated to select an appropriate orismilast dose for subsequent Phase 3 studies. The study will be conducted in approximately 40 centers in Europe and North America.

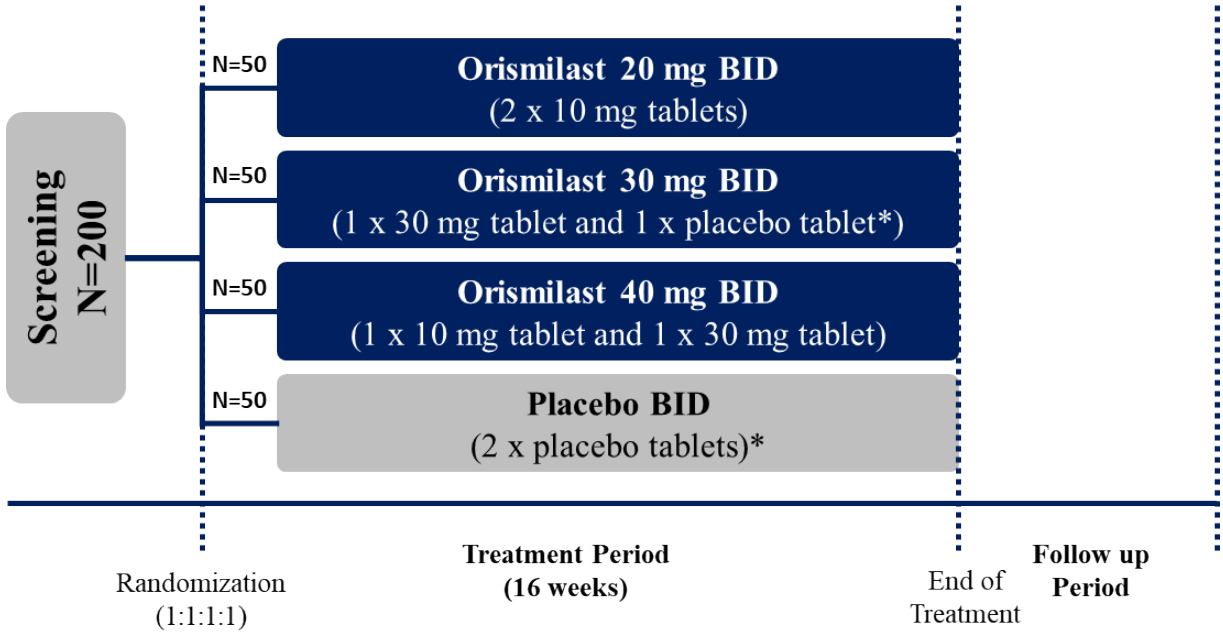
After a Screening visit up to 28 days before Baseline, approximately 200 patients will be assigned randomly in a 1:1:1:1 ratio to receive 1 of the 3 orismilast doses (20 mg, 30 mg, or 40 mg) or placebo twice daily (BID) for 16 weeks, with a 4-week Follow-up visit. Administration will begin at Baseline with a dose titration period. The maximum duration of study participation is approximately 24 weeks.

Patients will be seen at the site on Screening, Baseline (Day 1), and Weeks 1, 2, 4, 8, 12, 16 (End-of-Treatment [EOT] visit), and 20 (Follow-up visit, 4 weeks after treatment completion or discontinuation). Visits at Weeks 1 and 2 could be conducted via a telemedicine procedure at Investigator's discretion.

At Baseline and each visit from Week 4 onwards, PASI, BSA, IGA, and PSS will be assessed. Quality of life (QoL) will be assessed by administration of DLQI at Baseline and at Weeks 16 and 20 visits. Additional efficacy parameters include: an ss-IGA, a PGA of fingernail psoriasis (PGA-F), and [redacted]. These parameters will be assessed at Baseline and Weeks 16 and 20. Safety evaluations include AEs, laboratory and vital sign assessments, physical examinations as well as mood change evaluation by patient (HADS) and suicidal ideation evaluation by Investigator (C-SSRS). A panel of cardiovascular risk factors will be assessed at Baseline and Week 16.

Before administration of the study drug at Baseline and on Weeks 4, 8, and 16, blood will be collected for orismilast concentration determination. [redacted] See Figure 1 for the study design.

Figure 1. Study Design



*To maintain the study blind.

Abbreviation: BID, twice a day

7.2. Discussion of Study Design

A double-blind, randomized, placebo-controlled study is considered a gold-standard for conducting any interventional and dose-finding study. A sample size of 50 patients per treatment arm is also adequate to get robust outcome data for a comparison among doses and with placebo.

Psoriasis is a chronic condition requiring long-term therapy. Primary efficacy assessments of psoriasis clinical trials are usually performed at 12 or 16 weeks after initiation of study treatment. Because of the initial titration period of up to 2 weeks duration, a treatment duration of 16 weeks, with the primary endpoint being evaluated at this time point is, therefore, considered the optimal strategy for this study. Primary evaluations of apremilast, the only PDE4 inhibitor currently approved for psoriasis treatment, were also conducted at Week 16. A 16-week Treatment Period was also deemed acceptable for the placebo arm because psoriasis is not a life-threatening disease warranting immediate treatment.

Besides the usual psoriasis assessments including the PASI, the IGA, and the BSA, the effects of study treatment on nail and scalp psoriasis that represent location of disease more refractory to treatment will be explored. In patients with PsA, any potential effect on [redacted] will be also assessed. A number of patient-reported outcome (PROs) will be administered to explore the patient's perception of his or her condition and the related QoL, as recommended by regulatory agencies. This comprehensive evaluation of the psoriatic condition of patients will contribute to the selection of the most suitable dose(s) for the Phase 3 clinical program.

[redacted]

7.3. End of Study

A patient will have fulfilled the requirements for study completion if/when the patient has completed all study periods, including the Follow-up visit or the last scheduled visit as indicated in the Schedule of Assessments (Table 4).

The end of the study will be the last patient's last visit as indicated in the Schedule of Assessments (Table 4).

8. SELECTION OF STUDY POPULATION

8.1. Inclusion Criteria

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

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in the protocol.
2. Male and female patients ≥18 years of age at the time of signing the ICF.
3. Body weight of >40 kg at the time of signing the ICF.
4. Diagnosis of chronic, stable plaque-type psoriasis at least 2 months before the Screening visit. If the patient is diagnosed with psoriasis arthritis, the arthritis should be stable.
5. Moderate-to-severe plaque-type psoriasis as defined by PASI ≥12, BSA ≥10%, and IGA ≥3 at the screening and baseline visits.
6. Candidate for systemic antipsoriatic treatment or phototherapy.
7. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at the Baseline visit. In addition, sexually active WOCBP must agree to use a highly effective method of contraception until at least 4 weeks after the end of study treatment. Highly effective methods of contraception are those that have a failure rate of <1% (when implemented consistently and correctly) and include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implantable); progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable); intrauterine devices or systems; self or partner vasectomy; or bilateral tubal ligation. Patients must have been on a stable dose of hormonal contraceptives for at least 4 weeks before the Baseline visit. Abstinence from heterosexual intercourse is an accepted method of contraception if it is the patient's lifestyle and is practiced for the entire duration of the study. Note: A woman of nonchildbearing potential is defined as a woman with surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or a woman in a postmenopausal status defined as cessation of menses for at least 12 months without an alternative medical cause and a confirmatory follicle-stimulating hormone (FSH) test or as cessation of menses for at least 24 months without an alternative medical cause.

8.2. Exclusion Criteria

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

1. Therapy-resistant psoriasis defined as ≥2 treatment failures due to inadequate efficacy within the past 5 years of any biologic therapies (including but not limited to etanercept,

adalimumab, infliximab, certolizumab pegol, guselkumab, secukinumab, risankizumab, ixekizumab, tildrakizumab, or ustekinumab) administered in adequate dose and duration according to the label or local/national guidelines (patients who stopped systemic treatment for reasons not related to lack of efficacy are not excluded).

