CLINICAL STUDY PROTOCOL

Protocol title:	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled 16-Week Study (with a 52-Week Open-Label Extension) to Assess the Safety and Efficacy of Etrasimod in Subjects with Moderate-to-Severe Atopic Dermatitis
Protocol number:	APD334-201
Version:	Amendment 1.0, 19 August 2019
Compound name or number:	Etrasimod (APD334)
Study phase:	Phase 2
Indication:	Atopic dermatitis
Sponsor name:	Arena Pharmaceuticals, Inc.
Legal registered address:	6154 Nancy Ridge Drive San Diego, California 92121
Clinical lead:	[redacted] Senior Medical Director and Clinical Development Lead Arena Pharmaceuticals, Inc. [redacted]
SAE reporting:	IQVIA Pharmacovigilance [redacted]
Sponsor approval:	This protocol was approved by the Sponsor's Responsible Medical Officer, or delegate. The electronic signature page is appended.

Confidentiality Statement

SYNOPSIS

Sponsor: Arena Pharmaceuticals, Inc.

Name of Investigational Study Drug: APD334 (etrasimod)

Protocol Title: A Multicenter, Randomized, Double-Blinded, Placebo-Controlled 16-Week Study (with a 52-Week Open-Label Extension) to Assess the Safety and Efficacy of Etrasimod in Subjects with Moderate-to-Severe Atopic Dermatitis

Protocol Number: APD334-201

Phase: 2

Country(ies)/Region(s) (planned): North America (USA, Canada) and Australia

Objectives:

Primary Objective: To assess the efficacy of etrasimod monotherapy (1 or 2 mg) in subjects with moderate-to-severe atopic dermatitis (AD) during the Double-Blind Treatment Period.

Safety Objective: To assess the safety and tolerability of etrasimod monotherapy (1 or 2 mg) in subjects with moderate-to-severe AD during the Double-Blind Treatment Period.

Open-Label Extension Objective: To assess the long-term safety, tolerability, and efficacy of etrasimod monotherapy (2 mg) in subjects with moderate-to-severe AD.

Study Design:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study that includes multiple periods: up to a 4-week Screening Period (to determine subject eligibility); a 12-week Double-Blind Treatment Period with a 4-week Safety Follow-Up Period following the last dose of double-blind study treatment; and eligible subjects may enter a 52-week Open-Label Extension Period also followed by a 4-week Safety Follow-Up Period. Subjects with chronic AD for at least 1 year as defined by Hanifin and Rajka criteria ([redacted]) despite optimized skin care (ie, use of emollients, avoidance of irritants) whose disease is not adequately controlled with topical therapies, or for whom those therapies are not advisable, will be equally randomized (1:1:1 ratio) to receive etrasimod (1 or 2 mg) or placebo.

Randomization will be stratified by a validated Investigator's Global Assessment (vIGA) score at Baseline (3 versus 4) and region (as appropriate). Subjects will receive etrasimod 1 mg or 2 mg or placebo orally, once daily, in a double-blind manner for 12 weeks. During the Open-Label Extension Period, all eligible subjects will receive etrasimod 2 mg orally, once daily. The application of topical moisturizers will be required at least once daily for at least 1 week prior to randomization and throughout the study without change (ie, type, frequency, application). [redacted] Rescue therapy will be permitted for uncontrolled symptoms at the discretion of the investigator based on an exacerbation of disease severity or subject self-reporting of worsened symptoms.

Number of Subjects (planned):

Approximately 120 subjects are planned to be enrolled in the study (40 subjects each in 1 mg etrasimod, 2 mg etrasimod, and placebo groups).

Eligibility Criteria for the Double-Blind Treatment Period:

Inclusion Criteria:

Subjects must meet ALL of the following inclusion criteria to be eligible for enrollment into the study.

