Statistical Analysis Plan for Interventional Studies

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Sponsor Name: UNION therapeutics A/S

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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 Atopic Dermatitis

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Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	21-Nov-2022	[redacted]	Initial Release Version
2.0	26-Jul-2023	[redacted]	Updates based on learnings from the psoriasis study

I confirm that I have reviewed this document and agree with the content.

Approvals

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1. Glossary of Abbreviations

Abbreviation	Description
AD	Atopic dermatitis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Coviariance
ATC	Anatomical Therapeutic Chemical
bpm	Beats per minute
BDRM	Blinded Data Review Meeting
BID	Twice a day
BMI	Body Mass Index
BSA	Body Surface Area
CFB	Change from Baseline
CI	Confidence Interval
C_{max}	Maximum (or peak) serum concentration
CMH	Cochran-Mantel-Haenszel
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50	50% reduction in EASI
EASI75	75% reduction in EASI
EASI90	90% reduction in EASI
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
HADS	Hospital Anxiety and Depression scale
HBcAb	Antihepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus

Abbreviation	Description
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IGA-AD	Investigator Global Assessment for AD
IRB	Institutional Review Board
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
JAK	Janus kinase inhibitors
LS	Least squares
MAR	Missing At Random
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model for Repeated Measures
N/A	Not Applicable
NCI	National Cancer Institute
NRS	Numeric Rating Scale
PCFB	Percentage Change from Baseline
PD	Pharmacodynamics
PDE	Phosphodiesterase
Pdf	Portable document format
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PP	Per Protocol
PRO	Patient-Reported Outcome
PT	Preferred Term
Q1	First quartile, 25th percentile of the data
Q3	Third quartile, 75th percentile of the data
QC	Quality Control

Abbreviation	Description
QoL	Quality of Life
QTc	Corrected QT Interval
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SoA	Schedule of Assessments
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives based on Protocol v2.0.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety and efficacy and the pharmacokinetic analysis are planned after all patients complete the final study visit or terminate early from the study.

3. Study Objectives

3.1. Primary Objective

The primary objective is to evaluate the efficacy and safety of a modified-release orismilast tablet versus placebo in patients aged at least 18 years with moderate to severe atopic dermatitis (AD).

3.2. Secondary Objectives

The secondary objectives are to evaluate the dose response of orismilast and identify the dose to be further evaluated in a Phase 3 program.

3.3. Exploratory Objectives

The exploratory objectives are to:

- Evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) parameters relevant to AD.
- Evaluate the effect of orismilast on the pulmonary status and course of the disease in patients with asthma.

4. Study Details/Design

4.1. Brief Description

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 patients aged at least 18 years with moderate to severe AD. Efficacy and safety outcomes will be evaluated to select an appropriate orismilast dose for subsequent Phase 3 studies. The study will be conducted at approximately 48 centers in Europe and the United States.

After a Screening visit up to 28 days before Baseline, approximately 210 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 BID for 16 weeks, with a 4-week follow-up visit. Administration will begin at Baseline with a dose titration period of up to 2 weeks' duration depending on the dose level. The maximum duration of study participation for each patient is approximately 24 weeks.

Patients will be seen at the site at Screening, Baseline (Day 1), and Weeks 1, 2, 4, 8, 12, 16 (EOT visit), and 20 (Follow-up visit, 4 weeks after treatment completion or discontinuation). The visit at Week 1 can be conducted via a telemedicine procedure at the Investigator's discretion.

Patients who have been diagnosed with moderate to severe AD for a minimum of 1 year (before the Screening visit) using the Hanifin and Rajka criteria with affected BSA of at least 10%, Eczema Area and Severity Index (EASI) score of at least 16, and Investigator Global Assessment for Atopic Dermatitis (IGA-AD) grade of at least 3 at the screening and baseline visits will be included in the study. Patients must also have a documented history of inadequate response to treatment with topical medications given for at least 4 weeks (at least 2 weeks for high potency topical corticosteroids), or as labeled, or for whom topical treatments are otherwise medically inadvisable.

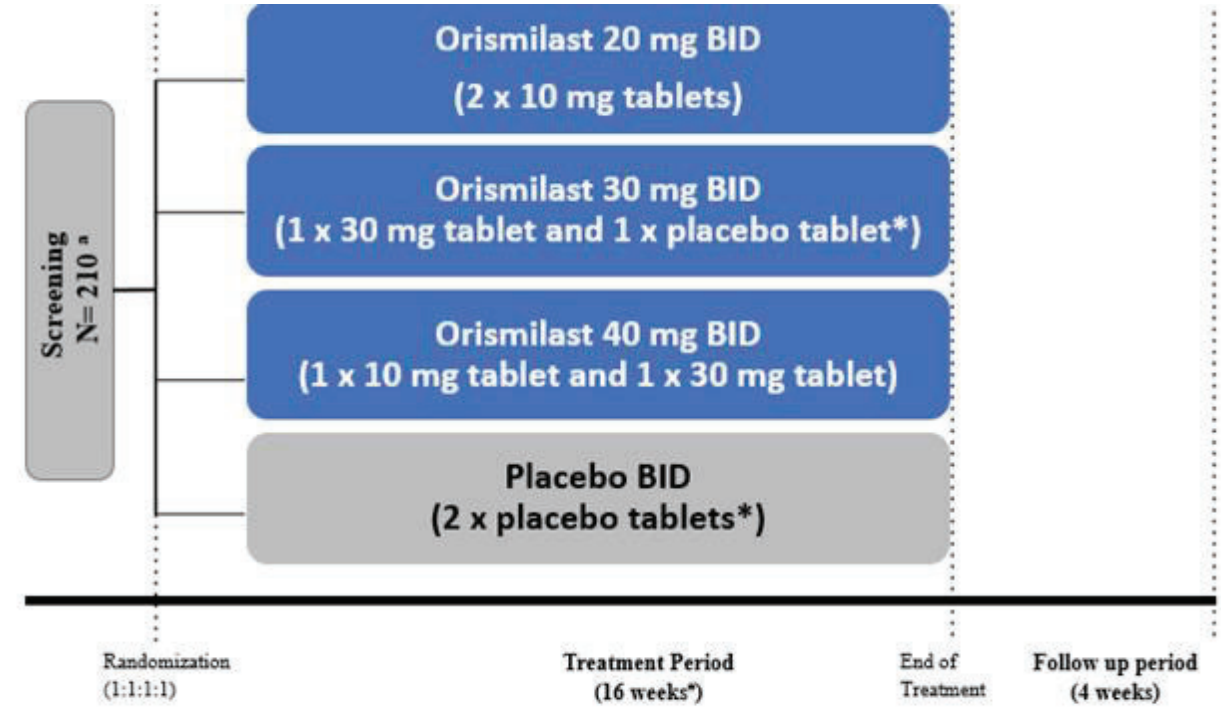
At Screening, Baseline and at each visit from Week 2 onwards, EASI, affected body surface area (BSA), and IGA-AD will be assessed. BSA is defined as all areas with eczematous lesional skin and does not include xerosis (dryness), ichthyosis, keratosis pilaris, urticaria, infection (unless there is underlying eczema), or postinflammatory pigmentation changes. If patients need to manage areas with dry skin and/or pruritus, they are allowed to continue using their current emollient. However, emollients that contain pharmacologically active ingredients such as lactic acid, salicylic acid, urea, alpha-hydroxy acids, or fruit acids are not allowed from the Screening visit. The severity of itch will be assessed by peak pruritus numerical rating scale (NRS) at each visit from baseline to end of the treatment. Disease symptoms will be assessed by Patient Oriented Eczema Measure (POEM) scores at Baseline and at the Weeks 2, 4, 8, 12, 16, and 20 visits. Quality of life related to the disease will be assessed by Dermatology Life Quality Index (DLQI) scores at Baseline and at the Weeks 8, 16, and 20 visits. Pulmonary disease status will be assessed in patients with asthma by pulmonary status NRS at Baseline and at the Weeks 4, 8, 12, 16, and 20 visits. The severity of disease will be assessed by Patient Global Impression of Severity (PGIS) at Baseline and at the Weeks 2, 4, 8, 12, 16, and 20 visits and Patient Global Impression of Change (PGIC) scores at the Weeks 2, 4, 8, 12, 16, and 20 visits. In addition, the sleep disturbance NRS and skin pain NRS will be administered at Baseline and at the Weeks 1, 2, 4, 8, 12, 16, and 20 visits.