2. Unstable psoriasis or PsA with acute deterioration within 4 weeks of the Screening visit.
3. History of allergy or hypersensitivity to any component of the study treatment.
4. Active infection (eg, bacteria, viral, fungal) requiring treatment with systemic antibiotics within 4 weeks of the Screening visit.
5. Malignancy or history of malignancy except for treated (ie, cured) basal cell skin carcinomas.
6. Current diagnosis of predominant guttate, erythrodermic, exfoliative, or pustular psoriasis, or of drug-induced psoriasis, or other skin conditions that might confound the evaluation of psoriasis vulgaris, as judged by the Investigator (eg, AD, lupus).
7. Any recurrent medical condition associated with serious GI diseases, such as inflammatory bowel disease.
8. Any medical or psychiatric condition (eg, current major depression with a score for depressive symptoms ≥15 of HADS at Baseline, schizophrenia, suicidal behavior, psychiatric hospitalization within the prior year) which, in the Investigator's opinion, would preclude the patient from adhering to the protocol, completing the study per protocol, and/or would place the patient at unacceptable risk for receiving the investigational therapy.
9. Any therapies and systemic treatments as described in Table 3 which do not comply with the indicated washout interval.
10. Any previous treatment with orismilast or failure of treatment with apremilast or any other systemic PDE4 inhibitor as described in Table 3.
11. Any condition, including laboratory or ECG abnormalities, that places the patient at unacceptable risk to participate in the study or confounds the ability to interpret data from the study.
12. Severe hepatic impairment based upon medical history and laboratory abnormalities (eg, low albumin and abnormal bilirubin).
13. Any of the following abnormalities in clinical laboratory tests at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:
    a. Absolute neutrophil count of $<3.0 \times 10^9$/L ($<3000/mm^3$)
    b. Hemoglobin of <10.0 g /dL or hematocrit <30%
    c. Platelet count of $<100 \times 10^3$ cells/mm^3 (SI: $<100 \times 10^9$ cells/L).
    d. Absolute lymphocyte count of $<1.0 \times 10^9$/L ($<1000/mm^3$)

e. Total bilirubin >1.5 × the upper limit of normal (ULN); patients with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ULN
f. Alanine aminotransferase or aspartate aminotransferase >2.5 × the ULN.
g. Serum creatinine ≥1.5 mg/dL. For a patient with a value of ≥1.5 mg/dL, a creatinine clearance of ≥60 mL/min (calculated using the CKD-EPI Creatinine Equation) is allowed.

14. History or evidence of hepatitis B virus (HBV) infection at Screening. Patients with positive hepatitis B surface antigen (HBsAg) are excluded. For patients with isolated positive antihepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb) result must also be positive to be considered for this study.
15. History or positive test result for hepatitis C virus (HCV) antibody, indicating ongoing infection, at Screening. Confirmatory testing for HCV RNA will be conducted for patients who have a positive test result. Patients who have a negative result for HCV RNA will be eligible to participate in the study.
16. History of positive HIV, or have congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease). Patients who are positive for HIV antibodies (HIV-1 or HIV-2) at Screening are excluded from the study.
17. Suicidal ideation or behavior in the past 12 months as indicated by a positive response (yes) to questions 4 or 5 on the C-SSRS completed at the Screening visit or the C-SSRS completed at the Baseline visit.
18. Pregnant or breastfeeding.
19. History of alcohol or substance abuse within 6 months before Baseline that, in the opinion of the Investigator, will preclude participation in the study.
20. Institutionalized by court order or by local authority.

8.3. Rescreening

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria and therefore do not enroll (screen failures) may be rescreened. Such individuals may be allowed to rescreen up to one time.

8.4. Study Withdrawal, Removal, and Replacement of Patients

If a patient discontinues study treatment and is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study discontinuation must be recorded on the electronic case report form (eCRF). Patients who complete or discontinue early from the study will be asked to return to the study site within 4 weeks of the last administration of study drug to complete EOT assessments as indicated in the

Schedule of Assessments (Table 4). If the study treatment is permanently discontinued, the patient will remain in the study to be evaluated for safety.

In the event that a patient discontinues prematurely from the study because of a TEAE or serious TEAE assessed as ≥Grade 3 (≥Grade 2 for the system organ class [SOC] of cardiac disorders) according to Common Terminology Criteria for Adverse Events version 5 (CTCAE v 5), the TEAE or serious TEAE will be followed up until it resolves (returns to normal or Baseline values) or stabilizes, or until it is judged by the Investigator to no longer be clinically significant.

Once a patient is withdrawn from the study, the patient cannot reenter the study.

A patient may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- unacceptable toxicity or AE
- patient's withdrawal of consent: at any time, a patient's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment. The reason for patient withdrawal will be noted on the eCRF.
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the patient's termination from the study
- general or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria
- patient fails to adhere to the protocol requirements (eg, drug noncompliance, failure to return for defined number of visits)
- lost to Follow up: the patient stopped coming for visits, and study personnel were unable to contact the patient
- pregnancy, as indicated in Section 12.9.6.

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with good clinical practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

8.5. Suspension or Premature Termination of the Clinical Investigation

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-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 study site by the sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further development of the study drug

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the institutional review board (IRB)/independent ethics committee (IEC) or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow up.

9. TREATMENTS

9.1. Details of Study Treatments and Dosage Schedule

Tablets should be taken in the morning and in the evening approximately every 12 hours. The minimum time interval between 2 consecutive doses is 6 hours. The first dose of the study drug should be taken in the evening of Day 1. Pharmacokinetic (PK) studies have shown no difference whether the product is taken under fasted condition or during a low-fat meal. Intake during a high-fat meal leads to higher blood concentrations, and possibly higher incidence of GI side effects and must, therefore, be avoided. Refer to Table 1 for details about study treatment and dosage schedule.

Table 1. Study Treatment and Dosage Schedule

ARM name:	**Orismilast 20 mg BID**	**Orismilast 30 mg BID**	**Orismilast 40 mg BID**	**Placebo**
Name:	Orismilast	Orismilast	Orismilast	Placebo
Type:	Drug			
Dose formulation:	10 mg and 30 mg tablet or matching placebo tablet			
Frequency:	BID (approximately every 12 hours)			
Administered tablets:	2 × 10 mg orismilast tablets BID	1 × 30 mg orismilast tablet and 1 x placebo tablet BID	1 × 10 mg and 1 × 30 mg orismilast tablets BID	2 × placebo tablets BID
Route:	Oral			
Use:	Experimental			Placebo
Sourcing:	Provided centrally by the Sponsor			
Packaging and labeling:	Investigational medicinal product will be provided in individually labeled wallet cards with blistered tablets. Each card will be labeled as required per country requirement			

Abbreviation: BID, twice daily.

9.2. Measures to Minimize Bias: Study Treatments

9.2.1. Method of Study Treatment Assignment

At the investigational site, each screened patient will be assigned a patient identifier number during Screening that will be used on all patient documentation. The patient identifier number will contain the site number and the patient number and will be assigned in numerical order at the Screening visit based on chronological order of Screening dates (eg, 01-010 for the 10th patient screened at the Site #01).

Randomization will occur prior to first study treatment administration, at the Baseline visit. Patients will be assigned randomly in a 1:1:1:1 ratio to 1 of 3 orismilast dose groups (20 mg, 30 mg, or 40 mg) or placebo.

A randomization list will be used to assign the treatments to each patient. The randomization list will be kept secured with access restricted to only the designated personnel directly responsible for labeling and handling the study drug until the study blind is broken at the end of study (database lock). Further guidance and information can be obtained in the study manual.

9.2.2. Blinding

To facilitate the double blind, the tablets will be packaged in the same type of blister and the active and placebo tablets will have the same appearance (in terms of size, form, weight, and color). One dose consists of 2 identical tablets (a 10 mg or 30 mg orismilast tablet or a matching placebo).

Blinding codes should only be broken in emergency situations for reasons of patient safety. When the blind for a patient has been broken, the reason must be fully documented in the source document and eCRF. Whenever possible, the Investigator should contact the sponsor or its designee before breaking the blind. If the blind is broken, the Investigator should promptly inform the medical monitor. Documentation of breaking the blind should be recorded with the date/time and reason why the blind was broken, and the names of the personnel involved.

The patient for whom the blind has been broken will be discontinued from the study and undergo the early termination procedures. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded.

The Interactive Web Response System (IWRS) will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patients' treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the sponsor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

All patients will be centrally assigned to randomized study treatment using an IWRS. Before the study is initiated, the telephone number and call-in directions for the log in information and directions for the IWRS will be provided to each site.

Study drug will be dispensed at the study visits summarized in the Schedule of Assessments (Table 4). Returned study drug should not be redispensed to the patients.

Sponsor safety staff may unblind the study drug assignment for any patient with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the patient's study drug assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

9.3. Dosage Modification

If a patient experiences a TEAE assessed as ≥Grade 3 (≥Grade 2 for the SOC of Cardiac Disorders) according to CTCAE v 5, the patient should be permanently discontinued from the study drug and not receive additional doses. As a reminder Grade 3 is defined as "Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ADL)".