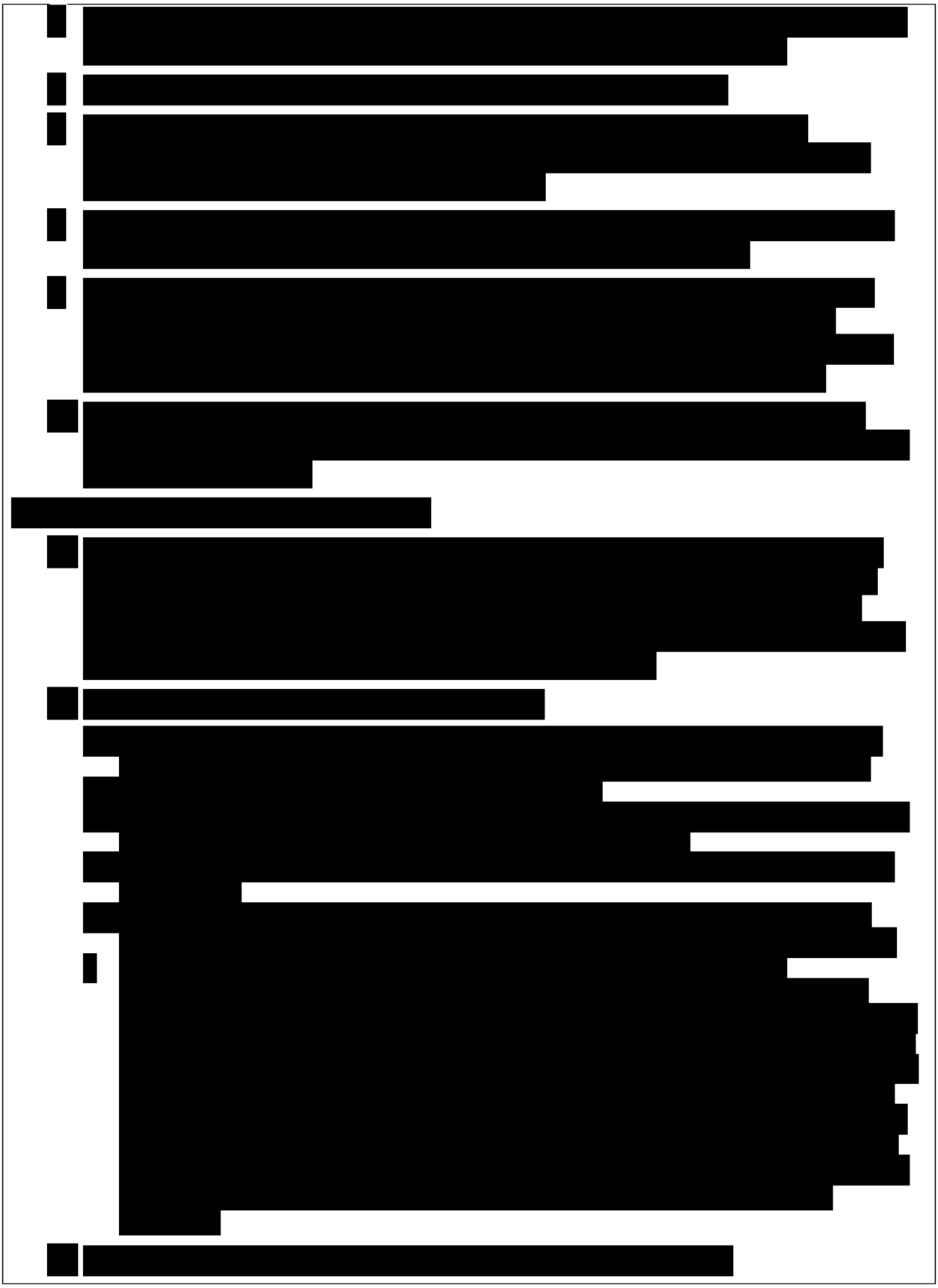
1. Men or women between ≥ 18 and ≤ 70 years of age at the time of informed consent.
2. Chronic AD, defined by Hanifin and Rajka criteria ([redacted]), that has been present for at least 1 year prior to the Screening Visit.
3. Eczema Area and Severity Index (EASI) ≥ 12 at the Screening Visit and ≥ 16 at the Baseline Visit.
4. vIGA score ≥ 3 (on the 0 to 4 vIGA scale, in which 3 = moderate and 4 = severe) involvement at the Screening and Baseline visits.
5. Body surface area (BSA) ≥ 10% of AD involvement at the Screening and Baseline visits.
6. Recent history (within 6 months prior to the Screening Visit) of inadequate response to treatment with topical medications, or when topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks), which can be documented by medical records or by the history provided to the investigator by the subject despite optimized skin care (ie, avoidance of irritants, use of emollients).
7. Willing to apply a dose of topical emollient/moisturizer at least once daily for ≥ 1 week prior to the Baseline Visit and willing to continue daily application over the course of the study without change (ie, type, frequency, application).
8. Willing and able to comply with all clinic visits and study-related procedures and understand and complete study-related questionnaires.
9. Provide signed informed consent prior to conducting any procedures.

