FINAL CLINICAL STUDY PROTOCOL

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 Atopic Dermatitis

Protocol Number: UNI50001-202

IND Number:	129386
EudraCT Number:	2021-006707-15
Name of Investigational Product:	Orismilast
Phase of Development:	2b
Indication:	Treatment of moderate to severe atopic dermatitis
Sponsor:	UNION therapeutics A/S Tuborg Havnevej 18 DK-2900 Hellerup, Denmark Tel: +45 61 77 74 35
Sponsor Signatory:	[redacted] Tel: [redacted] Email: [redacted]
Protocol Version:	3.0
Protocol Date:	14. April 2023

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 Atopic Dermatitis

Protocol Number: UNI50001-202

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

[redacted]

Signature

Date (DD-Mmm-YYYY)

Biostatistician

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Date (DD-Mmm-YYYY)

Coordinating Investigator

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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 appendixes, 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>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

1 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 Atopic Dermatitis
Protocol Number:	UNI50001-202
Investigators/Study Sites:	48 centers in Europe and the United States
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 atopic dermatitis (AD). **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. **Exploratory Objectives**: The exploratory objectives are to: • Evaluate pharmacokinetic (PK) and pharmacodynamic parameters relevant to AD • Evaluate the effect of orismilast on the pulmonary status and course of the disease in patients with asthma
Study Endpoints:	**Primary endpoint:** • The primary endpoint of this study is the percentage change in Eczema Area and Severity Index (EASI) score from Baseline at Week 16. **Key secondary endpoints:** The key secondary endpoints are as follows: • 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 Investigator Global Assessment for AD (IGA-AD) at Week 16 **Other secondary endpoints:** The other secondary endpoints of this study are as follows: • 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 numerical rating scale (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 • Change from Baseline in affected body surface area (BSA) at Weeks 2, 4, 8, 12, 16, and 20

	• Change from Baseline in Dermatology Life Quality Index score at Weeks 8, 16, and 20 • Change from Baseline in Patient Oriented Eczema Measure score at Weeks 2, 4, 8, 12, 16, and 20 • Change from Baseline in Patient Global Impression of Severity score at Weeks 2, 4, 8, 12, 16, and 20 • Change from Baseline in Patient Global Impression of Change 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 **Safety endpoints:** The safety endpoints of this study are as follows: • The occurrence, severity, and seriousness of treatment-emergent adverse events 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 electrocardiogram (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 Hospital Anxiety and Depression Scale score at each visit except Week 1 • Columbia-Suicide Severity Rating Scale (C-SSRS) score at each visit except Week 1 **Exploratory endpoints:** The exploratory endpoints of this study are as follows: • Change from Baseline in skin biomarkers at Week 16 collected via tape stripping and analyzed using proteomic methods • 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 • Plasma levels of the drug and its metabolites at Weeks 4, 8, and 16 • Change from Baseline in pulmonary status NRS in patients with asthma at Weeks 4, 8, 12, 16, and 20
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 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 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 twice daily (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 (End-of-Treatment 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%, EASI score of at least 16, and 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 Baseline and at each visit from Week 2 onwards, EASI, affected 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 post inflammatory 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 NRS at each visit from baseline to end of the treatment. Disease symptoms will be assessed by Patient Oriented Eczema Measure 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 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 and Patient Global Impression of Change scores at Baseline and 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, adverse events (AEs), laboratory and vital sign assessments, physical examination including body weight and height, 12-lead ECG, and mood change evaluations by the patient (Hospital Anxiety and Depression Scale score) and suicidal behavior and ideation evaluation by the Investigator (C-SSRS). Before administration of the study drug at Baseline and Weeks 4, 8, and 16, blood will be collected for orismilast and the major human metabolite LEO 40815 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.
Selection of Patients	Main Inclusion Criteria: Patients are eligible to be included in the study only if all of 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 at least 18 years of age 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 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. Main Exclusion Criteria: 1. Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study: 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 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 [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 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 phosphodiesterase-4 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: • Absolute neutrophil count of less than the lower normal range of the Central Laboratory (LNR) i.e. 1.7 x 10^9/L (1700/mm^3) • Hemoglobin of less than 10.0 g/dL or hematocrit less than 30% • Platelet count of less than 100,000 mm^3 • Absolute lymphocyte count of less than the lower normal range of the Central Laboratory (LNR) i.e. 0,9 x 10^9/L (900/mm^3) • 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 • Alanine aminotransferase or aspartate aminotransferase greater than 2.5 × the ULN • 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 questions 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
Planned 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 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 of approximately 10%, an additional 22 patients will be randomized.
Investigational Therapy:	Name: orismilast Unit doses strength and dose formulation: 20 mg (2 × 10-mg tablets), 30 mg (1 × 30-mg tablet and 1 placebo tablet), and 40 mg (1 × 10-mg tablet and 1 × 30-mg tablet) Route and frequency of administration: oral, 2 tablets BID (approximately every 12 hours) 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:	Blood samples for PK analysis of orismilast and its major metabolite levels will be collected at the time points indicated in the Schedule of Assessments (Table 4). The actual date and time of each blood sample collection will be recorded. Patients will be offered optional participation in specific blood sampling for calculation of PK profiles. Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual. The concentration of study drug and main metabolite 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.
Pharmacodynamics:	Stratum corneum skin samples will be collected at the time points indicated in the Schedule of Assessments (Table 4) using the tape stripping method to evaluate biomarker expression levels. Tape stripping is a minimally invasive, nonscarring approach using 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 areas sampled at Baseline. Details of stratum corneum skin samples storage, and shipping procedures are provided in a separate laboratory manual.
Statistical Methods and Planned Analyses:	Details of the statistical analysis will be provided in a separate Statistical Analysis Plan. 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 intent-to-treat (ITT) population. Missing data for primary and key secondary endpoints will be handled with the multiple imputation method. For a categorical efficacy endpoint based on a continuous variable, the multiple imputation will be first done for the continuous variable, then the category will be determined using the imputed values. Analyses will be repeated on the per-protocol population for primary and key 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 EASI score, will be analyzed using an analysis of covariance with treatment group as the factor and Baseline EASI score as the covariate. The mixed model for repeated measures may 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% CI of the difference between each active treatment and placebo will be calculated. The primary analysis set will be the ITT population with a multiple imputation approach to handle missing values. The same analyses will be repeated backward at earlier visits. The key secondary and other binary endpoints (IGA-AD success, EASI50, EASI75, EASI90, and 4-point improvement in the peak pruritus NRS) will be analyzed using the Mantel-Haenszel (MH) test, comparing each active treatment group with placebo in the ITT population. 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-AD scores/full scale will be analyzed using the MH test and the row mean score statistics with the ridit transformation. The other continuous secondary endpoints will be analyzed using mixed model for repeated measures. The above endpoints (EASI changes and percentage changes, IGA-AD success, EASI50, EASI75, and EASI90) 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 occurs. All exploratory endpoints, including change from baseline in pulmonary status NRS in patients with asthma and skin biomarkers at Week 16, and patients achieving at least a 2-point improvement in peak pruritis NRS from baseline will be summarized descriptively in the ITT population or a subgroup. All safety analyses will be conducted using the safety population. AE data will be presented and tabulated according to Medical Dictionary for Regulatory Activities 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, urinalysis and hematology) parameters, 12-lead ECG values, 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. The plasma levels of the drug and its metabolites will be summarized descriptively by visit in this study. No interim analysis is planned in this study.

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
AUC	area under the curve
BID	twice daily
BSA	body surface area
cAMP	cyclic adenosine monophosphate
C_{max}	maximum (or peak) serum concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50	50% reduction in Eczema Area and Severity Index
EASI75	75% reduction in Eczema Area and Severity Index
EASI90	90% reduction in Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
GCP	Good Clinical Practice
GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
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	interferon
IGA-AD	Investigator Global Assessment for Atopic Dermatitis
IL	interleukin
IRB	institutional review board
ITT	intent-to-treat
IWRS	Interactive Web Response System

Abbreviation	Definition
JAK	Janus kinase inhibitors
LS	least squares
MH	Mantel-Haenszel
NRS	numerical rating scale
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic
PDE	phosphodiesterase
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic
POEM	Patient Oriented Eczema Measure
PRO	patient-reported outcomes
PT	preferred term
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
Th	T helper
t_{max}	time drug was present at the maximum concentration in serum
TNF	tumor necrosis factor
TSS	total sign score
WOCBP	women of childbearing potential
ULN	upper limit of normal

4 INTRODUCTION

4.1 Background on Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory disease characterized by eczematous lesions and intense itching. Inflammatory infiltrates in these cutaneous lesions consist of T-lymphocytes, neutrophils, eosinophils, monocytes, macrophages, and mast cells (Cooper KD, 1994). High levels of phosphodiesterase (PDE)-4 activity are also found in leukocytes of these patients (Butler JM, 1983). AD usually begins in childhood. It is estimated that 50% of patients with AD have additional allergy symptoms within the first year of life, and up to 85% have symptoms that begin before the age of 5 years. Patients often outgrow the condition in late childhood, with approximately 70% of patients experiencing spontaneous remission before adolescence. Early childhood AD, on the other hand, is often the first sign that a child may develop asthma and/or allergic rhinitis (hay fever) later in life (Spergel JM, 2010). The prevalence of adult AD has been reported to range from 2.1% to 4.9% across countries, and patients with severe AD represent a small proportion of the overall AD population regardless of measure or region (Barbarot S, 2018).

There is a limited number of treatments available for moderate to severe AD. Current treatments include phototherapy (eg, ultraviolet A light with or without psoralen, ultraviolet B light narrowband or broadband) and systemic immunotherapies (eg, corticosteroids, cyclosporine, methotrexate, and dupilumab) (Slater NA, 2015; Newsom M, 2020). More recently, systemic therapy options for moderate to severe AD have increased after the approval of the Janus kinase inhibitors baricitinib and upadacitinib and the anti–interleukin (IL)-13 monoclonal antibody tralokinumab (Bieber T, 2021).

AD is treated primarily with topical therapies, mainly with intermittent, preventive application of topical corticosteroids and/or topical calcineurin inhibitors, paired with daily emollient use (McGregor SP, 2017). Intermittent topical corticosteroid use poses risk of corticosteroid-associated adverse effects like skin atrophy, striae formation in sensitive or thin-skinned areas, and systemic effects that limit their long-term use (Hanifin J, 2002). The rate of long-term adherence to topical therapy, however, is low (Snyder A, 2015). Off-label use of other conventional systemic oral immunomodulatory agents, such as azathioprine and methotrexate, in adults with AD can be effective, but patients have reported adverse events (AEs) or ineffectiveness as reasons for discontinuation of treatment; use of these drugs poses well-known safety limitations and requires regular laboratory monitoring (Roekevisch E, 2018; Sidbury R, 2014). Moderate to severe AD is often refractory to first-line topical treatments; while systemic immunosuppressants are efficacious, they have significant adverse effects. The desire for new treatments along with an improved understanding of the pathophysiology of AD has spurred the development of novel treatments targeting IL-13, IL-31, and the Janus kinase family of proteins (Silverberg JI, 2017). Thus, there is interest in investigating a systemic approach for more severe forms of AD.