If GI or other AEs considered probably or definitely related to the study drug are reported with a severity not compatible with maintaining the treatment as per protocol during the treatment up-titration and/or during maintenance period, the Investigator might consider decreasing the regimen as described in Section 9.3.1.

If the study drug is permanently discontinued, the patient will remain in the study to be evaluated for safety.

9.3.1. Titration

Titration of oral apremilast was shown to improve the GI tolerance and overall acceptability of the drug (Zerilli 2015). Similarly, a slow increase in orismilast dose was associated with less GI side effects when compared with a rapid increase. Consistent with this approach, this study will titrate the study treatment dose over a period of maximum 2 weeks (see Table 2).

If tolerability issues arise during the treatment up-titration and/or during maintenance period, the following treatment pauses are allowed only if instructed by the Investigator:

- First day: The Investigator is informed of the tolerability issue; thus, the evening dose can be skipped.
- Second day: Morning dose can be skipped. The patient must take the evening dose.
- Third day: Similar to Day 2, morning dose can be skipped. The patient must take the evening dose.
- Fourth day: BID daily dosing regimen is reintroduced.

The aforementioned treatment pauses do not impact calculation of dosing days and duration of titration is not prolonged. Treatment pauses will be captured in the eCRFs. This titration will not break the blind as all patients will receive 2 of indistinguishable orismilast or placebo tablets BID.

Table 2. Dose Titration Schedule

Arm	Day 1	Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8		Day 9		Day 10		Day 11		Day 12		Day 13		Day 14		From Day 15	
20 mg BID	10	10	10	10	10	10	10	10	20	10	20	10	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
30 mg BID	10	10	10	10	20	20	20	20	20	20	30	20	30	20	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
40 mg BID	10	10	10	10	20	20	20	20	20	20	30	20	30	20	30	30	30	30	30	30	30	30	40	30	40	30	40	40	40
Placebo	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P

Abbreviation: BID, twice daily

9.4. Treatment Accountability and Compliance

The patients will receive the study drug at the site directly from the Investigator or designee who will also give instruction for dose administration. The date of study drug dispensed to the patients will be recorded in eCRF and patient's source document. At all site visits, patients will return all study drug, including packaging, dispensed at the previous visit.

The dose of study drug and study patient identification will be confirmed at the time of administration by a member of the study site staff other than the person administering the study drug.

When patients self-administer the study drug at home, compliance with the protocol will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and relevant form. Deviation from the prescribed dosage regimen should be recorded.

A record of the quantity of study drug dispensed to and administered by each patient must be maintained and reconciled with study drug and compliance records. Study drug administration dates, including dates for administration delays and/or dose reductions will also be recorded.

9.5. Prior and Concomitant Therapy

Any concomitant medication, supplement, or procedure within 6 months prior to Baseline or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Patients may take any medication that is not restricted by the protocol and would not be expected to interfere with the conduct of the study or affect assessments. Chronic medication should be dosed on a stable regimen.

9.5.1. Allowed Treatments and Rescue Medications

All medications (prescription and nonprescription), treatments and therapies taken from Screening throughout their entire participation in the study, including those initiated prior to the start of the study, must be recorded on the patient's source document and on the appropriate page of the eCRF. The dose, unit, frequency, route, indication, date the medication was started and the date the medication was stopped (if not ongoing) must be recorded. The recording of any permitted topical medications taken for psoriasis should also include the area of the body to which they are applied and the frequency of application.

The following topical therapies will be permitted during the study:

- For psoriasis body lesions: nonmedicated emollients or low potency corticosteroids used only for treatment of the face, axillae, and groin

  Examples of low potency corticosteroids (Groups VI and VII):

  - Betamethasone valerate lotion 0.05%
  - Desonide cream 0.05%
  - Fluocinolone acetonide solution 0.01%
  - Dexamethasone sodium phosphate cream 0.1%
  - Hydrocortisone lotion, cream, or ointment 2.5%
  - Hydrocortisone acetate cream 1%
  - Methylprednisolone acetate cream 0.25%
- For scalp psoriasis lesions: coal tar shampoos and/or salicylic acid scalp preparations but only if on a stable use since Screening

Topical preparations should not be applied within 24 hours of the clinic visit.

9.5.2. Prior and Concomitant Medications

Restricted prior therapies are provided in Table 3. In addition, patients with any prior treatment with orismilast or failure of treatment with apremilast or any other systemic PDE4 inhibitor are ineligible.

Table 3. Disallowed therapies and treatments

Compound	Washout
Topical medications/treatments that could affect psoriasis or study evaluations (eg, corticosteroids, anthralin, calcipotriene, vitamin D derivatives, retinoids, tazarotene, pimecrolimus, tacrolimus, or PDE4 inhibitor)	Within 2 weeks prior to Baseline and throughout the study
Systemic treatment with therapies other than biologics with a possible effect on psoriasis like apremilast, corticosteroids, retinoids, systemic immunosuppressants (eg, methotrexate, azathioprine, cyclosporine), protein	Within 4 weeks prior to Baseline or 5 half-lives (whichever is longer) and throughout the study

Compound	Washout
kinase inhibitors (eg, tofacitinib, baricitinib, or upadacitinib) or fumaric acid	
Investigational drugs other than the study drug	Within 4 weeks of randomization, or 5 half-lives, if known (whichever is longer) and throughout the study
Initiation of or changes of doses to concomitant medication that could exacerbate psoriasis (for example, beta blockers, angiotensin-converting enzyme inhibitors, antimalarial drugs, lithium)	Within 4 weeks prior to Baseline and throughout the study
Use of phototherapy or prolonged sun exposure or use of tanning booths or other ultraviolet light sources (ie, UVB, psoralens and long-wave ultraviolet radiation)	Within 4 weeks of Baseline and throughout the study
Etanercept	Within 8 weeks prior to Baseline and throughout the study
TNF inhibitors like adalimumab, certolizumab pegol, or infliximab	Within 12 weeks prior to Baseline and throughout the study
Any biologic agents targeting IL-12, IL-17, or IL-23 like ustekinumab, secukinumab, brodalumab, guselkumab, ixekizumab, risankizumab, or tildrakizumab	Within 16 weeks prior to Baseline and throughout the study
Rituximab and any B-cell depleting agent	Within 24 weeks prior to Baseline and throughout the study
Concomitant medication mainly metabolized via cytochrome 2D6 isozyme and with narrow therapeutic window such as tricyclic antidepressants (e.g., nortriptyline, amitriptyline, imipramine, desipramine) or Type 1C antiarrhythmics (propafenone, flecainide and encainide) or via cytochrome 3A4 with a narrow therapeutic index	4 weeks prior to Baseline and throughout the study

Abbreviations: IL, interleukin; PDE4, phosphodiesterase-4; TNF, tumor necrosis factor alpha

Concomitant medication mainly metabolized via cytochrome 3A4 and with narrow therapeutic window (such as anticoagulant or digoxine) are not to be excluded but require close medical monitoring.

The Medical Monitor should be contacted for questions regarding concomitant or prior therapy.

9.5.3. Drug-Drug Interactions

From clinical studies, orismilast can be considered a mild inhibitor of CYP3A4/5, and systemic exposure to medicinal products metabolized by CYP3A4 may be increased when co-administered with orismilast. Concomitant use of orismilast with CYP3A4 substrates may

increase the systemic exposure to these medicinal products. Patients receiving orismilast concurrently with these medicinal products should be monitored for related AEs especially if they have a narrow therapeutic window. Refer to the following link for examples of clinical inhibitors for P450-mediated metabolisms: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2.

In vitro orismilast is a competitive direct inhibitor of CYP2D6. Concomitant use of orismilast with other drugs mainly metabolized by cytochrome CYP2D6 has not been studied clinically. Because of a potential increase of systemic exposure to medicinal products metabolized by CYP2D6 when concomitantly administered with orismilast patients should be monitored for AEs related to these medicinal products. Co-administration of drugs with a narrow therapeutic index such as tricyclic antidepressants (e.g., nortriptyline, amitriptyline, imipramine, desipramine) or Type 1C antiarrhythmics (propafenone, flecainide and encainide) is prohibited (see Table 3).

10. STUDY PROCEDURES

Table 4 outlines the timing of procedures and assessments to be performed throughout the study. Section 12.5 specifies laboratory assessment samples to be obtained. See Sections 11 and 12 for additional details regarding efficacy assessments and safety assessments, respectively.