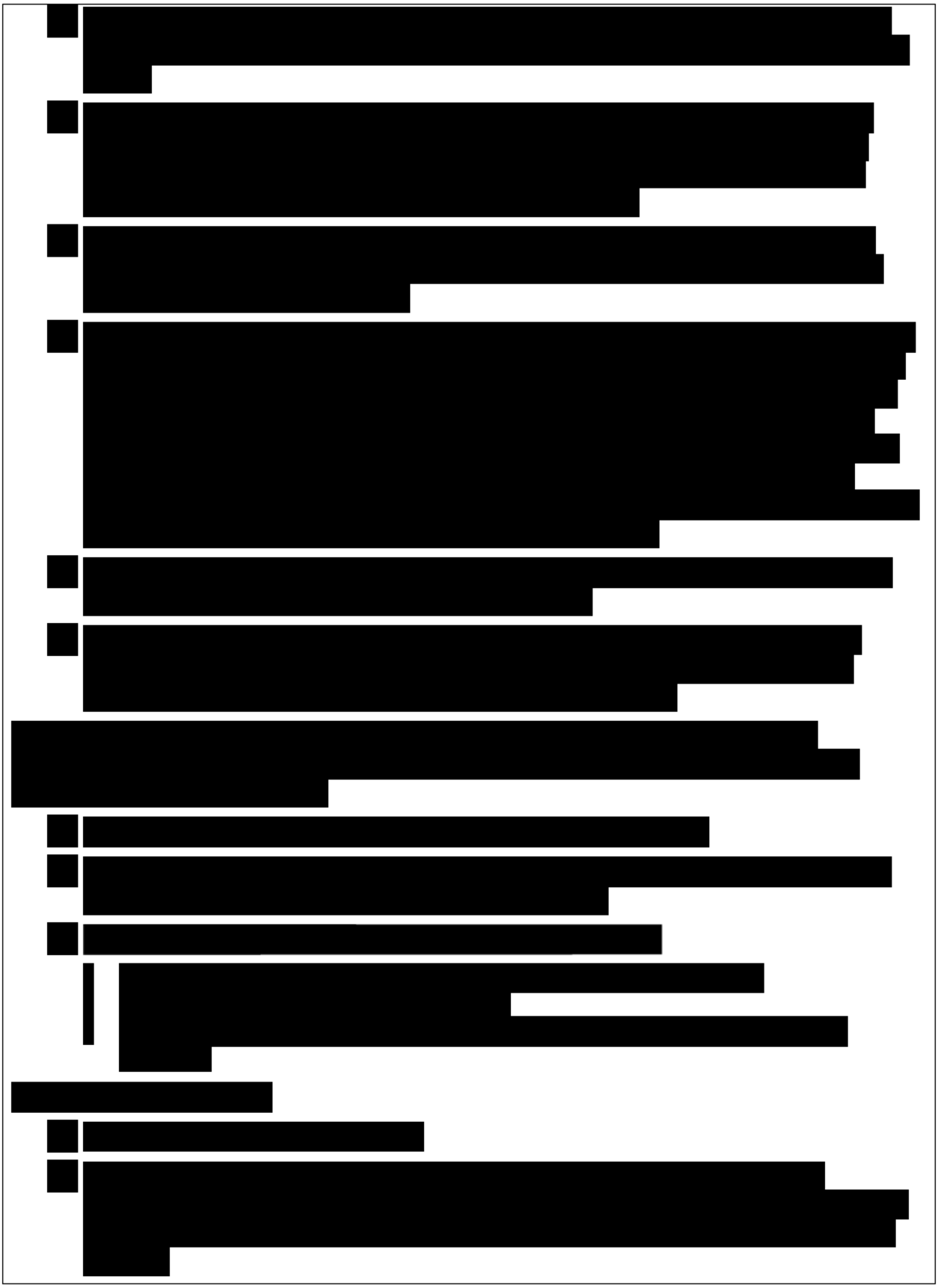
Exclusion Criteria:

Subjects will be excluded from the study if they meet ANY of the following exclusion criteria.