Safety evaluations include medical history, AEs, laboratory and vital sign assessments, physical examination including body weight and height, BMI, 12-lead ECG, and mood change evaluations by the patient (HADS score) and suicidal behavior and ideation evaluation by the Investigator (C-SSRS).

Before administration of the study drug at Baseline (Day 1) and Weeks 4, 8, and 16, blood will be collected for orismilast and the major human metabolites LEO 40815 and LEO32728 for PK concentration determination. In addition, noninvasive superficial skin sampling using tape stripping will be conducted on

a target lesion (lesional and nonlesional skin sample) at Baseline and Week 16 (only lesional skin sample) in all patients for proteomic analysis. See Figure 1 Study Design for the study design.

Figure 1 Study Design



* to maintain the study blind.
# initial titration period of up to 2 weeks.
a total 210 patients = 47 patients in each treatment group (188 total) + 22 patients to account for the early drop out.

Abbreviation: BID, twice daily; and N, total number of patients.

4.2. Patient Selection

4.2.1. Inclusion Criteria

Patients are eligible to be included in the study only if all the following criteria apply at both the screening and baseline visits:

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 aged at least 18 years at the time of signing the ICF.
3. Body weight of greater than 40 kg at the time of signing the ICF.
4. Diagnosis of AD for a minimum of 1 year (before the Screening visit) using the Hanifin and Rajka criteria.
5. Moderate to severe AD (affected BSA of at least 10%, IGA-AD grade of at least 3, and EASI score of at least 16) at the screening and baseline visits.
6. Candidate for systemic treatment or phototherapy for AD.
7. Patients having a documented history of inadequate response to treatment with topical medications given for at least 4 weeks (at least 2 weeks for high potency topical corticosteroids), or as labeled, or for whom topical treatments are otherwise medically inadvisable.

8. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test result at the Screening visit and a negative urine pregnancy test result at the Baseline visit. In addition, sexually active WOCBP must agree to use a highly effective method of contraception throughout the study and until at least 4 weeks after the end of study treatment. Highly effective methods of contraception are those that have a failure rate of less than 1% per year (when implemented consistently and correctly and when applicable, in accordance with the product label) 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 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 consecutive months without an alternative medical cause and a confirmatory follicle-stimulating hormone test result or as cessation of menses for at least 24 consecutive months without an alternative medical cause.

4.2.2. Exclusion Criteria

Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:

1. Therapy-resistant AD, defined as ≥2 treatment failures due to inadequate efficacy within the past 2 years of any biologic therapy, JAK inhibitor treatment or phototherapy administered at an 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 AD with acute deterioration, requiring rescue therapy for AD within 4 weeks of the Screening visit or expected to require rescue therapy within 2 weeks after randomization.
3. History of allergy or hypersensitivity to any component of the study treatment.
4. Currently have active forms of other inflammatory skin disease or have evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, lupus) at the Baseline visit that would interfere with evaluation of AD or response to treatment.
5. Active infection (eg, bacterial, viral, fungal) requiring treatment with systemic antibiotics within 4 weeks of the Screening visit.
6. Malignancy or history of malignancy except for treated (ie, cured) basal cell skin carcinoma.
7. Any chronic or 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) that, 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 while receiving the investigational therapy.
9. Individuals with severe or uncontrolled asthma or any other concomitant condition that is likely to require systemic corticosteroid bursts during the study.
10. Any therapies and systemic treatments as described in protocol Table 3 "Nonallowed therapies and treatments" that do not comply with the indicated washout interval.
11. Any previous treatment with orismilast or failure of treatment for AD with apremilast or any other systemic PDE4 inhibitor.

12. 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.
13. Severe hepatic impairment based upon medical history and laboratory abnormalities (eg, low albumin and abnormal bilirubin levels).
14. Any of the following abnormalities in clinical laboratory test results at Screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:
    a) Absolute neutrophil count of less than 3.0 × 10^9/L (less than 3000/mm^3).
    b) Hemoglobin of less than 10.0 g/dL or hematocrit less than 30%.
    c) Platelet count of less than 100,000 mm^3.
    d) Absolute lymphocyte count of less than 1.0 × 10^9/L (less than 1000/mm^3).
    e) Total bilirubin greater than 1.5 × the upper limit of normal (ULN); patients with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin result is less than or equal to the ULN.
    f) Alanine aminotransferase or aspartate aminotransferase greater than 2.5 × the ULN.
    g) Serum creatinine greater than or equal to 1.5 mg/dL. For patients with a value of greater than or equal to 1.5 mg/dL, if their creatinine clearance is at least 60 mL/min (calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation), enrollment may be allowed.
15. History or evidence of hepatitis B virus infection at Screening. Patients with a positive hepatitis B surface antigen result are excluded. For patients with an isolated positive antihepatitis B core antibody result, the hepatitis B surface antibody result must also be positive to be eligible for this study.
16. 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.
17. History of positive HIV test result or 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.
18. Suicidal ideation or behavior in the past 12 months as indicated by a positive response (yes) to question 4 or 5 on the C-SSRS completed at the Screening visit or at Baseline.
19. Pregnant or breastfeeding.
20. History of alcohol or substance abuse within 6 months before Baseline that, in the opinion of the Investigator, will preclude participation in the study.
21. Institutionalized by court order or by local authority.
22. Regular use (more than 2 visits per week) of a tanning booth/parlor.

4.3. Determination of Sample Size

Approximately 210 patients will be randomly assigned to receive orismilast 20 mg, 30 mg, or 40 mg BID or placebo for 16 weeks.