PDEs constitute a superfamily of enzymes catalyzing the hydrolysis of the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate that play key roles in mediating biological responses generated by a variety of extracellular signals. Eleven families of PDE enzymes have been identified, with the PDE4 family constituting approximately 20 members (Houslay MD, 2005). PDEs represent the only cellular pathway for the degradation of cyclic nucleotides, which emphasizes their critical role in the regulation of the intracellular levels of these secondary messengers and, consequently, various functional responses of cells (Dastidar SG, 2007). PDE4 is a cAMP specific PDE expressed by immune and inflammatory cells, including T-lymphocytes, neutrophils, eosinophils, monocytes, dendritic cells, and macrophages (Spina D, 2008). In these cells, PDE4 is the predominant PDE form, and PDE4 inhibitors increase cAMP levels. High cAMP levels tend to decrease proliferation and cytokine production, whereas low concentrations have the opposite effect. In allergic skin disease, PDE4 inhibitors inhibit the migration of skin dendritic cells, and this inhibition is accompanied by an inhibition of matrix metalloproteinase 9 activity in epidermis and dermis. Furthermore, cytokine secretion (tumor necrosis factor [TNF]-α, IL-1β and IL-12) of human dendritic cells is inhibited by PDE4 inhibitors, and an inhibition of T cell activation is also demonstrated *in vitro*. Both T helper (Th)1 and Th2 cytokines are reduced by PDE4 inhibitors *in vitro* and in inflamed murine skin (Jin SL, 2012).

Inhibition of PDE4 has therapeutic potential in the treatment of psoriasis and other skin diseases with an immuno-inflammatory component (Dastidar SG, 2007). Several PDE4-specific inhibitors are in late stages of clinical development or have recently been marketed. For example, the oral PDE4 inhibitor roflumilast (Daxas®/Daliresp®) is approved in the United States and Europe to reduce the risk of exacerbation in patients with chronic obstructive pulmonary disease and chronic bronchitis (Roflumilast Summary of Product Characteristics). The oral PDE4 inhibitor apremilast (Otezla®) is approved in the United States and Europe for psoriatic arthritis and psoriasis (Apremilast Summary of Product Characteristics) and it has been studied for AD and other chronic inflammatory diseases (Samrao A, 2012). Anacor Pharmaceuticals (a subsidiary of Pfizer) has developed a topical PDE4 inhibitor for treatment of mild to moderate AD (Crisaborole [AN 2728]), which has been approved in the United States (under the tradename Eucrisa®) and in Europe (under the tradename Staquis®) (Crisaborole – Pfizer Adis Insight; Staquis – Assessment Report).

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 and apremilast some years later. Both therapies had tolerability issues affecting, primarily but not exclusively, the gastrointestinal (GI) tract, characterized by nausea and diarrhea. 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 over 1 month) to reduce side effects (Roflumilast Summary of Product Characteristics; Apremilast Summary of Product Characteristics).

4.1.1 Rationale for the Clinical Development of Orismilast for Atopic Dermatitis

A study in Japan looked at the effects of PDE4 inhibitors, cilomilast, roflumilast, and rolipram on induced dermatitis in mice models. Cilomilast, roflumilast, and, to a lesser extent, rolipram suppressed myeloperoxidase activity, a quantitative index of neutrophils accumulating in skin associated with chronic inflammation. After 18 days of treatment, cilomilast and roflumilast showed a 47% and 36% recovery in skin severity score, respectively. This effect was more potent than the 25% recovery seen with cyclosporine A, especially in the earlier stages of treatment (Harada D, 2008).

An open-label prospective trial of oral apremilast in 16 patients with moderate to severe AD was conducted to assess the safety, efficacy, and possible mechanism of action of apremilast in AD (Samrao A, 2012). The study showed a trend towards an improvement of AD following treatment with apremilast. One cohort consisted of 6 patients treated with apremilast 20 mg twice daily (BID) for 3 months, while the second cohort consisted of 10 patients treated with apremilast 30 mg BID for 6 months. Patients in the study were required to remain on topical triamcinolone acetonide 0.1% for 2 weeks before the start of the study as well as throughout the trial. Nausea, the most common AE, appeared to be dose related was rated as mild and improved over the course of the study in all patients. After 3 months of treatment, a significant reduction of itch from baseline and improvement in quality of life (assessed via Dermatology Life Quality Index [DLQI] score) was seen in cohort 1 (P =.02 and P =.003, respectively), while Eczema Area and Severity Index (EASI) and DLQI scores improved in cohort 2 (P =.008 and P =.01, respectively). At 6 months, statistically significant improvement was seen in all outcomes in cohort 2, including the itch visual analog scale (P =.03), DLQI (P =.03), and EASI (P =.002).

A placebo-controlled study showed only modest efficacy for oral apremilast 40 mg BID versus placebo, which was not seen at the 30 mg BID dose. In addition, there were increased rates of AEs (6 cases of cellulitis) in the apremilast 40 mg BID group versus none in the placebo or 30 mg BID group, and thus, treatment with 40 mg BID was halted in this trial (Simpson EL, 2019).

4.2 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 AD. During initial development (Phase 1/2a), different oral formulations were 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 was selected for further development. This new formulation was shown to improve GI tolerability without change in systemic exposure.

4.2.1 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 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 the human ether-à-go-go–related gene ion channel current amplitudes at 10 µM.

The pharmacokinetics (PK) of orismilast have been investigated in mice, rats, rabbits, and minipigs after administration by oral gavage. In rats, the area under the curve (AUC) and maximum (or peak) serum concentration (C_{max}) generally increased in proportion to dose in the tested range (0.5 to 1.75 mg/kg), with female rats having AUC and C_{max} values 1.5 to 3 times higher than those in male rats. In mice, rabbits, and minipigs, AUC and C_{max} increased less than, or proportional to, the investigated doses (5 to 500 mg/kg, BID dosing, and 1.0 to 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 to 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 feces in rats and minipigs.

The *in vitro* plasma protein binding of orismilast was low to moderate (35% to 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 human ether-à-go-go–related gene tail current recorded from human embryonic kidney-293 cells gave a half maximal inhibitory concentration value of 11.4 µM. In conscious telemetered minipigs, oral administration of orismilast produced no treatment-related effects on heart rate; body temperature (measured in the ear); 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.

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 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.

4.2.2 Clinical Studies

As of 01 October 2021, the orismilast clinical development program consists of 8 completed trials with an oral formulation (including 7 Phase 1 trials in healthy subjects and 1 Phase 2a trial in patients with moderate to severe plaque-type psoriasis) and 1 Phase 1 trial with a topical formulation.

Oral program: 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; trial LP0058-1362), a PK trial evaluating the PK and safety/tolerability profiles of several new formulations (trial LP0058-1442), 2 drug-drug interaction trials using an orismilast immediate-release tablet formulation and midazolam (trials LP0058-1267 and LP0058-1324), and a proof-of-concept Phase 2a trial in psoriasis using an immediate-release tablet formulation (trial LP0058-1072). Only one trial (LP0058-1442) used the modified-release tablet selected for further development.

Topical program: One Phase 1 proof-of-concept study (LP0108-1082) was conducted in male adult patients with mild to moderate AD.

4.2.2.1 Clinical Pharmacology

Oral Program

After single and multiple oral dosing of up to 60 mg BID of the initial capsule formulation, in the fasted state or after a standard breakfast, orismilast was steadily absorbed with a median time drug was present at the maximum concentration in serum (t_{max}) of 2 to 4 hours. Systemic exposure to orismilast increased in an approximately dose-proportional manner. Estimates of elimination half-lives varied across studies, from 4 to 6 hours (for dose levels up to 30 mg 3 times a day) and up to 10 hours (for the 60-mg BID 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 $AUC_{0-\infty}$ 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% to 75% lower than to 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, no differences in the PK profile of orismilast between races (LP0058-1362) or sex (LP0058-1114) has been identified.

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 BID compared with midazolam alone (geometric means of 132% for AUC_{0-t} and 137% for C_{max}). These results classify orismilast as a weak inhibitor of CYP3A4.

Pharmacodynamic (PD) evaluation from trial LP0058-S01 using an ex vivo cytokine release assay indicated that orismilast inhibited the secretion of TNF-α and interferon (IFN)-γ. Maximum inhibition generally occurred between 4 to 6 hours post dose. 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% to 70% for TNF-α and 52% to 77% for IFN-γ levels across dose groups receiving 10, 20, and 30 mg orismilast 3 times a day. In accordance, reduced levels of TNF-α, IFN-γ, macrophage inflammatory protein-1α, and macrophage inflammatory protein-1βwere observed in lipopolysaccharide -stimulated blood from patients treated with orismilast in the LP0058-1072 trial, suggesting that pharmacologically relevant levels of orismilast were present.

4.2.2.2 Efficacy in Atopic Dermatitis

A single-center, prospective, randomized, vehicle-controlled, double-blinded, intra-individual trial was conducted to compare the effect of orismilast cream 20 mg/g and cream vehicle when applied BID for 3 weeks on 2 small treatment areas in adults with mild to moderate AD (right/left design, on symmetrically located lesions). Efficacy assessments were performed at baseline, Days 8, 15, and 22 on site with the primary endpoint being the total sign score (TSS) assessed at the End-of-Treatment (EOT). The TSS was defined as the sum of the individual sign scores: erythema, edema/papulation, oozing/crusting, excoriations, lichenification, and dryness. A total of 30 subjects were randomized and treated with at least 1 application/dose of orismilast cream; 29 subjects completed the trial (ie, attended visit 5), but all 30 subjects did complete the full treatment period. The TSS at the end of the treatment was 5.2 (least squares [LS] mean: 5.1) for orismilast cream 20 mg/g and 6.2 (LS mean: 6.3) for the cream vehicle. This corresponds to a reduction in disease severity (TSS) of approximately 39% in the orismilast cream 20 mg/g treatment and of approximately 25% for the vehicle treatment. The vehicle-effect subtracted difference in LS means accounted to -1.2 (95% CI ranging from -2.2 to -0.3), providing evidence for a statistically significant difference (P =.014) between both treatments. This result was confirmed by the analyses of the secondary efficacy endpoints. The administration of orismilast cream 20 mg/g was found to be safe and well tolerated in patients with AD. No clinically

relevant effects in any vital sign parameters, ECG, or laboratory safety values (hematology, biochemistry, urinalysis) were detected.

4.2.2.3 Efficacy in Other Dermatological Disorders

To date, 1 efficacy trial (LP0058-1072) with orismilast immediate-release tablets has been completed. A total of 36 patients with moderate to severe plaque-type psoriasis were randomized in the trial in a 1:1 ratio to treatment with either 30 mg orismilast or placebo, administered orally as 3 tablets BID 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 patients treated with orismilast tablets (LS mean: 7.1) compared with patients in the placebo group (LS mean: 13.1). Mean PASI at entry was 14.9. A higher proportion of patients achieved a 75% improvement in PASI in the orismilast group (44.4%) versus placebo (5.6%; P =.019). In addition, treatment success (defined as clear or almost clear) according to Physician's Global Assessment of disease severity at Week 16 was higher in the orismilast group (7 of 18 patients, 38.9%) than in the placebo group (1 of 18 patients, 5.6%). The estimated itch score was numerically lower at Week 16 in the orismilast group (LS mean: 3.4) compared with the placebo group (LS mean: 5.7).