[redacted]

3. Phototherapy for AD or artificial tanning (beds, booths, or lamps) within 4 weeks prior to Screening or during Screening.
4. Presence of skin comorbidities that will interfere with study assessments of the underlying disease.





[redacted]

Test Product, Dose, and Mode of Administration:

Etrasimod 1 or 2 mg tablets taken orally once daily during the Double-Blind Treatment Period.
Etrasimod 2 mg tablets taken orally once daily during the Open-Label Extension Period.

Duration of Study:

The overall duration of the study will be up to 76 weeks, including:

- Up to 4-week Screening Period
- 12-week Double-Blind Treatment Period
- Safety Follow-Up Visit 4 weeks after the last dose of double-blind treatment
- 52-week Open-Label Extension Period
- Safety Follow-Up Visit 4 weeks after the last dose of open-label treatment

Reference Therapy, Dose, and Mode of Administration

Matching placebo tablets taken orally once daily during the Double-Blind Treatment Period. There is no reference therapy (no placebo) during the Open-Label Extension Period.

Efficacy Assessments:

Efficacy will be assessed by changes in AD severity using EASI, vIGA, SCORing Atopic Dermatitis (SCORAD), and BSA. Symptoms of itch will be assessed using the pruritus numeric rating scale (NRS). Patient-reported outcomes will also be assessed using the Dermatology Life Quality Index (DLQI), Patient Oriented Eczema Measure (POEM), and Patient Global Assessment (PGA).

Primary efficacy endpoint:

- Percent change in EASI from Baseline to Week 12.

Key secondary efficacy endpoints:

- Proportion of subjects achieving EASI-75, defined as a 75% reduction of EASI from Baseline to Week 12.
- Proportion of subjects with a vIGA 0 to 1 (on a 5-point scale) score and a reduction from Baseline of $\geq$ 2 points at Week 12.

Secondary efficacy endpoints:

- Percent change in peak pruritus NRS from an itch daily diary from Baseline to Week 12.
- Proportion of subjects with improvement (reduction) in peak pruritus NRS $\geq$ 3 from an itch daily diary from Baseline to Week 12.
- Proportion of subjects achieving EASI-50, defined as a $\geq$ 50% reduction of EASI from Baseline to Week 12.
- Proportion of subjects achieving EASI-90, defined as a $\geq$ 90% reduction of EASI from Baseline to Week 12.
- Change and percentage change in percent BSA AD involvement from Baseline to Week 12.

Exploratory efficacy endpoints:

- Change in DLQI from Baseline to Week 12.
- Change in POEM from Baseline to Week 12.
- Percent change in SCORAD from Baseline to Week 12.
- [redacted]

[redacted]

Efficacy assessment during open-label extension:

These efficacy outcomes will be measured at scheduled visits up to 52 weeks: EASI, vIGA, SCORAD, BSA, pruritus NRS, POEM, DLQI, and PGA. Dichotomous response outcomes derived from specific scores will be assessed.

[redacted]

[redacted]

Safety Assessments:

Safety will be assessed through the incidence of AEs, clinical laboratory findings, [redacted] physical examinations, vital signs [redacted] ophthalmoscopy, [redacted]

Statistical Methods for the Double-Blind Treatment Period:

Sample Size:

Assuming a 1:1:1 randomization, 120 subjects (40 subjects each in 1 mg etrasimod, 2 mg etrasimod, and placebo groups) is sufficient to achieve at least 90% power to detect a difference of 35% in EASI from Baseline to Week 12 between each of the etrasimod treatment groups and placebo by a 2-sample t-test using a 1-sided significance level of 0.025 with estimated standard deviation (SD) at 41%. This sample size also accounts for an estimated drop-out rate of up to 25%.

Testing strategy:

No formal testing strategy or adjustments of the Type I error will be employed for the primary and key secondary endpoints. Estimates and confidence intervals (CIs) for treatment groups and from pairwise comparisons will be reported in an exploratory manner.

Statistical Analysis:

The primary and key secondary endpoints will be analyzed using the Full Analysis Set (FAS) and demographic and safety analyses will be performed using the Safety Set. Other important statistical considerations, such as handling rescue medication uses during study treatment, missing data imputation strategies, sensitivity analyses, and subgroup analyses will be described in the protocol and the statistical analysis plan (SAP).