This sample size is based on assumptions that there is a difference of 25.0% in the percent change from baseline in EASI scores between each orismilast dose group with placebo, respectively, and that the common standard deviation in the percent change from baseline in EASI score is 43%. Using a 2-sided 2-sample t-test, 47 patients in each treatment group (188 in total) will achieve a power of 80% at the significance level of 5%. To account for an early dropout rate of approximately 10%, an additional 22 patients will be randomized.

4.4. Treatment Assignment and Blinding

Randomization will occur before the 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. The randomization is stratified by site. All patients will be assigned to randomized study treatment using an Interactive Web Response System (IWRS).

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).

To facilitate the double blinding, 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 tablet).

Blinding codes should only be broken in emergency situations for reasons of patient safety. 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 Sponsor's 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 1 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.

4.5. Administration of Study Medication

The patients will receive the study drug at the site directly from the Investigator or designee. The date of the first dose should be recorded in the source documents and recorded in the eCRF. At all site visits beginning with the Week 2 visit, patients will return all study drug, including packaging, dispensed at the previous visit, and it will be documented using the IWRS.

The patients will self-administer the study drug at home, and compliance with the protocol will be assessed at each visit beginning with the Week 2 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. Discontinuation for noncompliance is at the investigator's discretion and is to be noted on the eCRF.

4.6. Study Procedures and Flowchart

The Schedule of assessments is in Protocol Section 9.

5. Endpoints

5.1. Primary Efficacy Endpoint

- Percentage change in EASI score from Baseline at Week 16.

5.2. Secondary Efficacy Endpoints

Key Secondary Efficacy Endpoints:

- Patients achieving 75% reduction in EASI (EASI75) response at Week 16.
- Patients achieving a score of clear (0) or almost clear (1) and at least a 2-point improvement in IGA-AD at Week 16.

Other Secondary Efficacy Endpoints:

- Patients achieving a score of clear (0) or almost clear (1) and at least a 2-point improvement in IGA-AD at Weeks 2, 4, 8, 12, and 20.
- Patients achieving EASI75 at Weeks 2, 4, 8, 12, and 20.
- Patients achieving 50% reduction in EASI (EASI50) and 90% reduction in EASI (EASI90) response at Weeks 2, 4, 8, 12, 16, and 20.
- Percent change from Baseline in EASI at Weeks 2, 4, 8, 12, and 20.
- Change from Baseline in the peak pruritus NRS score at Weeks 1, 2, 4, 8, 12, 16, and 20.
- Patients achieving at least a 4-point improvement in the peak pruritus NRS from baseline at Weeks 1, 2, 4, 8, 12, 16, and 20 among patients with a baseline score ≥4.
- Change from Baseline in affected BSA at Weeks 2, 4, 8, 12, 16, and 20.
- Change from Baseline in DLQI score at Weeks 8, 16, and 20.
- Change from Baseline in POEM score at Weeks 2, 4, 8, 12, 16, and 20.
- Change from Baseline in PGIS score at Weeks 2, 4, 8, 12, 16, and 20.
- PGIC score at Weeks 2, 4, 8, 12, 16, and 20.
- Change from Baseline in sleep disturbance NRS score at Weeks 1, 2, 4, 8, 12, 16, and 20.
- Change from Baseline in skin pain NRS score at Weeks 1, 2, 4, 8, 12, 16, and 20.

5.3. Exploratory Endpoints

- Patients achieving at least a 2-point improvement in the peak pruritus NRS from baseline at Weeks 1, 2, 4, 8, 12, 16, and 20 among patients with a baseline score ≥4.
- Change from Baseline in pulmonary status NRS in patients with asthma at Weeks 4, 8, 12, 16, and 20.
- Patients achieving 100% reduction in EASI (EASI100) response at Weeks 2, 4, 8, 12, 16, and 20.

5.4. Pharmacokinetic Endpoint

- Plasma levels of the drug and its metabolites at Weeks 4, 8, and 16.

5.5. Safety Endpoints

- The occurrence, severity, and seriousness of treatment-emergent AEs (TEAEs) reported over the 16-week Treatment Period and the 4-week Follow-up Period.

- Changes from Baseline in physical examination findings; vital signs 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.
- Clinically significant abnormal changes in ECG findings over the 16-week Treatment Period.
- Changes from Baseline in safety laboratory values (hematology, serum chemistry, and urinalysis) over the 16-week Treatment Period.
- Change from Baseline in HADS score at each visit except Week 1.
- C-SSRS score at each visit except Week 1.

5.6. Pharmacodynamic Endpoint

- Change from Baseline in skin biomarkers at Week 16 collected via tape stripping and analyzed using proteomic methods.

6. Analysis Populations

6.1. Randomized Population

The randomized population will include all patients randomized. Unless specified otherwise, this population will be used for patient listings and for summaries of patient disposition.

6.2. 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.

6.3. 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.

6.4. 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 EASI assessment, and who do not have any major protocol deviations affecting efficacy analysis. The treatment group assignment in this population will be designated according to initial randomization. Efficacy analysis for primary and key secondary endpoints will be repeated on the PP Population.

6.5. Protocol Deviations

Protocol deviation management at Syneos Health is detailed in Protocol Deviation and Non-compliance Management (3101.W02). For details on the process for defining analysis datasets refer to (Blind) Data Review and Definition of Analysis Sets SOP (3911). The Protocol deviation criteria are graded as minor and major.

Patients with a major protocol deviation affecting efficacy analysis will be excluded from the PP population. The list of major protocol deviations potentially leading to PP population exclusion includes at least the following deviations:

- Violations of inclusion or exclusion criteria.
- Use of disallowed medication (that may influence the interpretation of efficacy results).
- Non-compliance with study medication intake: less than 80% of total number of tablets during entire treatment period or during the last 4 weeks.
- Major deviation from study specific instructions/procedures.

The final list of patients who are to be included in the PP population will be determined at the Blinded Data Review Meeting (BDRM). The BDRM will occur when all or nearly all queries have been resolved and the database is near to final. For the BDRM meeting, a BDRM Preparation Plan will be prepared. This plan will detail further the types of protocol deviation criteria and will include, as a minimum: 1) the exact criteria which will be used to determine if a patient will be excluded from the PP population; 2) the listings which will be prepared for sponsor review in order to determine which patients to exclude from the PP population. Details of patient specific exclusions from the PP population will be detailed in the BDRM Report.