Approximately half of the patients 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 effect on the estimated efficacy, it was not considered to disqualify the clear difference observed between the 2 treatments.

4.2.2.4 Safety

Extent of Exposure

As of 01 October 2021, the oral orismilast clinical development program for an oral formulation consists of 8 completed trials including 7 Phase 1 trials in healthy subjects and 1 Phase 2a trial in patients with moderate to severe plaque-type psoriasis. There are 343 participants in the 8 completed trials. There were 307 healthy subjects in Phase 1 trials, 274 of whom were exposed to orismilast, and 36 patients with moderate to severe plaque-type psoriasis in the Phase 2a trial, 18 of whom were exposed to orismilast. Of 343 participants, orismilast was given to 290 patients, while the other 53 patients received placebo. Among the 290 patients, 171 patients received a single dose and 119 patients received multiple doses of orismilast (up to 16 weeks). Only 1 study examined the new modified-release formulation in 63 healthy subjects (see Section 4.3).

Safety Profile

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 in trial LP0058-S01. Orismilast was moderately well tolerated in multiple doses up to 50 mg BID, after

gradual up-titration to the 50 mg BID level over 8 days in trial LP0058-1114. In both studies LP0058-S01 and LP0058-1114, poor tolerability at the 60-mg dose level was due to an increased incidence and severity of GI AEs. This was probably 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 BID level but was poorly tolerated when up-titrated to the 40-mg and 50-mg BID levels in trial LP0058-1267. Six patients were withdrawn from the trial by the Investigator because of AEs. Likewise, in the LP0058-1072 trial, orismilast tablets (30 mg BID) were poorly tolerated in patients with moderate to severe plaque-type psoriasis. AEs leading to withdrawal from the trial were reported for 50% of the patients 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 AEs (SAEs) were reported across all trials; 3 SAEs in 3 patients in the LP0058-1072 trial in patients with moderate to severe plaque-type psoriasis and 2 SAEs in 1 patient in the LP0058-1324 trial. In the LP0058-1072 trial, 2 patients 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 patient in the placebo group had 1 SAE ("condition aggravated", relating to pre-existing Scheuermann's disease and considered not related to the treatment). In the LP0058-1324 trial, 1 patient-reported SAEs (abdominal pain and abdominal cramps, considered possibly related to the treatment).

The reported AEs were consistent with reports from other PDE4 inhibitors with nausea, diarrhea and headache being the most frequently side effects reported. Most 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 doses 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). The GI tolerance appears to be improved with titration and low-fat meals.

Data from 2nd generation modified release tablet from the unblinded phase 2 trial UNI50001-203 (under reporting) in psoriasis indicate that the side effect profile of orismilast, with diarrhoea, nausea and headache, is similar to the two marketed oral PDE4-inhibitors (apremilast, roflumilast). The majority of these adverse events had an onset during the initial 4 weeks of treatment and very few of these events had an onset after 8 weeks of treatment.

In addition, seven cases of elevated ALT were observed and one patient in the orismilast 40 mg group had self-injurious behavior without suicidal intent at week 16. No deaths or serious infections were reported in UNI50001-203.

4.3 Clinical Risks/Benefits of Orismilast

4.3.1 Common PDE-4inhibition related side effects

Data from 2nd generation modified release tablet from the unblinded phase 2 trial UNI50001-203 (under reporting) in psoriasis indicate that the side effect profile of orismilast, with diarrhoea, nausea and headache, is similar to the two marketed oral PDE4-inhibitors (apremilast, roflumilast). The majority of these adverse events had an onset during the initial 4 weeks of treatment and very few of these events had an onset after 8 weeks of treatment. Thus, it is important that patients are adequately informed about these common side effects, and that the side effects are handled similarly to how they are handled for e.g. apremilast (Tello ED).

Occurrence and severity of GI disorders will be identified by monitoring the patients for any signs of abdominal discomfort, abdominal distension, abdominal pain, nausea, vomiting, loss of appetite, and diarrhea. Depending on their severity, these adverse events may qualify as an AE of special interest (AESI). On the basis of the occurrence of GI or other AEs considered to have 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 (see Section 8.3.1).

4.3.2 Monitoring of Cardiovascular, Psychiatric, Hepatic, and Metabolic Risks

In the unblinded phase 2 trial UNI50001-203 (under reporting) in psoriasis, seven cases of elevated ALT were observed, and one patient in the orismilast 40 mg group had self-injurious behavior without suicidal intent at week 16. No deaths or serious infections were reported in UNI50001-203. Hepatic laboratory parameters will be monitored. All patients will be monitored for any cardiovascular manifestations using vital signs and 12-lead ECG at scheduled visits. Drug class potential effects, such as weight loss and major depression, will be monitored during the study. Patients 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 the 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.

4.3.3 Tape Stripping

Risks associated with skin tape stripping, theoretically, include the rare possibility of an allergic reaction to the tape or a skin infection. The risk of skin infection is extremely low because only superficial skin layers are removed. A bandage could be applied to the area of tape stripping to reduce the small likelihood of an infection.

4.3.4 Stopping of Current Treatment

Risks associated with stopping the use of protocol-prohibited medications/procedures may include worsening of the condition being treated and will be reported as such. In an effort to

minimize these risks, patients with moderate to severe AD who may have difficulty tolerating periods without medication/procedure will be excluded from participating in the study, per exclusion criteria (see Section 7.2). 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.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of orismilast may be found in the recent version of the investigator's brochure.

4.4 Study Rationale

PDE4 inhibitors have demonstrated efficacy in psoriasis and/or 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 moderate to severe AD that requires a systemic therapeutic approach.

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 versus placebo administered orally BID over a period of 16 weeks in patients with moderate to severe AD. Efficacy and patient outcome will be assessed through a set of validated measures for AD. In addition, safety, PK, and 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.

4.4.1 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 subjects 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 subjects 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.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 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 AD.

5.1.2 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.

5.1.3 Exploratory Objectives

The exploratory objectives are to:

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

5.2 Study Endpoints

5.2.1 Primary Endpoint

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

5.2.2 Secondary Endpoints

5.2.2.1 Key Secondary Endpoints

The key secondary endpoints are as follows:

- 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 Investigator Global Assessment for AD (IGA-AD) at Week 16

5.2.2.2 Other Secondary Endpoints

The other secondary endpoints of this study are as follows:

- 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 numerical rating scale (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
- Change from Baseline in affected body surface area (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 Patient Oriented Eczema Measure (POEM) score at Weeks 2, 4, 8, 12, 16, and 20
- Change from Baseline in Patient Global Impression of Severity (PGIS) score at Weeks 2, 4, 8, 12, 16, and 20
- Change from Baseline in Patient Global Impression of Change (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

5.2.3 Safety Endpoints

The safety endpoints of this study are as follows:

- 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

5.2.4 Exploratory Endpoints

The exploratory endpoints of this study are as follows:

- Change from Baseline in skin biomarkers at Week 16 collected via tape stripping and analyzed using proteomic methods
- 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
- Plasma levels of the drug and its metabolites at Weeks 4, 8, and 16

- Change from Baseline in pulmonary status NRS in patients with asthma at Weeks 4, 8, 12, 16, and 20.

6 INVESTIGATIONAL PLAN

6.1 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 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.

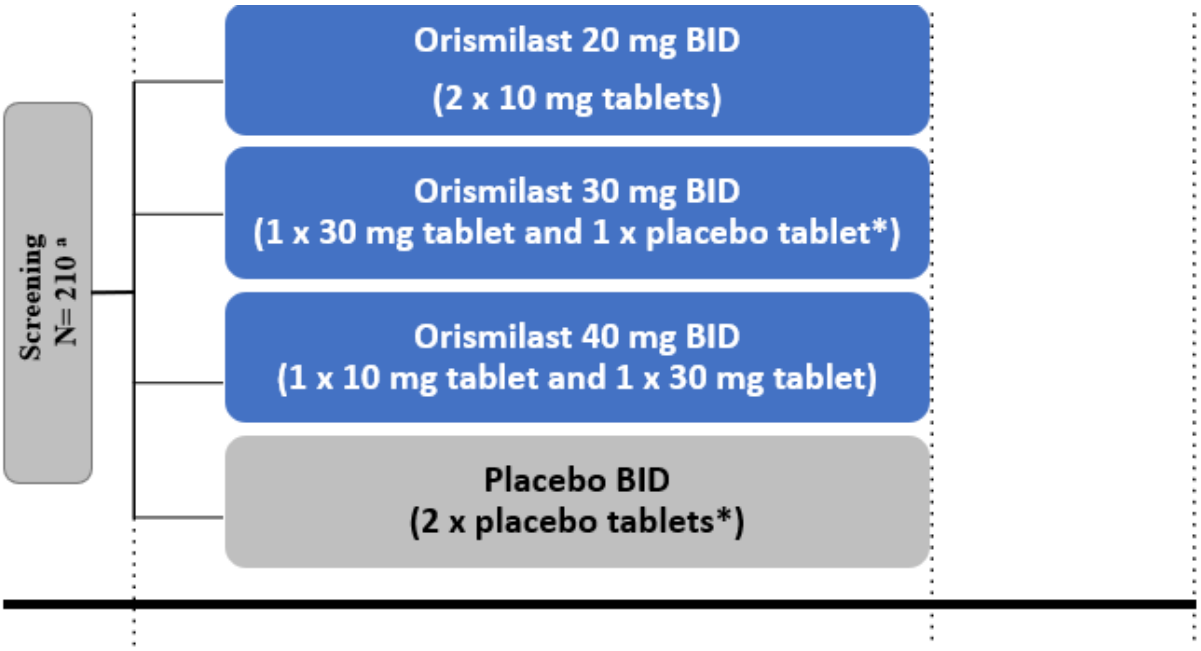
Patients who have been diagnosed with moderate to severe AD for a minimum of 1 year (before the Screening visit) using the Hanifin and Rajka criteria with affected BSA of at least 10%, EASI score of at least 16, and IGA-AD grade of at least 3 at the screening and baseline visits will be included in the 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 Baseline and at each visit from Week 2 onwards, EASI, affected 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 post inflammatory 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 NRS at each visit from baseline to end of the treatment. Disease symptoms will be assessed by 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 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 PGIS and PGIC scores at Baseline and 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, 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 and Weeks 4, 8, and 16, blood will be collected for orismilast and the major human metabolite LEO 40815 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 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.

6.2 Discussion of Study Design

A double-blind, randomized, placebo-controlled study is considered the gold standard for conducting an interventional and dose-finding study. A sample size of approximately 47 patients per treatment arm is also adequate to obtain robust outcome data for comparisons between placebo and treatment doses.

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 fewer 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. If tolerability issues arise during the treatment or titration period, a short dose reduction is allowed. For a detailed titration schedule, refer to Section 8.3.1.

AD is a chronic condition requiring long-term therapy. Primary efficacy assessments of AD clinical trials are usually performed at 12 or 16 weeks after initiation of study treatment. Because of the initial titration period of up to 3 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. A 16-week treatment period was also deemed acceptable for the placebo arm because AD is not a life threatening disease warranting immediate treatment. A follow-up period is established after the end of the treatment period to assess efficacy and safety, including risk of rebound AD (see Section 6.3).