The primary endpoint of percentage change in EASI from Baseline to Week 12 will be analyzed using analysis of covariance (ANCOVA) model. ANCOVA model will include treatment group as factor, Baseline EASI score and randomization factor as covariates. EASI score after rescue medication uses will be set to missing; all missing data will be imputed in the FAS using multiple imputation (MI) procedure. Multiple results of ANCOVA (least square [LS] means and LS mean difference from

placebo) for each MI dataset will be analyzed and reported along with 95% CI and p-value and using Rubin's method [redacted]).

Proportion-based key secondary endpoints (eg, EASI-75, vIGA 0 to 1) at Week 12 will be analyzed in the FAS; subjects who use rescue medication, or with missing data for any reason will be considered as "non-responder" or "failure." The analyses will be performed using the Cochran-Mantel-Haenszel method adjusted for randomization stratification factor. The number and percentage of subjects achieving the goal and the difference in proportion between treatment groups achieving the goal, along with p-value and the 95% CIs will be reported.

For other secondary endpoints, longitudinal continuous variables at scheduled visits up to Week 12 will be analyzed using a mixed effects model with repeated measures (MMRM) model. The MMRM model will include treatment group, visit, and interaction of treatment-by-visit as factors, and baseline measure and randomization stratification factor as covariates. An unstructured covariance matrix will be specified for the MMRM model. LS means at visit and LS mean differences between treatment group with p-values and corresponding 95% CIs will be reported. Longitudinal dichotomous measures at scheduled visits will be analyzed using a logistic regression model. The model will include treatment group as a factor, Baseline EASI score and randomization stratification factor as covariates. The odds ratios and 95% CIs, and associated p-value will be reported.

[redacted]

Safety Analysis:

All safety data will be listed and summarized by treatment group. All treatment-emergent AEs (TEAEs) will be coded using the Medical Dictionary for Regulatory Activities and tabulated by System Organ Class and Preferred Term. Incidence of AEs, SAEs, and AEs leading to study treatment discontinuation will be summarized and presented in descending order of frequency. Laboratory parameters will be summarized by treatment group at each scheduled assessment time point using descriptive statistics. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be noted. Shift tables and analyses of changes from Baseline will be produced. The change from Baseline for each of the vital signs and ECG parameters will be summarized. Incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

Interim Analysis:

No formal interim analysis of efficacy is planned. Periodic blinded assessments of the assumption regarding the SD of the percentage change in EASI from Baseline to Week 12 may be conducted. The planned sample size will not be reduced as a result of the SD assessments.

Statistical Methods for the Open-Label Extension Period:

No pair-wise comparison will be performed. Only descriptive statistics will be provided. Continuous variables will be summarized using the number of observations, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AD	atopic dermatitis
ADR	adverse drug reaction
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AV	atrioventricular
β-hCG	beta human chorionic gonadotropin
BP	blood pressure
bpm	beats per minute
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CRO	contract research organization
CYP	cytochrome P450
[redacted]	[redacted]
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EASI-50/-75/-90	50%/75%/90% reduction in Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
EoT	end of treatment
FA	fluorescein angiography
FAS	Full Analysis Set
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen

Abbreviation	Explanation
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
IAC	independent adjudication committee
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IgE	immunoglobulin E
IGRA	interferon-gamma release assay
IMID	immune-mediated inflammatory disorder
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IWRS	Interactive Web Response System
JAK	Janus kinase
LDH	lactate dehydrogenase
LFT	liver function test
LS	least square
mFAS	modified Full Analysis Set
MI	multiple imputation
MMRM	mixed effects model with repeated measures
NA	not applicable
NRS	numerical rating scale
[redacted]	[redacted]
OLE	Open-Label Extension
[redacted]	[redacted]
PGA	Patient Global Assessment
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviation	Explanation
POEM	Patient-Oriented Eczema Measure
[redacted]	[redacted]
PRO	patient-reported outcome
QoL	quality of life
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
RSI	reference safety information
S1P	sphingosine 1-phosphate
$S1P_{1,4,5}$	sphingosine 1-phosphate receptors 1, 4, 5
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SOP	standard operating procedure
TARC	thymus and activation-regulated chemokine
TB	tuberculosis
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
UC	ulcerative colitis
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
vIGA	validated Investigator's Global Assessment
WBC	white blood cell

1. INTRODUCTION

1.1. Atopic Dermatitis

Skin diseases are the fourth largest cause of disability worldwide (Karimkhani 2017). Atopic dermatitis (AD, also known as atopic eczema) is the most common chronic relapsing, inflammatory skin disease. The lifetime prevalence of AD is 10% to 20% in developed nations, and appears to be increasing (Weidinger 2016, Heratizadeh 2017).