Table 4. Schedule of Assessments

	Screening	Treatment Period							Follow up
Procedure	**Between Day -28 and -1**	**Day 1 (Baseline)**	**W1 (±1d)**	**W2 (±1d)**	**W4 (±2d)**	**W8 (±3d)**	**W12 (±3d)**	**W16 (EOT/ET; ±3d)**	**W20 (±3d)**
Informed consent (before any study procedures)	X								
Demography	X								
Medical history, including medication, alcohol, and smoking history (last 6 months)	X								
Concurrent medication review	X	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria	X	X							
Physical examination[a]	X	X						X	X
12-lead ECG (single measurement)	X				X	X		X	
Vital signs[b]	X	X			X	X	X	X	X
Weight[c]	X	X			X	X	X	X	X
Height[c]		X							
BMI[c]		X				X		X	X
Waist and hip circumferences[c]		X				X		X	X
Randomization		X							
Adverse events	X	X	X	X	X	X	X	X	X
Blood sample for serology (HIV antibody, HBV, HCV, HBsAg, HBcAb, and HBsAb)	X								
Safety laboratory assessments (hematology, serum chemistry, urinalysis)	X	X			X	X		X	
Cardiovascular risk factor laboratory assessments[c,d]		X						X	
Pregnancy test[e]	X	X			X	X	X	X	
Blood samples for drug and metabolite PK analysis: trough levels (before study drug administration)		X			X	X		X	
Blood samples for drug PK profile (optional)					X			X	
[redacted]		X						X	

	Screening	Treatment Period							Follow up
Procedure	**Between Day -28 and -1**	**Day 1 (Baseline)**	**W1 (±1d)**	**W2 (±1d)**	**W4 (±2d)**	**W8 (±3d)**	**W12 (±3d)**	**W16 (EOT/ET; ±3d)**	**W20 (±3d)**
IGA, BSA, and PASI	X	X			X	X	X	X	X
PGA-F		X						X	X
Scalp Psoriasis ss-IGA		X						X	X
Scalp itch NRS		X						X	
[redacted]		X						X	X
PSS		X			X	X	X	X	X
C-SSRS	X	X			X	X	X	X	X
DLQI		X						X	X
HADS		X			X	X	X	X	X
Dispense study drug		X	X[h]	X[h]	X	X	X		
Collect study drug including packaging			X[h]	X[h]	X	X	X	X	
Compliance check			X	X	X	X	X	X	

Abbreviations: BMI, body mass index; BSA, body surface area; CRP, c-reactive protein; C-SSR, Columbia-Suicide Severity Rating Scale; d, day; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EOT, end of trial; ET, early termination; HADS, Hospital Anxiety and Depression Scale; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; hCG, human chorionic gonadotropin; HDL, high-density lipoprotein; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IGA, Investigator Global Assessment; LDL, low-density lipoprotein; NRS, Numerical Rating Scale; PASI, Psoriasis Area and Severity Index; PGA-F, Physician Global Assessment of Fingernail Psoriasis; PK, pharmacokinetic; PSS, Psoriasis Symptoms Scale; ss-IGA, scalp-specific Investigator Global Assessment; W, week.

a. A complete physical examination will be performed at Screening (Visit 1) and Week 16. A limited physical examination will be conducted at Day 1 and Week 20.
b. All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes.
c. Cardiovascular risk assessments include: height, weight, BMI, waist and hip circumferences, blood pressure, fasting serum glucose, triglycerides, cholesterol (total and HDL/LDL fractions), and C-reactive protein.
d. Cardiovascular risk factor laboratory assessments include CRP, glucose, total cholesterol, HDL, LDL, and triglycerides. Patients should be in fasting condition (no food or fluids other than water for 8 hours) before sample collection at Baseline and Week 16.
e. Serum Beta-hCG and urine pregnancy test at Screening. Urine pregnancy test at all other visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study Treatment Period.
f. [redacted].
g. [redacted]
h. Only applicable if the visit is conducted in person.

10.1. Informed Consent

Before performing any study-related procedures, the Investigator (or designee) will obtain written ICF from the patient.

In the event that rescreening occurs, the individual is required to sign a new ICF and must be assigned a new identification number.

10.2. Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 4). Section 12.5 specifies laboratory assessment samples to be obtained.

All PROs should be administered prior to any other visit procedure. Furthermore, vital signs, weight measurement, and ECG must be done prior to blood sampling. The study drug is administered after completion of all other procedures.

Assessments and procedures scheduled at a visit where study drug is administered should be performed before administration of treatment.

Efficacy assessments are described in Section 11 and include PASI, IGA, BSA, ss-IGA, IGA-F, PSS, [redacted], scalp itch, and DLQI.

Safety assessments are described in Section 12 and include vital signs, physical examinations, ECGs, laboratory assessments, HADS, C-SSRS, and AEs.

PK assessments are described in Section 13 and PD assessments are described in Section 14.

11. EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 4) outlines the efficacy assessments to be performed throughout the study and their timing.

Assessors must be trained and certified by the Sponsor or delegate before conducting the Physician's assessments. The same assessor should perform all evaluations within the same patient throughout their study participation.

11.1. Investigator Assessments

11.1.1. Psoriasis Area and Severity Index

The PASI is a measure of psoriatic disease severity, taking into account qualitative lesion characteristics (erythema, induration, and desquamation) and percentage of affected skin surface area on defined anatomical regions. The PASI is a validated instrument that is the most widely used tool for measurement of severity of psoriasis.

Psoriasis Area Severity Index scores range from 0 to 72, with higher scores reflecting greater disease severity (Fredriksson 1978). Erythema, induration/thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. The scores for each anatomic region are combined to yield the final PASI.

11.1.2. Investigator Global Assessment

The IGA is a measure used by physicians to determine the patient's overall severity of disease. The static version (Langley 2015) is used in this trial for measurement at a single point in time as indicated in the schedule of assessments. The Investigator will rate the severity of patient's psoriasis on a 5-point scale ranging from 0 (clear) to 4 (severe).

11.1.3. Scalp-specific Investigator Global Assessment

The ss-IGA assesses lesions on the scalp for degree of redness, thickness, and scaling on a 5-point scale, with 0 indicating absence of disease and 4 indicating severe disease.

11.1.4. Physician's Global Assessment of Fingernail Psoriasis

The PGA-F is used in this trial to evaluate abnormalities in the fingernails, and the severity of these, in patients with nail psoriasis. It is a simple and reliable clinician-rated scale, which is easy to use in clinical practice and research. The scale rates the overall condition of the fingernails and is based on a 5-point scale, with 0 indicating clear and 4 indicating severe.

11.1.5. Body Surface Area

The BSA assessment estimates the extent of disease or skin affected by psoriasis and is expressed as a percentage of total body surface. BSA will be determined by the Investigator or designee using the patient palm = 1% BSA rule.

11.2. Patient-Reported Outcomes

11.2.1. Psoriasis Symptom Scale

The PSS is a 4-item patient-completed questionnaire (Rentz et al 2017). It is patient relevant, its domains are reliable and valid, and it takes few minutes to complete. The PSS assesses severity of pain, itching, redness, and burning during the past 24 hours using a 5-point severity scale from 0 = none to 4 = very severe.

11.2.2. Scalp Itch

Scalp itch will be assessed by requesting the patients to grade their worst scalp itch over the past 24 hours on a 11-point with an NRS with 0 corresponding to No itch and 10 to Worst imaginable itch.

[redacted]

11.2.4. Dermatology Life Quality Index

The DLQI is a 10-item validated questionnaire completed by the patient used to assess the impact of skin disease on the patient's QoL during the previous week. The 10 questions cover the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, and treatment. Each question is scored from 0 to 3 ("not at all," "a little," "a lot," and "very much," respectively), giving a total score ranging from 0 to 30. A high score is indicative of a poor QoL. DLQI responses will be captured as outlined in the SoA.

12. SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, ECG recording, AEs, HADS, C-SSRS, clinical laboratory results [routine hematology and biochemistry]) are to be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 4).

12.1. Medical History

Medical history will be recorded at Screening. Investigators should document the occurrence, signs, and symptoms of the patient's preexisting conditions, including all prior significant illnesses. Additional preexisting conditions present at the time when informed consent is given, and up to the time of first dosing, are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study, and/or worsening of a concomitant illness during the study, are to be documented as AEs on the eCRF in accordance with Section 12.7. All changes not present at Baseline or described in the past medical history (last 6 months), and identified as clinically noteworthy, must be recorded as AEs.

Additionally, demographic data will be collected for all patients and include date of birth or age according to applicable regulations, sex, ethnicity, etc.

12.2. Vital Signs

Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments (Table 4). Using of tympanic/ear thermometer is recommended for body temperature.