In addition to the AD assessments of the EASI, IGA-AD, BSA, peak pruritus NRS, PGIS, PGIC, sleep disturbance NRS, and skin pain NRS, the effects of study treatment on the pulmonary status and course of the disease in patients with asthma will be explored. A number of patient-reported outcomes (PROs) will be administered to explore the patient's perception of his or her condition and the related quality of life, as recommended by regulatory agencies. This comprehensive evaluation of the AD condition of patients will contribute to the selection of the most suitable dose for the Phase 3 clinical program.

Conduct of superficial skin sampling by tape stripping is considered a minimally invasive technique that can allow for evaluation of a panel of skin biomarkers to better characterize the biological activity of orismilast.

6.3 Follow-up Period

A follow-up period is established after the end of the treatment period to assess efficacy, safety, and the risk of rebound (ie, flaring with worse severity than before treatment). During the follow-up period, no other treatments are permitted, except topical emollients (between the EOT and the follow-up visit). If the investigator determines that additional treatment must be initiated during the follow-up period, the patient will end participation in the trial and the last follow-up visit should be performed before adding new treatment and withdrawing the patient from the trial.

If the patient is withdrawn because of initiation of a nonallowed treatment, as described above, the patient will be considered a study completer if the full 16-week treatment period is completed, including the follow-up visit upon initiation of the nonallowed treatment.

6.4 End of Study

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

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).

7 SELECTION OF STUDY POPULATION

7.1 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.

7.2 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 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:
    - Absolute neutrophil count of less than the lower normal range of the Central Laboratory (LNR) i.e. 1.7 x 10^9/L (1700/mm^3)
    - Hemoglobin of less than 10.0 g/dL or hematocrit less than 30%
    - Platelet count of less than 100,000 mm^3
    - Absolute lymphocyte count of less than the lower normal range of the Central Laboratory (LNR) i.e. 0,9 x 10^9/L (900/mm^3)
    - 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
    - Alanine aminotransferase or aspartate aminotransferase greater than 2.5 × the ULN
    - 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

7.3 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 timet the investigator's discretion (period from screen failure to rescreening to be determined by the investigator). If rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number. Additionally, all screening procedures must be conducted at rescreening to ensure all eligibility criteria are met.

7.4 Treatment Discontinuation and Withdrawal

An additional 22 patients will be randomized to account for an estimated early dropout rate of approximately 10%.

If a patient discontinues study treatment prematurely or is withdrawn from the study for any reason, the study site must immediately notify the Medical Monitor. The date and the reason for treatment discontinuation or study withdrawal must be recorded on the electronic case report form (eCRF). Patients who discontinue treatment prematurely will be asked to complete the assessments corresponding to Week 16 at the time of treatment discontinuation. The patient will be asked to return to the study site within 4 weeks of the last administration of study drug to complete the follow-up visit and have the assessments corresponding to the Week 20 assessments done (Table 4). If possible and deemed safe by the investigator, the patient should thereafter be offered to stay in the trial with no treatment and complete study visits as planned. If a patient withdraws from the study, attempts should be made to have him or her return to the study site within 4 weeks of the last administration of study drug to complete follow-up visit assessments.

In the event that a patient discontinues treatment prematurely because of a TEAE or serious TEAE ,this 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. The patient will also be asked to return to the study site for the follow-up visit within 4 weeks of the last administration of study drug to have the assessments corresponding to the Week 20 assessments done (Table 4).

Once withdrawn from the study, the patient cannot re-enter 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 circumstances:

- unacceptable toxicity or AE
- patient 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 patients' 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 11.8.5.

If a patient withdraws from the study, the Sponsor may retain and continue to use any data collected before the withdrawal for the purpose of the study or scientific research.

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 TREATMENTS

8.1 Details of Study Treatments and Dosage Schedule

The study treatment is formulated as modified-release tablets (10 mg and 30 mg) or placebo tablets for oral administration. 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 (Baseline visit). PK studies have shown no difference in PK properties whether the product is taken under fasted condition or with a low-fat meal. Intake with a high-fat meal leads to a higher incidence of GI side effects and should 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**
Drug 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 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.

8.2 Measures to Minimize Bias: Study Treatment Assignment and Blinding

8.2.1 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 on the basis of chronological order of Screening dates (eg, 01-010 for the 10th patient screened at Site No. 01).

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. All patients will be assigned to randomized study treatment using an Interactive Web Response System (IWRS). Further guidance and information can be obtained in the study manual.

8.2.2 Blinding

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).

Before the study is initiated, each site will be provided with an email address and/or telephone number as well as call-in directions for the log-in information and IWRS directions.

The IWRS will be programmed with blind-breaking instructions. Blinding codes should only be broken in emergency situations for reasons of patient safety. In case of an emergency, the Investigator has the sole responsibility for determining whether unblinding of a patient's 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 or its designee before unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the Investigator should promptly inform the Medical Monitor and the Sponsor within 24 hours after breaking the blind. When the blind for a patient has been broken, the date and reason that the blind was broken must be fully documented in the source document and eCRF. The primary reason for discontinuation (the event or condition that led to the unblinding) will be recorded, as applicable. Also, documentation of breaking the blind should be recorded using the IWRS 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 procedures for premature treatment discontinuation.

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.

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.

8.3 Planned Dosing Schedule and Adjustments

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, the Investigator might consider temporarily decreasing the dosage regimen, as described in Section 8.3.2 and Section 8.3.3.

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

8.3.1 Planned Dosing Schedule – Titration over a Maximum of 2 Weeks

Titration of oral apremilast was shown to improve the GI tolerance and overall acceptability of the drug. Consistent with this approach, this study will titrate the study treatment dose over a maximum period of 2 weeks (see Table 2).

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	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	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	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	P

Abbreviation: BID, twice daily.

8.3.2 Short Dose Reduction During the Titration Period

If GI intolerance or other AEs occur during the titration period, the Investigator might consider a short dose reduction in orismilast treatment until recovery.

If tolerability issues arise during the titration period (up to 2 weeks) dose reduction is allowed only if instructed by the Investigator and return to normal dosing should follow as below:

- 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 dose reductions do not affect calculation of dosing days and duration and titration is not prolonged. The short dose reductions will be captured in the eCRFs. Titrated tablets are prepackaged in wallet cards, thus ensuring that treatment is kept blinded.

8.3.3 Dose Reductions and Temporary Treatment Discontinuations After the Titration Period

If tolerability issues arise during the treatment which are unacceptable and cannot be controlled by medical treatment (e.g. metoclopramide for nausea/vomiting, loperamide for diarrhea, acetaminophen/paracetamol and NSAID for headache), the investigator might consider reducing the dose (up to 7 days) or transiently discontinuing the investigational drug (up to 3 days). Dose reduction can be done by administration of the evening dose or the morning dose only for

up to 7 days before reinitiating twice daily dosing.

If treatment has been temporarily discontinued due to side effect related circumstances (e.g. nausea) for up to 3 days, treatment re-initiation is done by administration of the evening dose or morning dose only for up to 7 days before reinitiating twice daily dosing.

If treatment has been temporarily discontinued due to non-side effect related circumstances (e.g. forgetting medication at home while on a weekend trip), re-initiation is done by resuming the planned twice daily dosing schedule without compensating for missing doses.

8.4 Treatment Accountability and Compliance

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.

8.5 Prior and Concomitant Therapy

Any concomitant medication, supplement, or procedure within 6 months before Baseline or received 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.

8.5.1 Emmolients

Emollients can be used at patient discretion for managing dry skin on noneczematous areas or for reducing pruritus on eczematous areas. The use of emollients is to be recorded as concomitant

treatment. In order not to generate local tolerance issues, patients should only use emollients that they have already used (and that they tolerated well) and refrain from initiating treatment with a new emollient. 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.

8.5.2 Supportive Treatment for Side Effects

Over the course of this trial, additional medications may be required to manage adverse events from trial treatment. At the discretion of the Investigator antiemetic or anti-diarrheic medications, or mild analgesics for headaches, may be administered. This approach is well established for other PDE4-inhibitors, and described by Tello ED et al. 2021 In brief:

The common PDE4-inhibition related side effect of secretory diarrhea is due to stimulation of the CFTR, a fluid transporter in the intestine. Usually, the diarrhea transforms to loose stools instead of diarrhea within a couple of weeks, but initial medical treatment with anti-diarrheic medications, e.g. loperamide, may support the patient during treatment initiation.

The common PDE4-inhibition related side effect of nausea is related to delayed gastric emptying, thus also related to large meals and energy dense meals. The patients should be advised to adjust their meals to be smaller and less fatty and less sugary and drink more water. Despite the advice, temporary use of antiemetic medications, e.g. metoclopramide, may support the patient during treatment initiation.

The advice to use mild analgesics (e.g. acetylsalicylic acid/aspirin or paracetamol/acetaminophen and NSAIDs) for the common PDE4-inhibition related side effect of headache may support the patient during treatment initiation.

8.5.3 Restricted Medications

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

Table 3. Nonallowed Therapies and Treatments

Compound	Washout and Prohibition During the Study
Topical medications/treatments that could affect AD or study evaluations (eg, antihistamines, corticosteroids, tazarotene, pimecrolimus, tacrolimus, or PDE4 inhibitor)	≥2 weeks before Baseline and throughout the study
Systemic treatment with medications other than biologics with a possible effect on AD, like apremilast, corticosteroids, retinoids, and systemic immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, Janus kinase inhibitors)	≥4 weeks before Baseline or 5 half-lives (whichever is longer) and throughout the study
Investigational drugs other than the study drug	≥4 weeks before Baseline, or 5 half-lives, if known (whichever is longer) and throughout the study

Compound	Washout and Prohibition During the Study
Use of phototherapy or prolonged sun exposure or use of tanning booths or other ultraviolet light sources (ie, ultraviolet B, psoralens, and long-wave ultraviolet radiation)	≥4 weeks before Baseline and throughout the study
Dupilumab or any biologic targeting the immune system	≥12 weeks before Baseline and throughout the study
Concomitant medication mainly metabolized via the cytochrome 2D6 isozyme and with a narrow therapeutic window, such as tricyclic antidepressants (eg, nortriptyline, amitriptyline, imipramine, and desipramine) or type 1C antiarrhythmics (propafenone, flecainide, and encainide)	≥4 weeks before Baseline and throughout the study
Systemic antibiotics	≥4 weeks before Screening visit
Initiation of new emollient or emollients containing pharmacologically active ingredients (such as lactic acid, salicylic acid, urea, alpha-hydroxy acids, or fruit acids) and regular use (more than 2 visits per week) of a tanning booth/parlor	From the Screening and throughout the study

Abbreviations: AD, atopic dermatitis; PDE, phosphodiesterase.
Concomitant medication mainly metabolized via cytochrome 3A4 and with a 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.

8.5.4 Drug-Drug Interactions

From clinical studies, orismilast can be considered a weak inhibitor of CYP3A4, and 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 the 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. Coadministration of drugs with a narrow therapeutic index, such as tricyclic antidepressants (e.g., nortriptyline, amitriptyline, imipramine, and desipramine) or type 1C antiarrhythmics (propafenone, flecainide, and encainide) is prohibited (see Table 3).