7. General Aspects for Statistical Analysis

7.1. General Methods

- All statistical analyses will be conducted using SAS® for Windows® Version 9.4 or higher.
- All data will be listed, and summary tables will be provided.
- In general, unscheduled visit data will be listed, but not included in the summary tables by visit. Unscheduled data will be included to identify the worst-case post-baseline for safety shift tables. Unscheduled data will be used in the statistical analysis to avoid missing data.
- 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, Q1, Q3, 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.
- There will be no adjustment for multiplicity, thus all p-values reported will be nominal.
- The randomized population will be used for patient data listings.
- Unless otherwise specified, listings will be sorted by randomized treatment, subject number and chronologically by assessment date and time.
- Missing records will be omitted from the listings, and missing data within a record will be left blank.
- Unless otherwise specified, baseline summaries will be presented for each treatment (Placebo, Orismilast 20 mg BID, Orismilast 30 mg BID, Orismilast 40 mg BID) and for Overall. Safety summaries will be presented for each treatment (Placebo, Orismilast 20 mg BID, Orismilast 30 mg BID, Orismilast 40 mg BID) and for Orismilast Total. Efficacy summaries will be presented for each treatment (Placebo, Orismilast 20 mg BID, Orismilast 30 mg BID, Orismilast 40 mg BID).

7.2. Key Definitions

Treatment period
The Treatment Period for this study is 16 weeks, from Day 1 to Week 16 (112 ± 3 days).

Study day
If the event date ≥ date of first dose of IP, study day = event date – date of first dose of IP + 1.
If the event date < date of first dose of IP, study day = event date – date of first dose of IP.

Baseline Value
Baseline value will be defined as the last non-missing value recorded prior to the first intake of study treatment.

Change from Baseline (CFB)
CFB = Post-baseline value – Value at baseline

Percentage change from baseline (PCFB)
PCFB = ((Post-baseline value – Value at baseline) / Value at baseline)*100%.

7.3. Missing Data

Missing data will be treated as missing, except in the following cases.

Efficacy

To ensure that we evaluate the effect of study treatment (and not the effect of study treatment + disallowed medications (e.g. topical medications)), patients efficacy data collected after date of first disallowed medication (which may influence efficacy assessments e.g. any medication given to control unacceptable atopic dermatitis symptoms) will be ‘set to missing’ / ‘treated as missing’ in the primary statistical analysis . If disallowed medication is introduced the same day as an efficacy assessment, the efficacy assessment will be used as is.

Missing data and data 'treated as missing’ for the primary analysis of primary and secondary binary endpoints will be handled with the multiple imputation method, assuming Missing At Random (MAR) within arm.

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.

Secondary continuous endpoints will be analyzed based on observed data using an MMRM, thus using a modelling approach assuming MAR for missing data.

For a supportive analysis of key secondary efficacy endpoints missing data will be handled as non-response.

Safety

- Missing AE relationship will be imputed by ‘definitely’.
- Missing AE severity will be imputed by ‘Grade 3’.
- Missing or incomplete dates in safety data:

In all listings, missing or incomplete dates will be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

I. The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing or incomplete, it is assumed to have occurred during the treatment period (i.e. a TEAE for AEs) except if the partial onset date indicates differently).
II. A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

7.4. Visit Windows

If there are multiple planned assessments for any study procedure at a given time point, the latest non-missing value will be used for summarization. Unscheduled assessments will be listed and will be used to flag baseline visit if this is the last non-missing assessment before the first dose of study drug, but unscheduled assessments will not be included in the summarization, unless to be used to avoid missing data at Week 16.

7.5. Pooling of Centers

Not applicable since no adjustment for center or by center analyses are planned.

7.6. Subgroups

Subgroup analyses only apply to some of the exploratory endpoints and are described in section 9.2.3.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Patient Disposition and Withdrawals

The following frequencies (number and percent) will be displayed for all patients screened, patients randomized, screen failures, and reasons for screen failure.”.

The analysis populations will be summarized with counts and percentages by treatment group. This table will include the following: number of patients screened, patients randomized, patients in safety population, reasons for exclusion from the safety population, patients in ITT population, reasons for exclusion from the ITT population, patients in PP population, and reasons for exclusion from the PP population.

The following frequencies (number and percent) will be displayed for all patients in the randomized population: patients in the safety population, patients in ITT population, patients in PP population, patients who completed the study (including follow-up), patients who discontinued early, study duration in days, patients who completed study treatment, patients who discontinued study treatment early also presented by reason for early discontinuation. The denominators will be the number of randomized patients.

A Kaplan-Meier plot of time to discontinuation of study treatment will be presented by treatment for the ITT population. Cumulative proportion of patients with discontinuation of study treatment by treatment group as a function of time since randomization will be presented for the ITT Population. Cumulative proportion of patients with discontinuation of study treatment by treatment group and reason for discontinuation as a function of time since randomization will be presented for the ITT population.

Listings of treatment assignments, including the subject’s identification, date and time of randomization, and assignment to treatment, will be presented.

Patient disposition, COVID-19 visit impact, inclusion/exclusion criteria violations and exclusions from analysis populations will be listed by patient.

8.2. Protocol Deviations

All protocol deviations (minor and major) observed during the conduct of the study will be listed. Major protocol deviations (patients with at least one major PD overall and split by PD category), and minor deviations (patients with at least one minor PD overall and split by PD category) will be summarized by treatment group for all randomized patients.

8.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, sex, child-bearing potential, race, ethnicity, asthma diagnosis, disease duration, height, body weight, and body mass index (BMI) will be summarized for the ITT population using standard descriptive statistics. This table will be repeated for the PP population.

Baseline efficacy assessments: EASI, IGA-AD, BSA, DLQI score, POEM, PGIS, skin pain NRS, sleep disturbance NRS, peak pruritus NRS, and pulmonary status NRS will be summarized for the ITT population. No formal statistical comparisons between populations will be performed. This table will be repeated for the PP population. Demographics will be listed for all patients in the randomized population.

8.4. Smoking and Alcohol History

Smoking and alcohol history will be summarized for the ITT population using standard descriptive statistics and listed for all patients in the randomized population.

8.5. Medical History

Medical history, including surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 24.0. Medical history and ongoing conditions will be summarized in separate tables for the ITT population presenting the number and percentages of patients within each preferred term (PT) grouped by the system organ class (SOC). A patient with multiple occurrences of an event in a PT is counted only once. Medical history will be listed for all patients in the randomized population.

8.6. Medication

The WHO Drug, March 2021, B3 will be used to classify prior and concomitant medications by therapeutic class and drug name.

Prior medication is defined as any medication taken before the date of the first dose of study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of study treatment.

The use of prior medications, concomitant medications, and concomitant disallowed medications will be summarized by the number and percentage of patients for the ITT population. If a patient takes a specific medication multiple times or takes multiple medications within a specific therapeutic class, that patient would be counted only once for the coded drug name or therapeutic class.

A table will be provided showing patients receiving disallowed medications that may influence efficacy assessments at any time during the initial 16-weeks (e.g. topical treatments, systemic treatments, biologics or phototherapy)

A figure will be provided with the cumulative proportion of patients over time receiving disallowed medication that may influence efficacy assessments. Patients will count as receiving disallowed medication that may influence efficacy from first initiation.

Prior medications, concomitant medications, and concomitant disallowed medications will be listed for all patients in the randomized population.