All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight (without shoes) will be recorded whenever vital signs are recorded; height (without shoes) will be recorded at Baseline only. A weight reduction of at least 5% from Baseline should be reported as a TEAE.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs on the eCRF.

12.3. Physical Examination

A complete physical examination (a check of the head, eyes, ears, nose and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological and musculoskeletal systems) will be performed at Screening (Visit 1) and Week 16. A limited physical examination will be conducted at Day 1 and Week 20 to verify continued patient eligibility and to Follow up regarding any change in medical history. Physical examinations will be performed by a physician.

Symptom-driven, limited physical examinations will be performed as clinically indicated at any study visit. Additionally, patients' BMI, height, weight, as well as waist and hip circumference will be measured at the visits indicated in the Schedule of Assessments (Table 4).

12.4. Electrocardiogram

A 12-lead, resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 4).

At Screening, the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the patient from the study. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed, or artifacts are present.

12.5. Waist and Hip Circumferences

The waist circumference should be measured at the top of the iliac crest, using a stretch-resistant tape. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor.

The individual should stand with feet close together, arms at the side, and body weight evenly distributed, and he or she should wear little clothing. The subject should be relaxed, and the measurements should be taken at the end of a normal respiration.

12.6. Laboratory Assessments

Laboratory assessment samples (Table 5) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 4). Patients should be in fasting condition (no food or fluids other than water for 8 hours) before sample collection at Baseline and Week 16.

Table 5. Laboratory Assessments

Hematology	Serum Chemistry	Urinanalysis (Dipstick)
Full and differential blood count Hct Hb MCH MCHC MCV Platelet count RBC count (% reticulocytes) WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)	Albumin ALT ALP AST BUN or urea Creatinine Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT LDH Total bilirubin Direct bilirubin	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urine hCG (premenopausal females only) Urobilinogen

Cardiovascular Risk Factors (fasting condition and at Baseline and Week 16 only)	Other Screening Tests
CRP Glucose Total cholesterol HDL LDL Triglycerides	HIV antibody HBV HCV HBsAg HBcAb HBsAb FSH (confirmatory test for female patients in a postmenopausal status defined as cessation of menses for at least 12 months without an alternative medical cause)

Pregnancy test: A serum pregnancy test will be performed on all women of childbearing potential at Screening, and a urine pregnancy test will be performed at all other visits as indicated in Table 4.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transpeptidase; CRP, c-reactive protein; hCG, human chorionic gonadotropin; Hb, hemoglobin; Hct, hematocrit; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell.

Samples will be analyzed at a central laboratory facility. Urine samples will be analyzed by dipstick at site; if the results of the dipstick indicate abnormalities a urine sample will be collected for microscopic analysis to be performed at a central laboratory for further investigation. All laboratory reports must be reviewed, signed, and dated by the Investigator. A legible copy of all reports must be filed with both the patient's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the Investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

12.7. The Hospital Anxiety and Depression Scale

The HADS is a PRO and comprises of 7 questions for anxiety and 7 questions for depression with each answer being graded from 0 to 3 with a higher score indicating a worse condition. For each group of questions, scores of less than 7 indicate noncases, whereas 8 to 10, 11 to 14, and 15 to 21, indicate mild, moderate, or severe anxiety or depression, respectively. The HADS is one of the National Institute for Health and Care Excellence recommended tools for diagnosis of depression and anxiety.

Any patient with a score for depressive symptoms ≥15 at Baseline will not be eligible for randomization in the study. Patients with a clinically significant worsening of depressive symptoms or new occurrence of clinically significant depression during the study may be referred to a mental health specialist (psychiatrist or clinical psychologist) for further evaluation.

After a mental health specialist evaluation, the final decision on restarting or permanently discontinuing study treatment will be at the discretion of the Investigator in consultation with the mental health specialist. These cases should be reported as an AESI. Refer to Section 0.

12.8. The Columbia-Suicide Severity Rating Scale

The C-SSRS, Investigator administered version, was designed to provide a prospective, standardized measure of suicidality. The scale allows clinicians and researchers alike to assess the severity and lethality of suicidal behaviors and ideations and can be used to monitor treatment outcomes and establish suicide risk in a variety of research and clinical settings. Requiring approximately 5 min for completion, the C-SSRS is administered in the form of a clinical interview.

This C-SSRS is available in 2 versions: 1 for use at Screening referring to the past year and 1 for use throughout the rest of the study referring to the time since the prior visit.

If at Screening or Baseline there are “yes” answers on items 4 or 5 in the past year, the patient will not be included in the study.

Any subject with a positive response on the C-SSRS (answers “yes” to questions 1-5) should be referred to a mental health specialist (psychiatrist or clinical psychologist) for further evaluation, and the study medication should be paused. After a mental health specialist evaluation, the final decision on restarting or permanently discontinuing study treatment will be at the discretion of the Investigator in consultation with the mental health specialist. These cases should be reported as an AESI. Refer to Section 0.

12.9. Adverse Events

AEs will be collected throughout the study as shown in the Schedule of Assessments (Table 4).

12.9.1. Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans. An AE can, therefore, be any unfavorable and unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related causally to the investigational product (US Code of Federal Regulations [CFR] Title 21 Section 312.32[a]). Any abnormal finding that is deemed not clinically significant is not an AE.

AEs include the onset of new illness and the exacerbation of preexisting conditions. Any medical condition that is present at the time when the patient is screened should be recorded on the medical history eCRF and not reported as an AE. However, if that condition deteriorates or severity changes at any time during the study, it should be recorded as an AE.

Any AEs that occur before dosing on study Baseline will be categorized as pretreatment events. TEAEs will be defined as those AEs that occur or worsen in severity after initial dosing and up to 7 days after the last dose of study drug.

Patients will be instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent until the Follow-up visit. Follow up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in Table 6 and Abbreviations: ADL, Activities of Daily Living; AE, adverse event

Table 7.

Table 6. National Cancer Institute Common Terminology Criteria for Adverse Events

GRADE 1: Mild, asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
GRADE 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
GRADE 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
GRADE 4: Life-threatening consequences; urgent intervention indicated.
GRADE 5: Death related to an AE.

Abbreviations: ADL, Activities of Daily Living; AE, adverse event

Table 7. Classification of Adverse Events by Relationship to Study Drug

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the test drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (3) it follows a known pattern of response to the test drug.
PROBABLY: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug.
DEFINITELY: This category applies to those AEs that the Investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug.

Abbreviations: AE, adverse event

12.9.2. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern, for which ongoing monitoring and rapid communication by the Investigator to the sponsor could be appropriate. AESIs must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event, following SAE reporting procedures (Section 12.9.4). Such an event might require

further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted.

In this trial, the following AEs are to be considered AESIs:

- Any AE of occurrence of suicidal ideation or behavior, including a positive response to question 1 to 5 of C-SSRS
- A depression assessed as moderate or worse by the Investigator or a score ≥15 in the HADS score
- Any grade 3 or higher psychiatric condition
- Any weight loss >5% compared to Baseline, and/or
- Any of the following GI TEAEs: vomiting, diarrhea with an increase of at least four stools per day over Baseline (Grade 2 CTCAE) for at least 3 days.

12.9.3. Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the Investigator or Sponsor, that:

- results in death,
- is life threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect
- results from overdose

Other important medical events that may not be immediately life threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.9.4. Serious Adverse Event Reporting

An SAE occurring from the time informed consent is obtained, during the study, or within 30 days of stopping the treatment must be reported to [redacted] Health Safety and Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported immediately, and under no circumstances later than

24 hours after the Investigator has become aware of the event. Notification can be made using the dedicated fax line or email for [redacted] Safety and Pharmacovigilance group:

- [redacted] Safety and Pharmacovigilance [redacted]
- [redacted] Safety and Pharmacovigilance email address: [redacted]

If the Investigator contacts the [redacted] Safety and Pharmacovigilance group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed to determine the etiology of the problem. The Investigator must report all additional Follow-up evaluations to [redacted] Safety and Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed up until it either resolves, stabilizes, returns to Baseline values (if a Baseline value is available), or is shown to not be attributable to the study drug or procedures.

12.9.5. Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the safety information in the Investigator's Brochure)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The Investigator will assess whether or not an event is causally related to study treatment. [redacted] will consider the Investigator's assessment and determine whether or not the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal, or life threatening must be reported to the regulatory authorities and the IEC/IRB (where

required) within 7 days after the [redacted]/UNION therapeutics A/S has first knowledge of them, with a Follow-up report (when applicable) submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the [redacted]/UNION therapeutics A/S first has knowledge of them.