9 STUDY PROCEDURES

Table 4 outlines the timing of procedures and assessments to be performed throughout the study. Section 11.5 specifies laboratory assessment samples to be obtained. See Section 10 and Section 11 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 -7**	**Day 1 (Baseline)**	**W1 (±1 d)[a, b]**	**W2 (±1 d)[a]**	**W4 (±3 d)[a]**	**W8 (±3 d)[a]**	**W12 (±3 d)[a]**	**W16 (EOT/ET; ±3 d)[a]**	**W20 (±3 d)[a] or 4 weeks after EOT/ET; ±3 d[a]**
Informed consent (before any study procedures)	X								
Demography	X								
Medical history, including medications, alcohol consumption, and smoking history (last 6 months)	X								
Concurrent medication review	X	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria review	X	X							
Physical examination [c]	X	X			X	X	X	X	X
12-lead ECG (single measurement)	X				X	X		X	
Vital signs [d]	X	X			X	X	X	X	X
Weight	X	X			X	X	X	X	X
Height		X							
BMI		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, HBsAb)	X								
Safety laboratory assessments (hematology, serum chemistry, urinalysis)	X	X			X	X	X	X	
Pregnancy test [e]	X	X		X	X	X	X	X	
Blood samples for drug and metabolite PK analysis: plasma levels		X			X	X		X	
Optional: blood samples for drug PK profile					X			X	

	Screening	Treatment Period							Follow-up
Procedure	**Between Day -28 and -7**	**Day 1 (Baseline)**	**W1 (±1 d)[a, b]**	**W2 (±1 d)[a]**	**W4 (±3 d)[a]**	**W8 (±3 d)[a]**	**W12 (±3 d)[a]**	**W16 (EOT/ET; ±3 d)[a]**	**W20 (±3 d)[a] or 4 weeks after EOT/ET; ±3 d[a]**
Superficial skin sample using tape stripping [f]		X						X	
IGA-AD, BSA, and EASI assessments	X	X		X	X	X	X	X	X
Peak pruritus NRS, sleep disturbance NRS, and skin pain NRS		X	X	X	X	X	X	X	X
PGIS, PGIC		X		X	X	X	X	X	X
C-SSRS	X	X		X	X	X	X	X	X
DLQI		X				X		X	X
POEM		X		X	X	X	X	X	X
HADS		X		X	X	X	X	X	X
Pulmonary status NRS [g]		X			X	X	X	X	X
Dispense study drug		X		X	X	X	X		
Collect study drug, including packaging				X	X	X	X	X	
Compliance check			X[h]	X	X	X	X	X	

Abbreviations: BMI, body mass index; BSA, body surface area; C-SSRS, Columbia-Suicide Severity Rating Scale; d, day; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; EOT, end-of-treatment; 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; HCV, hepatitis C virus; IGA-AD, Investigator Global Assessment for Atopic Dermatitis; NRS, numerical rating scale; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetic; POEM, Patient Oriented Eczema Measure; W, week.

[a] The time window is defined in relation to the baseline visit date. In addition, if the investigator determines that additional treatment is required for the patient because of a flare, a follow-up visit should be scheduled before adding new treatment and withdrawing the patient from the trial.
[b] Visit can be conducted via a telemedicine procedure at Investigator's discretion.
[c] 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 Weeks 4, 8, 12, and 20.
[d] All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes.
[e] Serum β-human chorionic gonadotropin testing will occur at Screening. Urine pregnancy testing will occur 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] 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.
[g] Only for patients diagnosed with asthma.
[h] Compliance check is performed only on-site.

9.1 Informed Consent

Before performing any study-related procedures, the Investigator (or designee) will obtain written informed consent 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.

9.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 4). Section 11.5 specifies laboratory assessment samples to be obtained.

All PROs (Section 10.2) should be administered before any other visit procedure. Vital signs, weight measurement, and ECG must be done before blood sampling, except visits where blood sampling for PK analysis is done.

Efficacy assessments are described in Section 10 and include the EASI, IGA-AD, and BSA and the PROs of POEM, peak pruritus NRS, PGIS, PGIC, sleep disturbance NRS, skin pain NRS, pulmonary status NRS (only in patients with asthma), and DLQI.

Safety assessments are described in Section 11 and include medical history, vital signs and body weight, physical examinations, ECGs, laboratory assessments, HADS, C-SSRS, and AEs. PK assessments are described in Section 12 and superficial skin sampling using tape stripping is described in Section 13.

10 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 Investigator's assessments. The same assessor should perform all evaluations for the same patient at Baseline and Week 16.

10.1 Investigator Assessments

10.1.1 Eczema Area and Severity Index

The EASI is an investigator-assessed instrument measuring the severity of clinical signs and the percentage of affected BSA in patients with AD. The EASI is a composite scoring system used by the AD clinical evaluator to evaluate the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of 4 body regions, with adjustment for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body (Hanifin JM, 2001).

EASI scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, induration/papulation, excoriation, and lichenification are scored on a scale of 0 (absent) to 3 (severe) for each body region: head and neck, upper limbs (including the external axillae and hands), trunk (including the internal axillae and groin), and lower limbs (including the buttocks and feet). The extent of affected skin in each body region is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The EASI assessment will exclude the scalp, palms, and soles from scoring.

10.1.2 The Investigator Global Assessment for Atopic Dermatitis

The IGA-AD is a measure used by physicians to determine a patient's overall severity of disease. The static version is used in this trial for measurement at a single point in time, as indicated in the Schedule of Assessments (Table 4). The Investigator will rate the severity of the patient's AD on a 5-point scale ranging from 0 (clear) to 4 (severe) (Simpson E, 2020).

10.1.3 Body Surface Area

The BSA assessment estimates the extent of disease or skin affected by AD and is expressed as a percentage of total BSA. BSA will be determined by the Investigator or designee using the patient's hand (palm + fingers) = 1% BSA rule.

10.2 Patient-Reported Outcomes

10.2.1 Peak Pruritus Numerical Rating Scale

The severity of itch (pruritus) due to AD will be assessed using a horizontal 11-point NRS. Patients will be asked to assess their “worst itching due to AD over the past 24 hours” on an NRS anchored by the terms “no itching” (0) and “worst possible itching” (10).

The item will be completed at each visit via an application on an electronic device in the clinic or the patient’s own electronic device from baseline through Week 20.

10.2.2 Skin Pain Numerical Rating Scale

The skin pain NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a participant's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours.

The item will be completed at each visit via an application on an electronic device in the clinic or the patient’s own electronic device from baseline through Week 20.

10.2.3 Sleep Disturbance Numerical Rating Scale

The sleep disturbance NRS is a scale used by the patients to report their degree of sleep loss related to AD. Patients will be asked the following question in their local language: how would you rate your sleep last night? On a scale of 0 to 10, with 0 being “no sleep loss related to signs/symptoms of AD” and 10 being “I cannot sleep at all because of the signs/symptoms of AD”. Higher scores indicate worse outcomes.

The item will be completed at each visit via an application on an electronic device in the clinic or the patient’s own electronic device from baseline through Week 20.

10.2.4 Patient Oriented Eczema Measure

The POEM is a 7-item, validated questionnaire completed by the patient to assess disease symptoms. Patients are asked to respond to questions on frequency of sleep loss and skin dryness, itching, flaking, cracking, bleeding, and weeping over the past week. All answers carry equal weight, with a total possible score ranging from 0 to 28. A high score is indicative of a poor quality of life.

The item will be completed at each visit via an application on an electronic device in the clinic or at the patient’s own electronic device from baseline through Week 20 except Week 1.

10.2.5 Patient Global Impression of Severity Scale

The PGIS scale is a single question asking the patient how he or she would rate his or her overall AD symptoms over the past 24 hours. The 5 categories of responses are (0) “no symptoms", (1) “very mild", (2) “mild", (3) “moderate", and (4) “severe."

The item will be completed at each visit via an application on an electronic device in the clinic or the patient's own electronic device from baseline through Week 20 except Week 1.

10.2.6 Patient Global Impression of Change Scale

The PGIC scale measures change in clinical status of AD. The PGIC is based on a 7-point scale, and the patient will rate the change from the start of treatment as 1 "very much improved," 2 "much improved," 3 "minimally improved," 4 "no change," 5 "minimally worse," 6 "much worse," and 7 "very much worse."

The item will be completed at each visit via an application on an electronic device in the clinic or the patient's own electronic device from baseline through Week 20 except Week 1.

10.2.7 Dermatology Life Quality Index

The DLQI is a 10-item validated questionnaire completed by the patient and used to assess the effect of skin disease on the patient's quality of life during the previous week. The 10 questions cover the following topics: symptoms; embarrassment; interference with shopping and home care, clothing choices, social and leisure activities, sports participation, work or study, close relationships, and 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 quality of life.

The item will be completed at each visit via an application on an electronic device in the clinic or the patient's own electronic device at baseline and Weeks 8, 16, and 20.

10.2.8 Pulmonary Status Numerical Rating Scale in Patients with Asthma

Pulmonary disease status will be assessed in patients with asthma using a horizontal NRS. Patients will be asked to assess their "symptoms due to asthma over the past 7 days" on an NRS anchored by the terms (0) "no symptoms" and (10) "very bad symptoms".

The item will be completed at each visit via an application on an electronic device in the clinic or the patient's own electronic device at baseline and Weeks 4, 8, 12, 16, and 20.

11 SAFETY ASSESSMENTS

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

11.1 Medical History

Medical history will be recorded at Screening. Investigators should document the occurrence, signs, and symptoms of the patient's pre-existing conditions, including any psychiatric treatment or hospitalization, covering all prior significant illnesses up to and including 6 months before screening. Additional pre-existing conditions present at the time when informed consent is given, and up to the time of first dosing (Visit 1), are to be regarded as concomitant. Medical history will include medications, 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 11.8.1. 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.

11.2 Vital Signs and Body Weight

Vital signs (body temperature [measured in the ear], 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). 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 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.

11.3 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 Weeks 4, 8, 12, and 20 to verify continued patient eligibility and

to follow-up regarding any change in medical history. Physical examinations will be performed by a physician at the visits indicated in the Schedule of Assessments (Table 4).

11.4 Electrocardiograms

A 12-lead, resting ECG will be conducted 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 results will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF, and the ECG will be repeated if clinically significant abnormalities are observed or artifacts are present.

11.5 Laboratory Assessments

Laboratory assessment samples (Table 5) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 4).

Table 5. Laboratory Assessments

Hematology	**Serum Chemistry**
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 Creatinine Electrolytes (sodium, potassium, chloride, calcium, phosphorus) GGT LDH Total bilirubin Direct bilirubin Total IgE
Other Screening Tests	Urinalysis (Dipstick)
HIV antibody HBV HCV HCV RNA 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)	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Specific gravity Urine hCG (premenopausal females only) Urobilinogen
Pregnancy test: A serum pregnancy test will be performed on all WOCBP 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; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl transpeptidase; Hb, hemoglobin; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; hCG, human chorionic gonadotropin; Hct, hematocrit; HCV, hepatitis C virus; IgE, Immunoglobulin E; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell; WOCBP, women of childbearing potential.