A summary table will be provided for previous treatments for atopic dermatitis (e.g. prior systemics, biologics). Previous treatments for atopic dermatitis and reasons for stopping previous treatments for atopic dermatitis will be summarized for the ITT population. Previous treatments for atopic dermatitis will be listed for all patients in the randomized population.

8.7. Extent of Exposure

Study drug administration data, study drug accountability data, and study drug compliance check data will be listed for all patients in the ITT population.

8.8. Treatment Compliance

When patients receive the study drug at the site, they will receive it 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. 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. 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.

Number of patients with missed doses, number of missed doses, reasons for dose interruption, duration of exposure, compliance rate and compliance rate until treatment discontinuation will be summarized overall by treatment group for the ITT population and separately for the titration period.

9. Efficacy

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

Patients who receive topical medications will be allowed to continue with study treatment while patients receiving systemic medication will be discontinued from study treatment. This means that some patients (particularly in the less effective arms) will have efficacy assessments collected after receiving topical medicals which may influence efficacy assessments.

To ensure that the primary analyses evaluate the effect of study treatment (and not the effect of study treatment + disallowed medications (e.g. topical medications) the following approach will be taken: Patients efficacy data collected after date of first disallowed medication (which may influence efficacy assessments e.g. any medication given to control unacceptable atopic dermatitis symptoms) will be first 'set to missing' / 'treated as missing'. If disallowed medication is introduced the same day as an efficacy assessment, the efficacy assessment will be used as is. Thereafter, the below described analyses should applied.

Primary and secondary efficacy endpoints are to be assessed in the ITT Population. Missing data and data 'treated as missing' for the primary analysis of primary and secondary binary endpoints will be handled with the following multiple imputation method: Intermittent missing data will first be imputed using the MCMC method implemented with the SAS MI procedure, which is appropriate for non-monotonic missing data. Data missing (including 'treated as missing') will then be multiply imputed with the SAS MI procedure using a regression statement (number of imputations: 50, seed: 3628479. At each time point, missing data will be assumed to be MAR and to follow a distribution similar to scores for patients who are still in the study and randomized to the same treatment group.

For categorical efficacy endpoints based on a continuous variable, the multiple imputation will be first done for the continuous variable, then determine the category using the imputed values. Efficacy analyses will be repeated on the PP Population for primary and key secondary endpoints.

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

9.1. Primary Efficacy Endpoint and Analysis

The primary endpoint in this study is the percentage change in EASI score from Baseline at Week 16.

The primary endpoint (primary analysis) will be analyzed using analysis of covariance (ANCOVA) with treatment group as factor and Baseline EASI as covariate. 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 population with multiple imputation approach to handle missing values. The same analyses will be repeated for Weeks 20, 12, 8, 4 and 2. These analyses will be repeated on the PP population.

LS Mean (+/-SE) percentage change of EASI score will be presented graphically over time from Baseline to Week 2, 4, 8, 12, 16, and 20.

Actual values, change from baseline values, and percentage change from baseline of EASI will be summarized by visit using descriptive statistics and presented graphically over time.

The mixed model for repeated measures (MMRM) will be used as a supportive analysis with data collected after date of first disallowed medication 'treated as missing'. If disallowed medication is introduced the same day as an efficacy assessment, the efficacy assessment will be used as is. Some patients may not have any post-baseline data collected before initiation of disallowed medication. To ensure that all patients are included in the analysis, the baseline value for these patients should be carried forward as the first post-baseline assessment, corresponding to imputing a change of 0 at the first post-baseline assessment. The MMRM model will be implemented using SAS PROC MIXED with treatment group, visit, and treatment-by-visit interaction as factors and baseline EASI score by-visit interaction as a covariate. A restricted maximum likelihood (REML) will be used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors. Least Squares Means Estimates and 95% confidence intervals will be given for each treatment group and for the difference between treatment groups (here also p-values will be presented). As an additional supportive analysis, this MMRM analysis will be repeated, with all observed data included irrespectively of disallowed medication or discontinuation of study drug.

EASI (including change from baseline values, percentage change from baseline values, EASI50, EASI75, and EASI90) will be listed.

9.2. Secondary Efficacy Endpoints and Analyses

Continuous secondary efficacy endpoints will be analyzed based on observed data prior to first initiation of disallowed medication using MMRM, using a modelling approach assuming MAR for missing data. If disallowed medication is introduced the same day as an efficacy assessment, the efficacy assessment will be used as is.

The binary secondary efficacy endpoints will be analyzed using difference in proportions, comparing each active treatment group to placebo in the ITT population with handling of missing data and data 'treated as missing' as specified in Section 9. Response by treatment group and difference in response rate and p-values compared to placebo will be presented.

The secondary endpoints 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-AD distribution. The EASI percentage changes from Baseline will be plotted to identify where the best separation between treatments occur. These figures and tables are based on observed cases, thus purely descriptive.

9.2.1. Key Secondary Endpoints

- Patients achieving 75% reduction in EASI (EASI75) response at Week 16.
- Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in IGA-AD at Week 16.

In addition to absolute EASI scores, response to treatment is presented as a percentage response rate: EASI50, EASI75, and EASI90. EASI75 represents the percentage of patients who have achieved a 75% or more reduction in their EASI score from baseline.

The key secondary endpoints (primary analysis) will be analyzed using difference in proportions, comparing each active treatment group to placebo in the ITT population. Response by treatment group and difference in response rate and p-values compared to placebo will be presented. These analyses will be repeated on the PP population. As supportive analysis, this analysis will be repeated, with handling of missing data and data 'treated as missing' as non-response. As an additional supportive analysis, for both key secondary endpoints, this analysis will be repeated with all observed data included irrespectively of disallowed medication or discontinuation of study treatment. Any other missing data should be imputed as non-response. In case of imbalance in baseline disease severity between treatment groups an additional supportive analysis stratifying for baseline IGA using a Cochran-Mantel-Haenszel (CMH) test will be performed. As an additional supportive analysis, for both key secondary endpoints, this analysis will be repeated (in a descriptive table and a table using non-response imputation if a score is missing or 'treated as missing')) by subgroups: baseline IGA (moderate / severe), body weight at baseline(<80, 80-100, ≥100 kg) and region (US vs non-US).

Actual values of IGA-AD will be summarized by visit using descriptive statistics and presented graphically over time.The percentage of patients with EASI75 and the percentage of patients achieving clear (0) or almost clear(1) will be presented graphically over time. These figures are based on observed cases, thus purely descriptive.