The Sponsor is responsible for reporting SUSARs, and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IRB/IEC of reportable events within the applicable timeframes.

12.9.6. Pregnancy

WOCBP must have a negative serum pregnancy test at Screening and are required to use one of the highly effective contraception methods (Inclusion Criterion 7). Women on hormone replacement therapy, and whose menopausal status is in doubt, will be required to use one of the highly effective contraception methods. Highly effective contraception is defined as having a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label.

Women of nonreproductive potential are defined as those with surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) and those in a postmenopausal status defined as cessation of menses for at least 12 months without an alternative medical cause, and a confirmatory FSH test or as cessation of menses for at least 24 months without an alternative medical cause.

After administration of study drug, any known cases of pregnancy in female patients will be reported until the patient completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to [redacted] Safety and Pharmacovigilance within 24 hours of knowledge of the event. If any patient becomes pregnant during the study, they are to immediately discontinue any UNION-supplied study drug and to have only safety assessments performed. The Investigator will Follow up with the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify [redacted] and Pharmacovigilance of the pregnancy outcome by submitting a Follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the Investigator will report the event by faxing/emailing a completed pregnancy report form to [redacted] and Pharmacovigilance within 24 hours of knowledge of the event. If the Investigator becomes aware of a pregnancy occurring in the partner of a patient participating in the study, the pregnancy should be reported to [redacted] and Pharmacovigilance within 24 hours of knowledge of the event. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The

Investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Upon discontinuation from the study, only those procedures that would not expose the patient to undue risk will be performed. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. If a patient is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to [redacted] and Pharmacovigilance after delivery.

12.9.7. Overdose

In case of suspected overdose, please contact the Sponsor immediately.

13. PHARMACOKINETICS

13.1. Pharmacokinetic Sampling

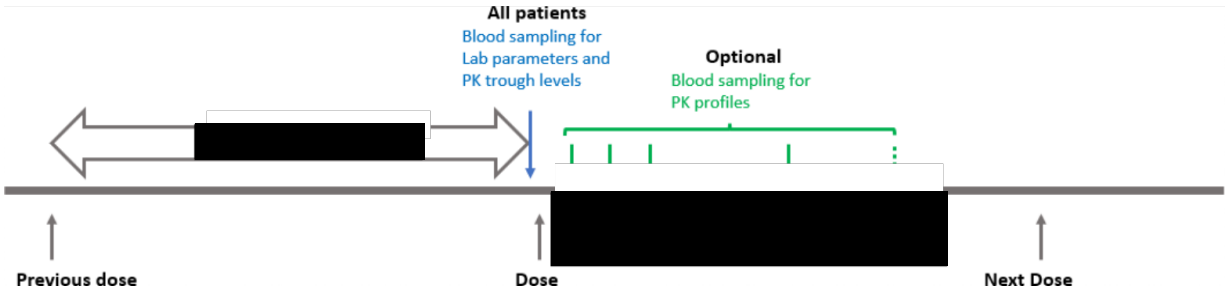
13.1.1. Blood Samples

Blood samples of approximately [redacted] mL will be collected for measurement of concentrations of orismilast and its major metabolite (LEO 40815) as specified in the Schedule of Assessments (Table 4) before dose of the study drug. The actual date and time of each blood sample collection will be recorded.

Blood sampling for measuring trough levels: The blood collection for PK analysis should preferably be conducted approximately [redacted] hours after the last study drug administration. It is recommended to have date and time of patient's last drug intake before PK sampling recorded in patient's source and in the eCRF as well.

Blood sampling for calculation of PK profiles: In addition to the sample collected for measuring trough levels, patients will be offered optional participation in specific blood sampling for calculation of PK profiles. This additional procedure is voluntary for patients and patient's consent will be obtained before collection of the blood samples. For PK profiling, [redacted] additional blood samples will be collected during each visit at [redacted] and [redacted]. The patient will be instructed to take the next dose of the study drug in the clinic and blood samples will be taken at the following timepoints: [redacted] (estimated C_{max}), [redacted] after intake of the study drug, as shown in Figure 2. An additional optional [redacted] blood sample will be collected if possible for the patient. The actual date and time of the study drug administration in the clinic and each blood sample collection will be recorded.

Figure 2 Pharmacokinetic Blood Sample Collection



Abbreviations: Lab, laboratory; PK, pharmacokinetics

Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

13.2. Pharmacokinetic Analytical Methodology

The concentration of study drug will be determined from the plasma samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

14. PHARMACODYNAMICS

15. STATISTICAL ANALYSIS

A statistical analysis plan will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The statistical analysis plan will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by treatment group. For continuous variables, data will be summarized with the number of patients (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of patients for each category by treatment group.

15.1. Determination of Sample Size

Approximately 200 patients will be enrolled to ensure approximately 50 patients per arm. This sample size is based on assumptions that the percentage change from Baseline in PASI is -32.2% and -50.9% for placebo and each orismilast dose group, respectively, and the standard deviation is 33%. Using a 2-sided 2-sample *t*-test, 50 patients in each treatment arm can achieve a power of 80% at the significance level of 5%.

15.2. Analysis Populations

Intent-to-Treat Population

The intent-to-treat (ITT) population will include all randomized patients who receive at least 1 dose of study drug. The treatment group assignment will be designated according to initial randomization. The ITT population will serve as the basis for the analysis of efficacy.

Per-Protocol Population

The Per-protocol (PP) population includes all randomized patients who receive at least 1 dose of study drug, have at least 1 post-Baseline PASI assessment, and without major protocol deviations affecting efficacy analysis. The treatment group assignment in this population will be designated according to initial randomization.

Safety Population

The safety population will include all randomized patients who receive at least 1 dose of study drug. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

15.3. Efficacy Analysis

For inferential analyses of primary and secondary efficacy endpoints, each active treatment group will be compared with the placebo group.

Primary and secondary efficacy endpoints are to be assessed in the ITT Analysis Population. Missing data for primary and key secondary endpoints will be handled with the multiple imputation method. For categorical efficacy endpoint based on a continuous variable, the multiple imputation will be first done for the continuous variable, then determine the category using the imputed values. Analyses will be repeated on the PP Population for primary and secondary endpoints.

When appropriate, the raw parameter, its change from Baseline, and percentage change from Baseline will be summarized.

15.3.1. Analysis of Primary Efficacy Endpoint

The primary endpoint, percentage change from Baseline to Week 16 in PASI, will be analyzed using analysis of covariance with treatment group as factor and Baseline PASI as covariate. As a supportive analysis, a mixed model for repeated measure (MMRM) will be performed with treatment group, visit and treatment-by-visit interaction as factors and Baseline PASI score by-visit interaction as a covariates.

Each active treatment dose will be compared with placebo. No adjustment for multiplicity will be made and the 0.05 level of significance will be used to claim efficacy compared with placebo. Least square means and the 95% confidence interval of the difference between each active treatment and placebo will be calculated. The primary analysis set will be the ITT Analysis Population with multiple imputation approach to handle missing values. The same analyses will be repeated for Weeks 20, 12, 8 and 4.

15.3.2. Analysis of Secondary Efficacy Endpoints

For continuous secondary efficacy endpoints including change from Baseline in PASI, total PSS, each individual item of the PSS, BSA and DLQI, a MMRM will be performed similar to the supportive MMRM for the primary endpoint.

The key secondary efficacy endpoints and other binary secondary efficacy endpoints (IGA success, PASI50, PASI75, PASI90) will be analyzed using the Mantel-Haenszel (MH) test, comparing each active treatment group to placebo in the ITT Analysis set.

For categorical endpoints, the MH procedure, with ridit scores, will be used; this test is the same as the nonparametric Wilcoxon test and enhances the analysis when the parameter is not normally distributed. Graphics will be added to facilitate interpretation. IGA scores/full scale will be analyzed using the MH test and the row mean score statistics and the ridit transformation.

The above endpoints (PASI changes and percentage changes, IGA success, PASI50, PASI75, PASI90) and the percentage change of BSA will be presented graphically over time from Baseline to Week 20. In addition, shift tables will be provided between Baseline and each visit for the IGA distribution. The PASI percentage changes from Baseline will be plotted to identify where the best separation between treatments occur.

15.3.3. Analysis of Exploratory Endpoints

All exploratory endpoints including change from Baseline in PGA-F, ss-IGA, scalp itch NRS, [redacted], risk factors, and [redacted] at Week 16 will be summarized descriptively in the ITT Population or a subgroup.