Blood and urine samples will be analyzed at a central laboratory facility. Urine samples will be analyzed by dipstick at clinical site, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the patients' 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.

11.6 The Hospital Anxiety and Depression Scale

The HADS is a 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 7 or less indicate cases without anxiety or depression, whereas scores of 8 to 10, 11 to 14, and 15 to 21 indicate mild, moderate, and severe cases, respectively. The HADS is one of the tools recommended by the National Institute for Health and Care Excellence for diagnosis of depression and anxiety.

Any patient with a score for depressive symptoms ≥ 15 at baseline will not be eligible for enrollment 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 11.8.2.

11.7 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 minutes 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 item 4 or 5, the patient will not be included in the study.

Any patient with a positive response at subsequent visits (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 11.8.2.

11.8 Adverse Events

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

11.8.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient’s medical history.

Any AEs that occur before dosing at 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).

All AEs must be graded by using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grading system version 5.0 (CTCAE- Version 5.0) with reference to the unique clinical descriptions of severity for each AE in the guidance document. Please see Table 6 for selected unique clinical descriptions of severity of AEs. Only if an AE is not uniquely described in the CTCAE grading system, the general guidance for classification is to be used. Please see Table 7 for the general guideline for classification.

If a patient experiences a TEAE assessed as Grade 3 or higher using the unique clinical descriptions of severity (Grade 2 or higher for the SOC of cardiac disorders) according to CTCAE version 5, the patient should be permanently discontinued from the study drug and not receive additional doses.

Specific guidelines for classifying AEs by intensity are given in Table 6 and Table 7 and relationship to study drug are given in Table 8.

Table 6. Selected unique clinical descriptions of severity of AEs from National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death

Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Other AEs	For other AEs not in this table, please refer to the CTCAE grading system version 5.0, with reference to the unique clinical descriptions of severity for each AE. Only if an AE is not uniquely described in the CTCAE grading system, the general guidance (see Table 7) for classification is to be used.				

Table 7. National Cancer Institute Common Terminology Criteria for Adverse Events general guideline for classification version 5.0

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 8. 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 patients' 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 patients' 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 patients' 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.

Abbreviation: AE, adverse event.

11.8.2 Adverse Events of Special Interest (AESI)

An AESI (serious or nonserious) 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 11.8.4). Such an event might require further investigation 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 AESI:

- 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, and/or
- any of the following GI TEAEs: vomiting, diarrhea with an increase of at least 4 stools per day over baseline (Grade 2 CTCAE) for at least 3 days.
- any signal that may arise from Sponsors ongoing safety review during the trial that may need closer monitoring.

11.8.3 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.

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.

11.8.4 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 the Syneos 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 within 24 hours of occurrence or when the Investigator becomes aware of the event. Notification can be made using the dedicated fax line or email for the Syneos Health Safety and Pharmacovigilance group:

Syneos Health Safety and Pharmacovigilance fax number: +1 (877) 464-7787

Syneos Health Safety and Pharmacovigilance email address: safetyreporting@syneoshealth.com

If the Investigator contacts the Syneos Health 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 the Syneos Health 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.

11.8.5 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 an event is causally related to study treatment. Syneos Health will consider the Investigator's assessment and determine whether 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 independent ethics committee (IEC)/institutional review boards (IRBs) (where required) within 7 days after the Sponsor (or Syneos Health) has first knowledge of them, with a follow-up report 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 Sponsor (or Syneos Health) first has knowledge of them.

The Sponsor (or Syneos Health) 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 IEC/IRBs of reportable events within the applicable timeframes.

11.8.6 Pregnancy

WOCBP must have a negative serum pregnancy test at Screening and are required to use 1 of the highly effective contraception methods (listed in Inclusion Criterion 8). Women on hormone replacement therapy, and whose menopausal status is in doubt, will be required to use 1 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 consecutive months without an alternative medical cause and a confirmatory follicle-stimulating hormone test or as cessation of menses for at least 24 consecutive 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 Syneos Health Safety and Pharmacovigilance within 24 hours of knowledge of the event. If any patient becomes pregnant during the study, she is to immediately discontinue any Sponsor-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 Syneos Health Safety 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 Syneos Health 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 Syneos Health Safety 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 Syneos Health Safety and Pharmacovigilance after delivery.

11.8.7 Overdose

The Investigator must immediately notify the Sponsor of any occurrence of overdose with study drug.

12 PHARMACOKINETICS

12.1 Pharmacokinetic Sampling

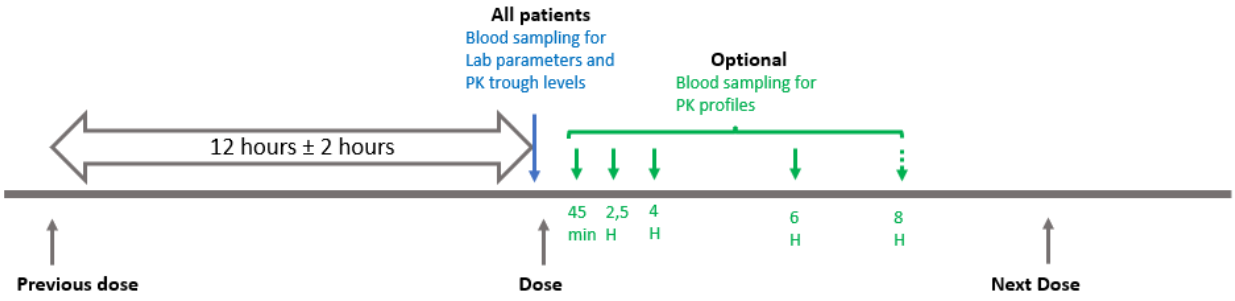
12.1.1 Blood Samples

Blood samples for PK analysis of orismilast and its major metabolite levels will be collected at the time points indicated in the Schedule of Assessments (Table 4). The actual date and time of each blood sample collection will be recorded.

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 plasma levels, patients will be offered optional participation in specific blood sampling for calculation of PK profiles. This additional procedure is voluntary for patients and a separate informed 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 W4 and W16. 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. See Figure 2 for the details of PK blood sample collection.

Figure 2. Pharmacokinetic Blood Sample Collection



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

12.2 Pharmacokinetic Analytical Methodology

The concentration of study drug and main metabolite 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.

13 PHARMACODYNAMICS

13.1 Superficial Skin Sampling Using Tape Stripping

Stratum corneum skin samples will be collected at the time points indicated in the Schedule of Assessments (Table 4) using the tape stripping method to evaluate biomarker expression levels. Tape stripping is a minimally invasive, nonscarring approach using 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 areas sampled at Baseline.

Details of stratum corneum skin samples storage, and shipping procedures are provided in a separate laboratory manual.

14 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 complement 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 dose group. For continuous variables, data will be summarized with the number of patients, 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.

14.1 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.

14.2 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 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.

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.

14.3 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 population. Missing data for primary and key secondary endpoints will be handled with the multiple imputation method. For a categorical efficacy endpoint based on a continuous variable, the multiple imputation will be first done for the continuous variable, then the category will be determined using the imputed values. Analyses will be repeated on the per-protocol population for primary and key secondary endpoints.

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

14.3.1 Analysis of the Primary Efficacy Endpoint

The primary endpoint, percentage change from Baseline to Week 16 in EASI score, will be analyzed using an analysis of covariance with treatment group as the factor and Baseline EASI score as the covariate. As a supportive analysis, a mixed model for repeated measures will be performed with treatment group, visit and treatment-by-visit interaction as factors and baseline EASI 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% CI of the difference between each active treatment and placebo will be calculated. The primary analysis set will be the ITT population with a multiple imputation approach to handle missing values. The same analyses will be repeated backward at earlier visits.

14.3.2 Analysis of Secondary Efficacy Endpoints

For the continuous secondary efficacy endpoints (peak pruritus NRS, BSA, PGIS, PGIC, sleep disturbance NRS, skin pain NRS, DLQI, and POEM examination), a mixed model for repeated measures will be performed similar to the supportive MMRM for the primary endpoint.

The key secondary efficacy endpoints and other binary secondary efficacy endpoints (IGA-AD success, EASI50, EASI75, EASI90, and 4-point improvement in the peak pruritus NRS) will be analyzed using the Mantel-Haenszel (MH) test, comparing each active treatment group with placebo in the ITT population.

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-AD scores/full scale will be analyzed using the MH test and the row mean score statistics with the ridit transformation.

The above endpoints (EASI changes and percentage changes, IGA-AD success, EASI50, EASI75, and EASI90) 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 occurs.

14.3.3 Analysis of Exploratory Endpoints

All exploratory endpoints, including change from baseline in pulmonary status NRS in patients with asthma and skin biomarkers at Week 16, and patients achieving at least a 2-point improvement in peak pruritis NRS from baseline will be summarized descriptively in the ITT population or a subgroup.

14.4 Safety Analysis

All safety analyses will be conducted using the safety population. AE data will be presented and tabulated according to Medical Dictionary for Regulatory Activities 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, urinalysis and hematology) parameters, 12-lead ECG values, 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.

14.5 Pharmacokinetic Analysis

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

14.6 Interim Analysis

No interim analysis is planned in this study.

15 STUDY MANAGEMENT

15.1 Approval and Consent

15.1.1 Regulatory Guidelines

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

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

The protocol, protocol amendments, ICF, 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 before initiation, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will have the following responsibilities:

- 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 the requirements of 21 CFR Parts 50, 56, 312, Subpart D; ICH guidelines; the IRB/IEC; European regulation 536/2014 for clinical studies (if applicable); and all other applicable local regulations

15.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), investigator's brochure, ICFs, recruitment material, and patient information sheets and other patient-facing material.

15.1.3 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 orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation 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 and that they can withdraw from the study at any time. 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 reconsented 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 any 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.

15.2 Data Handling

All patient data relating to the study will be recorded on the 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 electronically signing the eCRF. Access to the electronic data capture system will be restricted, and users 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 before 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.

15.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The Investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

15.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the General Data Protection Regulation, Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the HIPAA of 1996 Privacy Regulation). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with the HIPAA Privacy Regulation (if applicable) and in a form satisfactory to the Sponsor.

15.5 Monitoring

The study will be monitored according to the Sponsor's monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits, on-site and remote (telephone) or a combination, and contacts will be made at appropriate times during the study. The Investigator will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

The Investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the Investigator will

work closely with the clinical monitor and as needed, provide him or her appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

15.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

15.7 Protocol Amendment and Protocol Deviation

15.7.1 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 acknowledgment 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.

15.7.2 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.

15.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki, and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All patients are required to give written informed consent before participation in the study.

15.9 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.