9.2.2. Other Secondary Endpoints

- Patients achieving a score of clear (0) or almost clear (1) and at least a 2-point improvement in IGA-AD at Weeks 2, 4, 8, 12, and 20.
- Patients achieving EASI75 at Weeks 2, 4, 8, 12, and 20.
- Patients achieving EASI50 and EASI90 response at Weeks 2, 4, 8, 12, 16, and 20.
- Percent change from Baseline in EASI at Weeks 2, 4, 8, 12, and 20.
- Change from Baseline in the peak pruritus NRS score at Weeks 1, 2, 4, 8, 12, 16, and 20.
- Patients achieving at least a 4-point improvement in the peak pruritus NRS from baseline at Weeks 1, 2, 4, 8, 12, 16, and 20 among patients with a baseline score ≥4.
- Change from Baseline in affected BSA at Weeks 2, 4, 8, 12, 16, and 20.
- Change from Baseline in DLQI score at Weeks 8, 16, and 20.
- Change from Baseline in POEM score at Weeks 2, 4, 8, 12, 16, and 20.
- Change from Baseline in PGIS score at Weeks 2, 4, 8, 12, 16, and 20.
- PGIC score at Weeks 2, 4, 8, 12, 16, and 20.
- Change from Baseline in sleep disturbance NRS score at Weeks 1, 2, 4, 8, 12, 16, and 20.
- Change from Baseline in skin pain NRS score at Weeks 1, 2, 4, 8, 12, 16, and 20.

EASI50 represents the percentage of patients who have achieved a 50% or more reduction in their EASI score from baseline. EASI90 represents the percentage of patients who have achieved a 90% or more reduction in their EASI score from baseline.

Continuous secondary efficacy endpoints will be analyzed using MMRM, similar to the supportive MMRM for the primary endpoint, i.e. based on observed data prior to first initiation of disallowed medication.

The analysis on categorical secondary efficacy endpoints will be performed using difference in proprotions, comparing each active treatment group to placebo in the ITT population with handling of missing data and data 'treated as missing' as specified in Section 9. Response by treatment group and difference in response rate and p-values compared to placebo will be presented.

Actual values and change from baseline values of POEM, PGIS, sleep disturbance NRS and skin pain NRS will be summarized by visit using descriptive statistics and presented graphically over time. Actual values of PGIC will be summarized by visit using descriptive statistics and presented graphically over time. Actual values, change from baseline values and percentage change from baseline of BSA and DLQI will be summarized by visit using descriptive statistics and presented graphically over time. The percentage of patients with EASI50 and EASI90 will be presented graphically over time. These tables and figures are based on observed cases, thus purely descriptive. In addition a summary table presenting patients achieving reduction of DLQI score of ≥4 points at week 16 from baseline in patients in the ITT population with a baseline score ≥4 wil be provided.

POEM, PGIS, peak pruritis NRS, sleep disturbance NRS and skin pain NRS (including change from baseline values) will be listed. PGIC will be listed. BSA and DLQI (including change from baseline and percentage change from baseline values) will be listed.

9.2.3. Exploratory Endpoints

- Patients achieving at least a 2-point improvement in the peak pruritus NRS from baseline at Weeks 1, 2, 4, 8, 12, 16, and 20 among patients with a baseline score ≥4.
- Change from Baseline in pulmonary status NRS in patients with asthma at Weeks 4, 8, 12, 16, and 20.
- Patients achieving 100% reduction in EASI (EASI100) response at Weeks 2, 4, 8, 12, 16, and 20

All exploratory endpoints will be summarized descriptively in the ITT Population. A summary table of patients achieving EASI50, EASI75, EASI90, EASI100 and IGA 0/1 response at weeks 2, 4, 8, 12, 16 and 20 will be provided. Peak pruritus NRS, pulmonary status NRS will be listed.

10. Pharmacokinetics

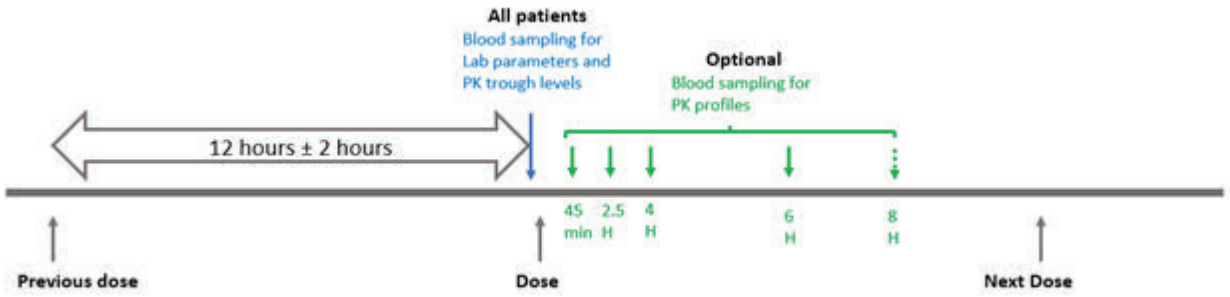
Exploratory endpoint: Plasma levels of the drug and its metabolites at Weeks 4, 8, and 16.

Blood samples will be collected for measurement of concentrations of orismilast and its major metabolites (LEO 40815 and LEO 32728) as specified in the SoA in Protocol Section 9 before the morning dose of the study drug. The concentration of study drug will be determined from the plasma samples using a validated analytical method.

Blood sampling for measuring plasma levels: The patients will be instructed to self-administer the study drug approximately 12 hours prior to the planned blood collection for PK analysis. The date and time of the dose taken prior to the PK blood sampling will be collected and registered.

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, 4 or 5 additional blood samples will be collected during each visit at Week 4 and Week 16. 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: 45 min, 2.5 hours (estimated C_{max}), 4 hours and 6 hours after intake of the study drug, as shown in the figure below. An additional optional 8-hour blood sample will be collected if the patient agrees. 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: H, hour; Lab, laboratory; PK, pharmacokinetic

The plasma levels of the drug and its metabolites will be summarized descriptively by visit and time categories: 'before 12 hours', 'at 12 hours (+/- 15%), 'after 12 hours'.

A listing of PK levels will be presented by treatment group, subject number, and collection date and time.

11. Pharmacodynamics

Exploratory endpoint: Change from Baseline in skin biomarkers at Week 16 collected via tape stripping and analyzed using proteomic methods.

Stratum corneum skin samples will be collected using the tape stripping method to evaluate biomarker expression levels. Tape stripping is a minimally invasive, nonscarring approach utilizing serial adhesive films to capture the stratum corneum and the upper part of the granular layer. At Baseline, before administration of study drug, 1 lesional and 1 nonlesional area will be identified, and 20 consecutive skin samples will be collected from each area. At Week 16, the same procedure will be repeated only from the same lesional area sampled at Baseline. Details of stratum corneum skin samples' storage, and shipping procedures are provided in a separate laboratory manual. Change from Baseline in skin biomarkers will be summarized descriptively.

A listing of skin biomarker results will be presented by treatment group, subject number, and collection date and time.

12. Safety

All safety analyses will be conducted using the safety population.

Safety will be assessed based on adverse event (AE) reports, physical examination, vital signs, ECGs, clinical laboratory data, HADS, and C-SSRS using descriptive statistics.

No inferential statistical analyses are planned on the safety parameters of this study.

12.1. Adverse Events

AEs for all patients in the safety population will be included in the AE summaries.