15.4. Safety Analysis

All safety analyses will be conducted using the Safety Analysis Population. AE data will be presented and tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) classification. Reported AEs will be summarized by the number of patients reporting the events, as well as by SOC and Preferred Term (PT), SOC, PT, and severity, and SOC, PT, and relationship to study drug.

Laboratory (chemistry and hematology) parameters and vital signs will be tabulated by visit using descriptive statistics and shift tables. The value at each visit, as well as the change from Baseline, will be presented.

15.5. Pharmacokinetic Analysis

The plasma levels of the drug and its metabolites will be summarized descriptively by visit in this study.

15.6. Interim Analysis

No interim analysis is planned in this study.

16. STUDY MANAGEMENT

16.1. Approval and Consent

16.1.1. Regulatory Guidelines and Ethical Considerations

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

- 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 Good Clinical Practice (GCP) Guidelines

Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

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

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 patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

16.1.2. Informed Consent

The Investigator is responsible for ensuring that patients do not undergo any study- related examination or activity before giving informed consent.

The Investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding the study. The patient must be given every opportunity to clarify any points not understood and must be provided with more information as requested. At the end of the interview, the patient may be given time to reflect and can request more time if needed.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

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

Patients 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 patient. Patients who are rescreened are required to sign a new ICF.

The ICF will have an additional form that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

16.2. Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

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

The patient must be informed that medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

16.3. Dissemination of Clinical Study Data

The Sponsor will list the study on a public database listing of clinical trials. Publication policy information is presented in Section 16.8.

16.4. Data Quality Assurance

All patient data relating to the study will be recorded on printed eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. Access to the electronic data capture system will be restricted and user will only be able to access the system via authorized individual accounts. Appropriate training will be completed with the Investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the eCRF.

A comprehensive Data Management Plan will be written outlining the standard operating procedures, internal/external security safeguards, system and change controls and training procedures and will be filed in the Sponsor's trial master file.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Protocol deviations from inclusion/exclusion criteria, concomitant medication restrictions and from any other protocol requirements that could result in significant risk to the patient and/or affect the outcome of the study will be collected. Additionally, nonadherence to the study procedures or schedule as defined by the protocol such as a missed procedure or an out-of-window study visit will be documented as protocol deviations.

Monitoring details describing strategy (eg, 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 noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data prior to data base closure.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

16.5. Source Documents

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

Data reported on the CRF or entered 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 study. Also, current medical records must be available.

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

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

16.6. Protocol Amendment and Protocol Deviation

16.6.1. Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

16.6.2. Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable regulatory authority mandates is an Investigator responsibility.

16.7. Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

16.8. Publication Policy/Disclosure of Data

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

17. REFERENCES

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18. APPENDICES

The assessments and scales included in the appendices are samples of what may be used during the study. The study-specific assessments and scales may be different.

Appendix 1. Protocol Amendment 1 and 2 Summary of Changes

Appendix 2. Psoriasis Area and Severity Index (PASI)

Appendix 3. Investigator Global Assessment (IGA)

Appendix 4. Scalp-specific Investigator Global Assessment (ss-IGA)

Appendix 5. Physician Global Assessment of Fingernail Psoriasis (PGA-F)

Appendix 6. Body Surface Area (BSA)

Appendix 7. Psoriasis Symptom Scale (PSS)

Appendix 8. Dermatology Life Quality Index (DLQI)

Appendix 9. The Hospital Anxiety and Depression Scale (HADS)

Appendix 10. The Columbia-Suicide Severity Rating Scale (C-SSRS)

Appendix 1. Protocol Amendment 1 Summary of Changes

Protocol version 1.0 dated 02 Oct 2020 is being amended to create Protocol Amendment version 2.0 dated 14 July 2021; the amended version of the protocol supersedes version 1.0. The purpose of this amendment is to update the protocol to provide further details about the study design, study objectives and endpoints, subject selection criteria, as well as data collection and analyses.

- Protocol structure was revised for better flow of information in a new template.
- Information regarding clinical studies revised as per the revised Investigator's Brochure.
- Safety added as a primary objective.
- [redacted]
- Change in psoriasis at "difficult to treat" anatomical areas were divided into 2 separate exploratory objectives for scalp and nails.
- Secondary endpoints were divided into "key secondary endpoints" and "other secondary endpoints".
- Timing of assessments were revised.
- A study schematic was added.
- Body weight of >40 kg at the time of signing the informed consent form was added as an inclusion criteria.
- Clarifying language was added regarding contraception requirements.
- History and evidence of severe hepatic impairment added as exclusionary criteria
- History and evidence of hepatitis B virus and hepatitis C virus added as exclusionary criteria.
- Blood pressure removed as an exclusionary criterion.
- A section of study withdrawal, removal, and replacement of patients was added.
- Further details on study treatments and dosage schedule were added.
- Clarification regarding blinding was provided.
- More information regarding prior and concomitant therapy was included.
- Proper order for assessments and procedures was specified.
- More details were added to the definition of assessments and patient-reported outcomes (PROs).
- The name of assessments and PROs used in trial was updated for consistency throughout the document.
- Details about particular tests as well as sample collection and analysis for laboratory assessments were added.
- Further information about adverse event and serious adverse event collection and reporting was included.
- PK assessment information was revised for clarity.
- [redacted]

- Statistical methods and planned analyses revised to provide further clarification on analyses populations and the overall data collection and analyses.
- Assessments and PROs used in this study added as appendices.

Protocol Amendment 2 Summary of Changes

Protocol Amendment version 2.0 dated 14 July 2021 is being amended to create Protocol Amendment version 3.0 dated 20 May 2022; the amended version of the protocol supersedes version 2.0. The main purpose of this amendment is to add PK sampling to enable meaningful PK data from the trial. Updates to the study design, study endpoint, subject selection criteria, as well as data collection and analyses were also made.

- Name of biostatistician was updated.
- "Patient" updated to "Participant" throughout the protocol.
- [redacted]
- Section 5.2.1: Addition of detailed information regarding nonclinical studies and to note that results from genotoxicity and reproductive toxicity studies did not raise any concerns.
- Addition of a new section, Section 5.4.1 Dose Rationale, to explain the rationale for choosing the doses of modified-release orismilast for this study.
- Synopsis and Section 8.1: Inclusion criterion 7 updated to remove male participants. "7. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at the Baseline visit. In addition, sexually active WOCBP ~~and male participants (including partners of male participants who are WOCBP)~~ must agree to use a highly effective method of contraception until at least 4 weeks after the end of study treatment."
- Inclusion Criteria#5 was elaborated (assessed at both Screening and Baseline).
- Example for psychiatric condition was updated in Exclusion Criteria#8 and actions to be taken in case of severe depression/suicidal thoughts were added.
- Unit was added in Exclusion Criteria#13c (platelet count).
- [redacted]
- HBsAg was corrected to HBsAb.
- Optional PK sampling was added; and PK-related text was updated.
- Statistical analysis section was updated based on the input provided for the Statistical Analysis Plan.
- General comments from the Food and Drug Administration on the Atopic Dermatitis (AD) protocol (UNI50001-202) were incorporated in this protocol amendment (Adverse Event of Special Interest definition and related text).
- Information was added to clarify which TEAEs would require follow-up after a patient discontinues prematurely from the study because of a TEAE.
- The full form of HADS was corrected from Hamilton Anxiety and Depression Scale to Hospital Anxiety and Depression Scale at few instances. Timepoints for HADS were corrected and description for HADS was updated.
- Timepoint for height (without shoes) was corrected from Screening to Baseline.

- Clarification for urine sampling was added.
- Initial titration period was corrected from up to 3 weeks to 2 weeks duration.
- Update made to reflect that dose administration in the clinic is not required.
- Examples of low potency corticosteroids was added.
- Description for the Columbia-Suicide Severity Rating Scale was updated.
- Appendix 10. The Columbia-Suicide Severity Rating Scale (C-SSRS) was updated.
- Appendix 11. QoL Questionnaire related to Nail Psoriasis was removed.