15.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such clinical study agreement. To facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

16 REFERENCES

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17 APPENDIXES

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

Appendix 1. Rajka and Hanifin Criteria for Atopic Dermatitis

Appendix 2. Eczema Area Severity Index (EASI)

Appendix 3. Investigator Global Assessment for Atopic Dermatitis (IGA-AD)

Appendix 4. Body Surface Area

Appendix 5. Peak Pruritus Numerical Rating Scale

Appendix 6. Skin Pain Numerical Rating Scale

Appendix 7. Sleep Disturbance Numerical Rating Scale

Appendix 8. Patient Oriented Eczema Measure (POEM)

Appendix 9. Patient Global Impression of Severity (PGIS) Scale

Appendix 10. Patient Global Impression of Change (PGIC) Scale

Appendix 11. Dermatology Life Quality Index (DLQI)

Appendix 12. Pulmonary Status NRS in Patients with Asthma

Appendix 13. The Columbia-Suicide Severity Rating Scale (C-SSRS)

Appendix 14. The Hospital Anxiety and Depression Scale (HADS)

Appendix 15. Protocol Amendment Summary

Appendix 1: Rajka and Hanifin Criteria for Atopic Dermatitis

MAJOR FEATURES

- Pruritus

- Chronic or chronically relapsing dermatitis

- Typical distribution of skin lesion

- Personal and/or family history of atopy

MINOR FEATURES

1. Xerosis: Rough skin surface, often with visible fine scaling, but without erythema, involving at least 20% of body surface

2a. Ichthyosis vulgaris: Dryness of skin, with small, flaky, or branny scales, most obvious on extensor surfaces of limbs and sparing flexural creases

2b. Palmar hyperlinearity: More than 5 prominent lines longer than 1 cm running across palm

2c. Keratosis pilaris: More than 20 follicular, keratotic papules involving at least the posterolateral aspects of upper arms or thighs

3. Immediate (type I) skin test reactivity: Positive skin prick test; white or red wheal with an area of at least 50% of the histamine (10 mg/mL) control and not less than 3 mm (at site of inoculation) 15 minutes after inoculation (Dreborg S, editor. Skin tests used in type I allergy testing: position paper. Allergy 1989; Suppl 44:1-59.)

4. Elevated total serum IgE: Determined by fluoroimmunoassay with the following reference values:

Age	**IgE kU/L**
Newborn	<0.1 to 1.3
6 weeks to 2 months	0.1 to 4.9
3 to 8 months	0.4 to 16.3
9 months to 4 years	0.4 to 22.3
5 to 19 years	1.3 to 263
Adult	1.6 to 122

5. Early age of onset: Symptoms of eczema before the age of 5 years

6a. Tendency toward cutaneous infections: At least 2 episodes of folliculitis, furunculosis, or impetiginization requiring antibacterial treatment, or verified herpes simplex infection during the past 12 months

6b. Impaired cell-mediated immunity

7a. Hand eczema: Pruritic lesions on 1 or both hands with erythema and papules/vesicles or scaling, with or without oozing, crusting, fissures, or lichenification

7b. Foot eczema: Pruritic lesions on 1 or both feet with erythema and papules/vesicles or scaling, with or without oozing, crusting, fissures, or lichenification

8. Nipple eczema: Pruritic lesions on 1 or both nipples with erythema and papules/vesicles or scaling, with or without oozing, crusting, fissures, or lichenification

9. Cheilitis: Scaling of 1 or both lips, with or without fissures, erosions, or crusts

10. Recurrent conjunctivitis: Conjunctival hyperemia, generally associated with discharge and itching, provoked, on at least 2 different occasions, by exposure to airborne allergens

11. Dennie-Morgan infraorbital fold: Secondary crease in the lower eyelid affecting 1 or both eyes, starting at inner canthus and extending beyond the midline of the pupil when gaze is directed anteriorly with the head upright

12. Keratoconus: Diagnosed by ophthalmologist

13. Anterior subcapsular cataracts: Diagnosed by ophthalmologist

14. Orbital darkening: Subtle symmetric brownish to grayish or bluish discoloration of periorbital skin

15a. Facial pallor: Skin pallor, often accentuated perinasally and periorally, as judged by a physician

15b. Facial erythema: Erythema on cheeks, with neither papules nor prominent scaling

16. Pityriasis alba: Hypopigmented scaling areas with or without erythema, round, or ovoid, with a diameter exceeding 1 cm

17. Anterior neck folds: Prominent horizontal skin crease(s) on anterior aspect of neck, when head is upright

18. Itch when sweating: Itching or scratching provoked by sweating, reported by patient, or observed by parents

19a. Intolerance of wool: Itching or scratching provoked by wool contact, reported by patient, or observed by parents

19b. Intolerance to lipid solvents: Dry and/or itchy skin or deterioration of eczema due to contact with lipid solvents (eg, soap, shampoo), reported by patient or observed by parents

20. Perifollicular accentuation: Dermatitis enhanced around hair follicles in 2 or more areas with a diameter more than 5 cm

21a. Skin reactions provoked by ingested food: Itching, erythema or whealing, or exacerbation of eczema, reported by patient or observed by parents

21b. Skin reactions provoked by skin contact with food: Itching, erythema or whealing, or exacerbation of eczema, reported by patient or observed by parents

22a. Course influenced by environmental factors: Deterioration of eczema due to environmental factors not mentioned elsewhere in the minor criteria (Hanifin JM, Rajka G. Acta Derm Venereol Suppl [Stockh] 1980;92:44-7), such as seasonal variation, or exacerbation caused by upper respiratory tract infections, airborne allergens, and excessive water contact

22b. Course influenced by emotional factors: Deterioration of eczema during periods of emotional stress as judged by patient or parents

23a. White dermographism in nonlesional skin: Linear blanching of skin occurring within 90 seconds of mechanical stroking of nonlesional skin with blunt instrument, diameter of white line exceeding that of instrument

23b. White dermographism in lesional skin: Linear blanching of skin occurring within 90 seconds of mechanical stroking of lesional skin with blunt instrument, diameter of white line exceeding that of instrument

23c. Delayed blanch: Delayed blanch provoked (eg, by intradermal injection of methacholine)

X1. Infra-auricular fissure: Fissure at lower attachment of the earlobe, affecting 1 or both ears, length greater than 2 mm

X2. Angular cheilitis (perlèche): Scaling and fissure(s) at 1 or both corners (commissures) of the mouth, with or without crusting

X3. Eczema of the scalp: Pruritic lesions on the scalp with erythema and papules/vesicles or scaling, with or without oozing, crusting, fissures, or lichenification

X4. Scalp scaling without eczema: Fine, dry scaling on the scalp without erythema

X5. Pulpite digitale: Dry, scaling, often erythematous skin on finger pulp, sometimes associated with fissures

X6. Juvenile plantar dermatosis: Dry, scaling, often erythematous plantar skin, especially on the forefoot and big toe, sometimes associated with fissures

Appendix 2: Eczema Area Severity Index

Eczema Area Severity Index

The Eczema Area and Severity Index scoring system uses a defined process (Steps 1 to 5 below) to grade the severity of the signs of eczema and the extent of body surface area affected. The EASI assessment will exclude the scalp, palms, and soles from scoring.

1. **Select a body region:**
   Four individual body regions are assessed:
   - Head/neck
   - Trunk (includes the internal axillae and groin)
   - Upper limbs (includes the external axillae and hands)
   - Lower limbs (includes the buttocks and feet).
2. **Assess the extent of eczema in that body region:**
   Area of Involvement: Each body region has potentially 100% involvement. Using the table below, give each respective body region a score of between 0 and 6 on the basis of the percentage involvement. Precise measurements are not required.

Percent involvement	0	1–9	10–29	30–49	50–69	70–89	90–100
Region score	0	1	2	3	4	5	6

3. **Assess the severity of each of the 4 signs in that body region:**
   Erythema
   Induration/papulation
   Excoriation
   Lichenification
4. **Grade the severity of each sign on a scale of 0 to 3.**

0	Absent
1	Mild
2	Moderate
3	Severe

- Take an average if the severity across the involved area.
- Half points (1.5 and 2.5) may be used. 0.5 is not permitted. If a sign is present, it should be at least mild.
- Palpation may be useful in assessing edema/papulation as well as lichenification.

5. **Sum the scores for each of the 4 body region scores for a total score = (0-72).**

Body region	Erythema (0–3)	Edema/ Papulation (0–3)	Excoriation (0–3)	Lichenification (0–3)	Region Score (0–6)	Multiplier	Score per body region
Head/ neck	(+	+	+	+)	X	× 0.1	
Trunk	(+	+	+	+)	X	× 0.3	
Upper extremities	(+	+	+	+)	X	× 0.2	
Lower extremities	(+	+	+	+)	X	× 0.4	
Final Eczema Area and Severity Index score is the sum of the 4 region scores:							(0–72)

Appendix 3: Investigator Global Assessment for Atopic Dermatitis

Status	Score	Definition
Clear	0	Minor, residual hypopigmentation/hyperpigmentation, no erythema or induration/papulation, no oozing/crusting.
Almost clear	1	Trace faint pink erythema, no induration/papulation and no oozing/crusting.
Mild	2	Faint pink erythema with mild induration/papulation and no oozing/crusting.
Moderate	3	Pink-red erythema with moderate induration/papulation with or without oozing/crusting.
Severe	4	Deep or bright red erythema with severe induration/papulation with oozing/crusting.

Adapted due to an FDA request from: Simpson E, Bissonnette R, Eichenfield LF, Guttman-Yassky E, King B, Silverberg JI, Beck LA, Bieber T, Reich K, Kabashima K, Seyger M, Siegfried E, Stingl G, Feldman SR, Menter A, van de Kerkhof P, Yosipovitch G, Paul C, Martel P, Dubost-Brama A, Armstrong J, Chavda R, Frey S, Joubert Y, Milutinovic M, Parneix A, Teixeira HD, Lin CY, Sun L, Klekotka P, Nickoloff B, Dutronc Y, Mallbris L, Janes JM, DeLozier AM, Nunes FP, Paller AS. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. J Am Acad Dermatol. 2020 Sep;83(3):839-846.

Appendix 4: Body Surface Area

The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total BSA.

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.

Determine BSA using the patient's hand (palm + fingers) = 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 area affected by AD. 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 1 patient palm.
2. Only include the edge of current lesions, not areas that have cleared.
3. Double check to see if the area derived matches the "eyeball method" of estimation.

Appendix 5: Peak Pruritus Numerical Rating Scale

Peak Pruritus Numerical Rating Scale

Numerical Rating Scale **On a scale of 0 (no itching) to 10 (worst possible itching) ….**
…. how was your worst itching due to AD over the past 24 hours? Please select 1 number.

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

Appendix 6: Skin Pain Numerical Rating Scale

Skin Pain Numerical Rating Scale

Numerical Rating Scale **On a scale 0 (no pain) to 10 (worst pain imaginable) ….**
…. how was your skin pain in the past 24 hours? Please select 1 number.

0	1	2	3	4	5	6	7	8	9	10

Appendix 7: Sleep Disturbance Numerical Rating Scale

Sleep Disturbance Numerical Rating Scale

Numerical Rating Scale **On a scale 0 (no sleep loss related to signs/symptoms of atopic dermatitis to 10 (I cannot sleep at all because of the signs/symptoms of atopic dermatitis) ….**
…. how would you rate your sleep last night? Please select 1 number.

0	1	2	3	4	5	6	7	8	9	10

Appendix 8: Patient Oriented Eczema Measure

The Patient Oriented Eczema Measure is a tool used for monitoring atopic eczema severity. It is a measurement using patient-reported symptoms in eczema and focuses on the illness as experienced by the patient.