Adverse events will be summarized by system organ class (SOC) and preferred term (PT) for each treatment and Orismilast total, based on the MedDRA dictionary version 24.0. Severity of AEs will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.

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.

Duration will be calculated for AEs that resolve as the difference between the resolution date and onset date plus 1 and expressed in days.

The summary tables will include the number of patients and the number of events. Percentages will be based on the number of patients in the safety population. For summaries by SOC and PT, a patient will be counted once at the SOC level and once at each PT within the SOC level.

For summaries by SOC, PT, and maximum severity, a patient will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, patients may only contribute once to each PT and once to each SOC level.

The summaries presenting frequency of AEs by SOC and PT will be ordered by Orismilast total descending frequency of SOC and then, within a SOC, by Orismilast total descending frequency of PT.

The following tables will be provided:

- An overall summary of the number of events and number and percentage of patients reporting TEAEs, related TEAEs (TEAEs recorded as “Relationship to study drug” = “Possibly” or Probably” or “Definitely”), serious TEAEs (TESAEs), TEAEs resulting in death, TEAEs of special interest, TEAEs leading to study drug discontinuation, TESAEs leading to study drug discontinuation, TEAEs by relationship and TEAEs by toxicity grade (including exposure adjusted incidence rates [EAIR]);.A similar summary will be presented starting within the dose titration period (initial 3 weeks).” (without EAIR).
- TEAEs overall by system organ class and preferred term (including EAIR);
- TEAEs overall by system organ class and preferred term starting within the dose titration period (initial 3 weeks)
- TEAEs by maximum toxicity grade, overall and by system organ class and preferred term;
- TEAEs by toxicity grade, overall and by system organ class and preferred term;

- TEAEs by maximum relationship to study medication, overall and by system organ class and preferred term;
- TEAEs by relationship to study medication, overall and by system organ class and preferred term;
- TEAEs leading to study drug discontinuation, overall and by system organ class and preferred term;
- TEAEs leading to study drug discontinuation, overall and by body weight at baseline system organ class and preferred term;
- TEAEs leading to study drug discontinuation, overall and by region, system organ class and preferred term; TEAE coded by MedDRA preferred term as diarrhoea, nausea, headache, dizziness and vomiting by time of onset of event;
- TEAEs of special interest, overall and by system organ class and preferred term;
- AEs starting in the 4-week Follow-up period overall by system organ class and preferred term;
- SAEs starting in the 4-week Follow-up period overall and by system organ class and preferred term;

Only TEAEs will be included in the summary tables, however separate listings for treatment-emergent AEs, non-treatment-emergent AEs, AEs starting within the dose titration period (initial 3 weeks), and AEs starting in the 4-week Follow-up period will be generated. Additional listings will be provided for deaths, AESIs, serious AEs, and AEs Leading to Study Drug Discontinuation.

12.2. Laboratory Evaluations

Safety laboratory samples for chemistry, hematology, and urinalysis will be collected at various visits. Refer to Section 9 of the Protocol for the schedule of activities indicating when the respective samples are taken.

The following parameters will be included:

Chemistry: Albumin, Alanine aminotransferase, Alkaline phosphatase, Aspartate aminotransferase, Blood urea nitrogen or urea, Creatinine, Electrolytes (sodium, potassium, chloride, calcium, phosphorus), Gamma glutamyltransferase, Lactate dehydrogenase, Total bilirubin, Direct bilirubin, and total Immunoglobulin E.

Hematology: Full and differential blood count, Hematocrit, Hemoglobin, Mean cell hemoglobin, Mean cell hemoglobin concentration, Mean cell volume, Platelet count, Red blood cell count (% reticulocytes), White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

Urinalysis: Appearance, pH, Protein, Glucose, Ketone bodies, Indicators of blood and white blood cells, Specific gravity, Urine human chorionic gonadotropin (premenopausal females only), and Urobilinogen.

Serology: HIV antibody, Hepatitis B virus, Hepatitis C virus, Hepatitis C virus RNA, Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis B surface antibody, and Follicle-stimulating hormone (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. Refer to Section 9 of the Protocol for the schedule of activities indicating when the respective pregnancy tests are performed.

All summaries will be based on results in SI (standard international system of units) units and will be output in the order listed above.

Actual values and changes from baseline in chemistry and hematology will be summarized by visit using descriptive statistics.

Shift tables, showing shifts from baseline to Week 16 relative to the normal ranges for chemistry and hematology will be provided. These summaries of normal range category changes illustrate the number and percentage of patients who fall into specified categories (Decrease to Low, Change to Normal or No Change, Increase to High) by comparing the baseline normal range category to the overall worst-case normal range category. The worst-case post-baseline row will be used to summarize the patients' overall worst-case normal range category change. The determination of the worst-case takes into account both planned and unscheduled assessments.

A liver safety analysis table summarizing values above the upper limit of normal for alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase and bilirubin will be provided.

Patients with missing baseline value are to be assumed to have a normal baseline value. Worst-case can be either High or Low. If a patient has a Decrease to Low and an Increase to High during the same time interval, then the patient is counted in both the 'Decrease to Low' and 'Increase to High' categories. If a patient was high at baseline and decreases to Low during the time interval, then the patient is counted in the 'Decrease to Low' category. Likewise, if a patient was Low at baseline and increases to High during the time interval, then the patient is counted in the 'Increase to High' category. Patients are only counted in the 'Change to Normal or No Change' category if they are:

- Normal at baseline and have no normal range High and no normal range Low values during the time interval.
- High at baseline and do not change to Low during the time interval.
- Low at baseline and do not change to High during the time interval.

All laboratory results will be included in data listings. Abnormal results for chemistry, hematology, and urinalysis will be listed separately. Laboratory results for serology and pregnancy tests will be listed only.

12.3. Vital Signs

Heart rate (beats per minute [bpm]), respiratory rate (breaths per minute), systolic and diastolic blood pressure (mmHg), BMI (kg/m^2)_and body temperature (degree Celsius) will be measured at different visits as per the SoA in Protocol Section 9.

The conversion for temperature is as follows: Temperature (in °C) = 5/9 (Temperature [in °F]-32).

Actual values and changes from baseline in vital sign measurements will be summarized by visit using descriptive statistics.

All vital signs will be provided in data listings.

12.4. ECG

A 12-lead, resting ECG will be obtained at the visits indicated in the SoA in Protocol Section 9.

Actual values and changes from baseline in ECG parameters (heart rate [bpm], PR Interval [msec], QRS Interval [msec], RR Interval [msec], QT Interval [msec], and QTc [msec]) will be summarized by visit using descriptive statistics. An outlier analysis will be performed that will summarize by treatment the frequency and percentage of participants who meet any of the following outlier criteria at each visit:

- QTc interval > 450 msec.
- QTc interval > 480 msec.
- QTc interval > 500 msec.
- QTc interval increases from baseline > 30 msec.
- QTc interval increases from baseline > 60 msec.

This outlier analysis will be repeated summarizing frequency and percentage of participants by treatment who meet any of these outlier criteria at any time during the study.