Appendix 2. Psoriasis Area and Severity Index (PASI)

The PASI was developed in 1978 by Fredriksson and Pettersson to assess the effects of retinoids in psoriasis. The PASI combines assessments of 4 body areas: the head and neck (H), the upper limbs (UL), the trunk (T) and the lower limbs (LL). The percentage of skin affected by psoriasis in each area is given a numerical score (A) representing the proportion involved: 1 (0–9%), 2 (10–29%), 3 (30–49%), 4 (50–69%), 5 (70–89%) or 6 (90–100%). Within each area (H, UL, T, LL) the severity of 3 plaque signs – erythema (E), thickness/induration (I) and desquamation/scaling (D) – is assessed on a 5-point scale: 0 (none), 1 (mild), 2 (moderate), 3 (severe) or 4 (very severe). The final PASI score ranges from 0 to 72, and is calculated using the following formula: PASI = 0.1 $(E_H+I_H+H_H)$ A_H + 0.2 $(E_{UL}+I_{UL}+H_{UL})$ A_{UL} + + 0.3 $(E_T+I_T+H_T)$ A_T + 0.4 $(E_{LL}+I_{LL}+H_{LL})$ A_{LL}

Appendix 3. Investigator Global Assessment (IGA)

Score	Definition
0=clear	• No signs of psoriasis (postinflammatory hyperpigmentation may be present)
1=almost Clear	• Normal to pink coloration of lesions • No thickening • No to minimal focal scaling
2=mild disease	• Pink to light red coloration • Just detectable to mild thickening • Predominantly fine scaling
3=moderate disease	• Dull to bright red, clearly distinguishable erythema • Clearly distinguishable to moderate thickening • Moderate scaling
4=severe disease	• Bright to deep dark red coloration • Severe thickening with hard edges • Severe/coarse scaling covering almost all of all lesions

Appendix 4. Scalp-specific Investigator Global Assessment (ss-IGA)

Patients with psoriasis of the scalp will be assessed using the 5-point ss-IGA presented below. Only patients with an ss-IGA score ≥2 at baseline will be included in the subset of patients analyzed for efficacy.

Score	Category	Description
0	Absence of Disease	No evidence of redness, no evidence of thickness, and no evidence of scaliness on the scalp.
1	Very Mild Disease	The overall clinical picture consists of flat lesions with barely perceptible erythema, with or without a trace of overlying fine scale
2	Mild Disease	The overall clinical picture consists of lesions with mild erythema, slight, but definite, thickness, and a thin scale layer
3	Moderate Disease	The overall clinical picture consists of lesions with moderate erythema, a moderate thickness, and a moderate scaled layer
4	Severe Disease	The overall clinical picture consists of lesions with bright erythema, severe thickness and a severe, coarse thick scale layer

Foley P, Gordon K, Griffiths CEM, et al. Efficacy of Guselkumab Compared With Adalimumab and Placebo for Psoriasis in Specific Body Regions: A Secondary Analysis of 2 Randomized Clinical Trials. JAMA Dermatol. 2018;154(6):676–683.

Appendix 5. Physician Global Assessment of Fingernail Psoriasis (PGA-F)

Fingernail psoriasis will be assessed using a 5-point PGA scale. The assessor should select the category that best represents the condition of all of the fingernails.

0 = Clear	Normal fingernails with no signs of psoriasis in the nail plates or nail beds
1 = Minimal	Just perceptible nail plate pitting, crumbling, onycholysis, oil drop discoloration, and/or nail bed hyperkeratosis
2 = Mild	Mild nail plate pitting, crumbling, onycholysis, oil drop discoloration, and/or nail bed hyperkeratosis
3 = Moderate	Moderate nail plate pitting, crumbling, onycholysis, oil drop discoloration, and/or nail bed hyperkeratosis
4 = Severe	Severe nail plate pitting, crumbling, onycholysis, oil drop discoloration, and/or nail bed hyperkeratosis

Foley P, Gordon K, Griffiths CEM, et al. Efficacy of Guselkumab Compared With Adalimumab and Placebo for Psoriasis in Specific Body Regions: A Secondary Analysis of 2 Randomized Clinical Trials. JAMA Dermatol. 2018;154(6):676–683.

Appendix 6. Body Surface Area (BSA)

The body surface area (BSA) assessment estimates the extent of disease or skin involvement with respect to atopic dermatitis (AD) and is expressed as a percentage of total body surface.

Determine BSA using the patient's palm = 1% BSA rule.

The patient's palm is measured from the wrist to the proximal interphalangeal and thumb.

Estimate the number of palms it takes to cover the affected AD area. Add up the number of palms to give a total estimate of the area covered in AD.

Additional rules:

1. When many small lesions are present, try to put several together to make one patient palm.
2. Only include the edge of current lesions, not areas that have cleared.
3. Double check to see if area derived matches eyeball method.

Appendix 7. Psoriasis Symptom Scale (PSS)

1. How severe was your pain from your psoriasis during the past 24 hours?
   - None
   - Mild
   - Moderate
   - Severe
   - Very severe
2. How severe was the redness from your psoriasis during the past 24 hours?
   - None
   - Mild
   - Moderate
   - Severe
   - Very severe
3. How severe was your itching from your psoriasis during the past 24 hours?
   - None
   - Mild
   - Moderate
   - Severe
   - Very severe
4. How severe was your burning from your psoriasis during the past 24 hours?
   - None
   - Mild
   - Moderate
   - Severe
   - Very severe

Appendix 8. Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (X) one box for each question.

1. Over the last week, how **itchy**, **sore**, **painful**, or **stinging** has your skin been?	Very much □ A lot □ A little □ Not at all □
2. Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much □ A lot □ A little □ Not at all □ Not relevant □
3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much □ A lot □ A little □ Not at all □ Not relevant □
4. Over the last week, how much has your skin influenced the **clothes** you wear?	Very much □ A lot □ A little □ Not at all □ Not relevant □
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much □ A lot □ A little □ Not at all □ Not relevant □
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much □ A lot □ A little □ Not at all □ Not relevant □
7. Over the last week, has your skin prevented you from **working** or **studying**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes □ No □ A lot □ A little □ Not at all □
8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much □ A lot □ A little □ Not at all □ Not relevant □
9. Over the last week, how much has your skin caused any **sexual difficulties**?	Very much □ A lot □ A little □ Not at all □ Not relevant □

10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or taking up time?	Very much □ A lot □ A little □ Not at all □ Not relevant □

□ **Please check you have answered EVERY question. Thank you.**

Appendix 9. The Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Appendix 10. The Columbia-Suicide Severity Rating Scale (C-SSRS)

For Screening

	Past Year	
Ask questions that are bolded and underlined.	**YES**	**NO**
Ask Questions 1 and 2		
1) Have you wished you were dead or wished you could go to sleep and not wake up?		
2) Have you actually had any thoughts of killing yourself?		
If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.		
3) Have you been thinking about how you might do this? E.g., "I thought about taking an overdose, but I never made a specific plan as to when where or how I would actually do it….and I would never go through with it."		
4) Have you had these thoughts and had some intention of acting on them? As opposed to "I have the thoughts, but I definitely will not do anything about them."		
5) Have you started to work out or worked out the details of how to kill yourself? Did you intend to carry out this plan?		
6) Have you ever done anything, started to do anything, or prepared to do anything to end your life? Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but did not swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but did not jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc. **If YES, ask: Was this within the past 3 months?**		

For Study

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore or wish to fall asleep and not wake up. Have you wished you were dead or wished you could go to sleep and not wake up? If yes, describe:	Yes □ No □
2. Nonspecific Active Suicidal Thoughts General nonspecific thoughts of wanting to end one's life/die by suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. Have you actually had any thoughts of killing yourself? If yes, describe:	Yes □ No □
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person	Yes □ No □

who would say, "I thought about taking an overdose, but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it." Have you been thinking about how you might do this? If yes, describe:	
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to "I have the thoughts, but I definitely will not do anything about them." Have you had these thoughts and had some intention of acting on them? If yes, describe:	Yes □ No □
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. Have you started to work out or worked out the details of how to kill yourself? Did you intend to carry out this plan? If yes, describe:	Yes □ No □
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - Most Severe Ideation _____Type # (1-5) _____ Description of Ideation Recent - Most Severe Ideation: _____Type # (1-5) _____ Description of Ideation	Most Severe
Frequency **How many times have you had these thoughts?** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration **When you have the thoughts how long do, they last?** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability **Could/can you stop thinking about killing yourself or wanting to die if you want to?** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents **Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of suicide?**	____

(1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	
Reasons for Ideation **What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge, or a reaction from others? Or both?** (1) Completely to get attention, revenge, or a reaction from others (2) Mostly to get attention, revenge, or a reaction from others (3) Equally to get attention, revenge, or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you could not go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you could not go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth, but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent, but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Nonsuicidal Self-Injurious Behavior?**	**Yes No** □ □ Total # of Attempts _____
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun	**Yes No** □ □ Total # of interrupted

fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed, and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	_____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life, but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** □ □ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** □ □ Total # of preparatory acts _____
	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (eg, comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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