Patient Oriented Eczema Measure

(Questionnaire for Adults)

Please circle one response for each of the 7 questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of the eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your sleep been disturbed because of the eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your skin been bleeding because of the eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of the eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your skin been cracked because of the eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your skin been flaking off because of the eczema?

No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your skin felt dry or rough because of the eczema?

No days 1-2 days 3-4 days 5-6 days Every day.

Total Score (maximum 28): ____

Appendix 9: Patient Global Impression of Severity Scale

Patient Global Impression of Severity Scale

Numerical Rating Scale **On a scale "(0) no symptoms", "(1) very mild", "(2) mild" "(3) moderate", and "(4) severe"**				
…. how would you describe overall atopic dermatitis symptoms over the past 24 hours on a single item? Please select 1 number.				
0	**1**	**2**	**3**	**4**

Appendix 10: Patient Global Impression of Change Scale

Patient Global Impression of Change Scale

Numerical Rating Scale **On a scale "(1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, and (7) very much worse"**
…. how would you describe the change (if any) from the start of treatment in activity limitations, symptoms, emotions, and overall quality of life, related to your atopic dermatitis? Please select one number.

1	2	3	4	5	6	7

Appendix 11: Dermatology Life Quality Index

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__ Not relevant_
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**?	Very much__ A lot__ A little__ Not at all_ Not relevant_
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 12: Pulmonary Status Numerical Rating Scale in Patients with Asthma

Numerical rating scale to assess the pulmonary status. Only for patients diagnosed with asthma.

Pulmonary Status Numerical Rating Scale in Patients with Asthma

Numerical Rating Scale **On a scale 0 (no symptoms) to 10 (very bad symptoms) ….**
…. how were your symptoms due to asthma over the past 7 days? Please select 1 number.

0	1	2	3	4	5	6	7	8	9	10

Appendix 13: The Columbia-Suicide Severity Rating Scale

For Screening

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.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 12 Months**
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** ☐ ☐	**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** ☐ ☐	**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 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:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, 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** ☐ ☐	**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** ☐ ☐	**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 Past 12 Months - ***Most Severe Ideation:*** _____ Type # (1-5) _____ Description of Ideation	Most Severe	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)*	**Lifetime**	**Past 12 Years**
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 Non-suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
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 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:	**Yes No** ☐ ☐ Total # of interrupted _____	**Yes No** ☐ ☐ Total # of interrupted _____
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 _____	**Yes No** ☐ ☐ Total # of aborted _____

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 _____	**Yes No** ☐ ☐ Total # of preparatory acts _____
Suicidal Behavior: Suicidal behavior was present during the assessment period?		**Yes No** ☐ ☐	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:	Most Lethal Attempt Date:	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* _____	*Enter Code* _____	*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* _____	*Enter Code* _____	*Enter Code* _____

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 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:	Yes □ No □
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, 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. <u>Lifetime</u> - Most Severe Ideation _____ Type # (1-5) _____ Description of Ideation <u>Recent</u> - Most Severe Ideation: _____ Type # (1-5) _____	Most Severe

Description of Ideation	
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 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:	**Yes No** □ □ Total # of interrupted _____
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).	**Yes No** □ □ Total # of preparatory acts

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:	____
	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* _____

Appendix 14: The Hospital Anxiety and Depression Scale

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 15: Protocol Amendment Summary

Protocol version 1.0 dated 09 Dec 2021 was amended to create Protocol Amendment 1 (Protocol version 2.0) dated 05-May-2022; the amended version of the protocol supersedes version 1.0. The purpose of this amendment was to update the protocol per FDA recommendations related to subject inclusion/exclusion criteria, AESIs, and the Investigator Global Assessment for Atopic Dermatitis scale. Additional updates were made to the statistical analyses per the Sponsor's statistician.

- The definition of therapy-resistant AD was revised in exclusion criteria #1 with the following updates:
  - Specification of ≥2 treatment failures was added.
  - "Systemic AD therapy" was changed to "biologic therapy".
  - (including phototherapy) was changed to "JAK inhibitor treatment or phototherapy".
- Clarification on the durations for documented history of topical medications was added to inclusion criterion #7 – "(at least 2 weeks for high potency topical corticosteroids), or as labeled".
- Additional information regarding prohibited emollients was included - "(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 following changes were made to the Schedule of Assessments table due to an administrative error in the original protocol. These have been changed to fit the packages for the study treatment.
  - A ±3-day window was changed to a ±1-day window (at certain visits).
  - "Optional: blood samples for drug PK profile" was removed from Week 8 and added at Week 16.
  - The requirement that patients should be in a fasted condition before sample collection at Baseline and Week 16 was removed.
- The following sentence was added to Vital signs and Body Weight to align with the updates made to the AESI definitions– "A weight reduction of least 5% from baseline should be reported as a TEAE."
- Additional specifics on psychiatric conditions were added to exclusion criterion #8 - "(eg, current major depression with a score for depressive symptoms ≥15 of HADS at baseline, schizophrenia, suicidal behavior, psychiatric hospitalization within the prior year)".
- Additional wording was added to Medical History to emphasize the focus on psychiatric conditions "including any psychiatric treatment or hospitalization, covering".
- The definitions of AESIs were updated as follows:
  - 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, and/or
  - any of the following GI TEAEs: vomiting, diarrhea with an increase of at least 4 stools per day over baseline (Grade 2 CTCAE) for at least 3 days.
- Additional wording was added to clarify that AESIs should be reported in the same manner as SAEs.
- Dose modification language was revised to clarify that patients will be permanently discontinued from the study drug in the event that a TEAE meets the discontinuation criteria.
- A typographical error was corrected in the Pregnancy section. The reference to "Inclusion Criterion 9" was changed to "Inclusion Criterion 8".
- Collection of PK samples were updated to collect and generate PK-profiles in patient within the psoriasis indication as follows:
  - PK samples were revised from "trough" to "plasma".
  - The number of optional PK blood samples was increased from "4" to "4 or 5".
  - The date of collection for optional PK samples was revised from Week 8 to Week 16.
  - PK timepoints were revised from "1.5 hours" to "45 minutes" and "4.5 hours" to "4 hours" after intake of the study drug.
  - An additional optional 8-hour blood sample was added.
- Statistical methods and planned analyses were revised as follows:
  - The ITT population was revised to include "all randomized patients who receive at least 1 dose of study drug" as the decision to withdraw patients cannot be biased by knowledge of the assigned treatment due to blinding.
  - Efficacy analysis was revised to remove the condition "using observed cases only" for consistency with the ITT and PP analyses. The only difference in the efficacy analysis should be the number of patients included.
  - The supportive analysis was clarified in the analysis of the primary efficacy endpoint. The sentence "The mixed model for repeated measures may be used as a supportive analysis." was changed to "As a supportive analysis, a mixed model for repeated measures will be performed with treatment group, visit and treatment-by-visit interaction as factors and baseline EASI score by-visit interaction as a covariates".
  - The analysis of secondary efficacy endpoints was revised for consistency and to allow for comparison of ITT analysis results between the primary endpoint and continuous secondary efficacy endpoints. The sentence "For the continuous secondary efficacy endpoints (peak pruritus NRS, BSA, PGIS, PGIC, sleep disturbance NRS, skin pain NRS, DLQI, and POEM examination), an analysis of covariance, with treatment and disease severity as factors and Baseline value as covariate, will be applied. The mixed model for repeated measures may be used as a supportive analysis if appropriate." was changed to " For the continuous secondary efficacy endpoints (peak pruritus NRS, BSA, PGIS, PGIC, sleep disturbance NRS, skin pain NRS, DLQI, and POEM examination), a mixed model

for repeated measures will be performed similar to the supportive MMRM for the primary endpoint.
    - PK analysis was revised from “trough” to “plasma”.
- Appendix 3 was modified as follows:
    - The definition for Status of “Almost clear” / Score=1 was revised from “Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting” to “Trace faint pink erythema, no induration/papulation and no oozing/crusting”.
    - As a result of the above change to the wording of the scale, the word “Validated” was removed from the title of the scale throughout.

Protocol version 2.0 dated 05 May 2022 was amended to create Protocol Amendment 2 (Protocol version 3.0) dated 14 April 2023; the amended version of the protocol supersedes version 2.0. The purpose of this amendment was to update the protocol per notification letter dated 09-FEB-2023 for adjustment of laboratory ranges in exclusion criterion No. 14, the update of the Investigators Brochure for orismilast version 15, dated 05. April 2023 and learnings from the recently completed clinical phase 2b trial, UNI50001-203, with orismilast in patients with moderate to severe psoriasis.

- General safety information regarding the use of orismilast is updated with the overall results from the UNI50001-203 trial in psoriasis patients, according to the updated Investigators Brochure version 15.
- The clinical risks and benefits of orismilast has been updated according to the recent learnings for the UNI50001-203 trial in patients with psoriasis and update of the Investigators Brochure version 15.
- The exclusion criteria no. 14 on absolute neutrophil count and absolute lymphocyte count are by mistake not consistent with the reference range of the central laboratory and was corrected per notification letter dated 09. February 2023, as follows:
    - Absolute neutrophil count of less than 3.0x109 /L (less than 3000/mm3) was corrected to the lower normal range of the Central Laboratory (LNR) i.e. 1.7 x 109 /L (1700/mm3).
    - Absolute lymphocyte count of less than 1.0 x 109 /L (less than 1000/mm3) was corrected to the lower normal range of the Central Laboratory (LNR) i.e. 0,9 x 109 /L (900/mm3).
- The section regarding treatment discontinuation has been updated to more clearly state the requirement that if a patient experiences a TEAE assessed as Grade 3 or higher using the unique clinical descriptions of severity (Grade 2 or higher for the SOC of cardiac disorders) according to CTCAE version 5, the patient should be permanently discontinued from the study drug and not receive additional doses.
- Planned dosing schedule and adjustments has been described in more detail. This to help guide the Investigator in case of temporarily decreasing the dosage regimen 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.
    - A section for planned dosing schedule – Titration over a maximum of 2 weeks has been created.

  - A section describing the short dose reduction during the titration period has been updated.
  - A section describing dose reductions and temporary treatment discontinuations after the titration period has been created.
- A section describing the examples of supportive treatment for side effects and medical treatment for tolerability issues that may arise during the treatment (e.g. metoclopramide for nausea/vomiting, loperamide for diarrhea, acetaminophen/paracetamol and NASID for headache) have been added.
- Safety blood samples for week 12 have been added in Table 4. Schedule of Assessments, to allow for closer monitoring of all safety laboratory assessments (hematology, serum chemistry, urinalysis) between weeks 8 and 16.
- The adverse events section has been updated with details to emphasize that all AEs must be graded by using the CTCAE grading system version 5.0, with reference to the unique clinical descriptions of severity for each AE in the guidance document.
- Table 6 has been added for selected unique clinical descriptions of severity of AEs. Only if an AE is not uniquely described in the CTCAE grading system, the general guidance for classification is to be used.
- The adverse events of special interest section (AESI) have been updated with an additional general criterion to allow sponsor to follow any signal that may arise from Sponsors ongoing safety review during the trial that may need closer monitoring.
- The Screening version of the Columbia Suicide Rating Scale in Annex 13 was the short version and initially inserted in error. The correct long version for Screening has been inserted.