All ECG parameters, including overall ECG evaluation, will be provided in data listings.

12.5. Physical Examination

A complete physical examination will be performed at Screening and Week 16. A limited physical examination will be conducted at Day 1 and Weeks 4, 8, 12, and 20.

A shift table to demonstrate changes in physical examination from baseline to all post-baseline visits by treatment will be generated.

Physical examination data will be listed.

12.6. The Hospital Anxiety and Depression Scale

The HADS is a patient reported outcome (PRO), comprises 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. HADS will be collected at different time points as per the SoA in Protocol Section 9.

Actual values and changes from baseline in HADS scores (depression, anxiety, and total) will be summarized by treatment group. A summary table presenting the frequency and percentage of participants by treatment group within categories (< 7, 8 – 10, 11 – 14 and 15 – 21) for anxiety and depression at each visit will be generated. A shift table to demonstrate changes in anxiety total score and depression total score from baseline to all post-baseline visits by treatment will be generated.

HADS scores, questions, and answers will be provided in data listings.

12.7. 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 3 versions:

For this study we are using the following versions: For screening: Lifetime/Recent version and for the remaining part of the study: Since Last Visit version.

C-SSRS will be collected at different time points as per the SoA in Protocol Section 9.

The C-SSRS categories have been re-ordered from the actual scale to facilitate the definitions of the endpoints, and to enable clarity in the presentation of the results: Category 1 – Wish to be Dead, Category 2 – Non-specific Active Suicidal Thoughts, Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act, Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan, Category 5 – Active Suicidal Ideation with Specific Plan and Intent, Category 6 – Preparatory Acts or Behavior, Category 7 – Aborted Attempt, Category 8 – Interrupted Attempt, Category 9 – Actual Attempt (non-fatal), Category 10 – Completed Suicide.

Suicidal ideation is defined as a “yes” answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS. Suicidal behavior is defined as a “yes” answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS. Suicidal ideation or behavior is defined as a “yes” answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

A summary table presenting number of patients with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent will be generated, as well as a shift table to demonstrate changes in C-SSRS suicidal ideation scores from baseline to all post-baseline visits by treatment. Patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent based on the C-SSRS will be listed.

13. Interim Analyses

No interim analysis is planned in this study.

14. Changes from Analysis Planned in Protocol

The randomized population is not specified in protocol, but this population is added for listings and disposition summaries.

Exploratory endpoint added: Patients achieving 100% reduction in EASI (EASI100) response at Weeks 2, 4, 8, 12, 16, and 20.

15. Reference List

16. Programming Considerations

Computer-generated TFL output will adhere to the following specifications.

All TFLs, and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA).

16.1. General Considerations

- A separate SAS program will be created for each output
- Each output will be stored in a separate file
- Output files will be delivered in Word format and portable document format (pdf)
- Numbering of TFLs will follow ICH E3 guidance

16.2. Table, Figure, and Listing Format

16.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- Legends will be used for all figures with more than one variable, group, or item displayed
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below)
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate

16.2.2. Headers

- All output will have the following header at the top left of each page:

- UNION therapeutics A/S Protocol UNI50001-202 (Syneos Health study number 7025424)

- Draft/Final Run <*date*>
- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)
- The date the output was generated will appear along with the program name as a footer on each page

16.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis population will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Safety population)

16.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment
- For numeric variables, include ‘unit’ in column or row heading when appropriate
- Analysis population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis population
- The order of treatments in the tables and listings will be Placebo first.

16.2.5. Body of the Data Display

16.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and

- Numbers containing fractional portions will be decimal aligned.

16.2.5.2. *Table Conventions*

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more patients
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

n	xxx
Mean (SD)	xx.x (x.xx)
Median	xx.x
Min, Max	Xx, xx

- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of patients in the analysis population for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC3 level), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'

- The percentage of patients will normally be calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, a footnote or programming note will be added describing whether the patient is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

16.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time

- Missing data will be represented on patient listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on patient listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the patient will be output as 'N/A', unless otherwise specified

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study

- Units will be included where available

16.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display

- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible

- Patient specific footnotes are avoided, where possible

- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z')

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

17. Quality Control

SAS programs are developed to produce output such as analysis data populations, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907).

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908), the Developing Statistical Programming and Validation Plan SOP (3920) End-to-End Process of the Production of Study Data Tabulation Model (SDTM) SOP (3921), End-to-End Process of the Production of Analysis Datasets and Tables, Figures and Listings SOP (3922), describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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	14.1.1.3.3	Cumulative Proportion of Patients with Discontinuation of Study Treatment by Treatment Group as a Function of Time Since Randomization	ITT Population
	14.1.1.3.4	Cumulative Proportion of Patients with Discontinuation of Study Treatment by Treatment Group and Reason for Discontinuation as a Function of Time Since Randomization	ITT Population
	14.1.4.5	Cumulative Proportion of Patients over Time Receiving Disallowed Medication that May Influence Efficacy	ITT Population
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	14.2.1.1.7	LSMean (+/-SE) of Percentage Change in Eczema Area and Severity Index (EASI) Score from Baseline at Weeks 4, 8, 12, 16, and 20 Primary Efficacy Analysis: Graphically Presented – Multiple Imputation	ITT Population
	14.2.2.3.6	Investigator Global Assessment for AD (IGA-AD) over Time	ITT Population
	14.2.2.3.7	Percentage of Patients Achieving a Score of Clear (0) or Almost Clear (1) and an at least 2-point Improvement in IGA-AD over Time	ITT Population
	14.2.2.4.2	Percentage of Patients with EASI75 Response over Time	ITT Population
	14.2.2.5.2	Percentage of Patients with EASI50 Response over Time	ITT Population
	14.2.2.5.5	Percentage of Patients with EASI90 Response over Time	ITT Population
	14.2.2.5.7	Percentage of Patients with EASI100 Response over Time	ITT Population
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	14.2.2.7.4	Change from Baseline in Peak Pruritus Numerical Rating Scale (NRS) Score over Time	ITT Population
	14.2.2.8.2	Percentage of Patients achieving at least a 4-point improvement in the peak pruritus NRS over Time	ITT Population
	14.2.2.9.3	Affected Body Surface Area (BSA) over Time	ITT Population
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Header	Figure Number	Name	Analysis Population
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	14.2.2.12.3	Patient Global Impression of Severity (PGIS) Score over Time	ITT Population
	14.2.2.12.4	Change from Baseline in Patient Global Impression of Severity (PGIS) Score over Time	ITT Population
	14.2.2.13.3	Patient Global Impression of Change (PGIC) Score over Time	ITT Population
	14.2.2.14.3	Sleep Disturbance NRS Score over Time	ITT Population
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	14.2.2.15.3	Skin Pain NRS Score over Time	ITT Population
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20. Index of Listings

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Header	Listing Number	Name	Analysis Population
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21. Shells

The TFL shells will be provided as a separate document.

22. Appendices

Not Applicable.