AD is more common in children. It is estimated that 90% of individuals with AD develop their first symptoms by age 5, and in approximately 60% of cases it manifests during the first year of life (Weidinger 2016, Boguniewicz 2017). The nature of AD is relapsing and remitting and patients diagnosed as children may even experience spontaneous disease remission later in adolescence (Bieber 2008, Eichenfield 2014). However, AD can remain a chronic and lifelong condition, with prevalence in adults ranging from 7% to 10% (Boguniewicz 2017). In a clinical study population, it was found that 50% of AD patients had been living with active disease for more than 27 years (Simpson 2016b).

AD is characterized by systemic cutaneous inflammation and perturbed epidermal-barrier function resulting in dry, red, skin and intense itch (Bieber 2008, Weidinger 2016). Essential features for diagnosis of AD are pruritus, eczematous dermatitis, and a chronic or relapsing history of disease (Weidinger 2016, Boguniewicz 2017). Patients with AD are more likely to have other allergic or atopic conditions. In a 2016 study of 380 adults with moderate-to-severe AD, 51.3% had allergic rhinitis, 40.3% had asthma, 24.2% had allergic conjunctivitis, and 60.5% had other allergies. The disease burden of those with AD significantly impacts quality of life and patients report that their condition affects social and leisure activities (43.9%), work or studying (41.8%), and even clothing choice (57.9%) (Simpson 2016a).

A combination of genetic, environmental, and immunologic factors appears to determine disease predisposition, while the pathogenesis of AD is thought to stem from the mutually reinforcing interaction between a disrupted epidermal barrier and an inappropriate immune response in the skin (Weidinger 2016, Heratizadeh 2017). Epidermal barrier disruption in AD facilitates penetration by allergens, immunoglobulin E (IgE) sensitization, and bacterial colonization (particularly *Staphylococcus aureus*), which induce persistent type 2 helper T cell responses (Salava 2014, Zhu 2018).

There are currently various topical and systemic therapeutic options that are used for the treatment and symptomatic relief of AD, including corticosteroids, moisturizers, and systemic immunosuppressants. However, these current therapies are limited by poor compliance, safety profiles that prohibit long-term use, limited efficacy that provides only transient or marginal symptomatic relief, invasive administration procedures, or off-label use. Thus, there remains a great unmet medical need for an effective, safe, and orally administered treatment.

1.2. Etrasimod

Etrasimod (APD334) is an orally administered, selective, sphingosine 1-phosphate (S1P) receptor 1, 4, and 5 ($S1P_{1,4,5}$) modulator that is being developed to treat immune-mediated inflammatory disorders (IMID), including ulcerative colitis (UC) and AD.

S1P acts as an extracellular signaling molecule via binding to a set of 5 high-affinity class A membrane bound G protein-coupled receptors, referred to as $S1P_{1-5}$ (Brinkmann 2007). Among these receptors, $S1P_1$ is a cell surface-expressed protein that has been shown to regulate lymphocyte egress from lymphoid organs (Brinkmann 2010). Synthetic $S1P_1$ modulators, such as etrasimod, have been observed to act as functional antagonists by inducing and sustaining receptor internalization. This results in the retention of lymphocytes within lymphoid tissue, and therefore lowers the amount of peripheral blood lymphocytes available to be recruited to sites of inflammation (Brinkmann 2010).

S1P receptor modulators have been shown to be clinically beneficial in multiple T cell-mediated diseases including, but not limited to, inflammatory bowel disease, multiple sclerosis, and plaque psoriasis (Brinkmann 2010, Kappos 2010, Vaclavkova 2014, Sandborn 2016). Etrasimod demonstrated positive results in a Phase 2, randomized, double-blind, placebo-controlled study in subjects with moderately to severely active UC (Study APD334-003 ([redacted]). Etrasimod significantly reduced circulating lymphocyte counts and demonstrated consistent and clinically meaningful improvements in endpoint measures reflecting cardinal symptoms of UC, and objective findings of endoscopic colorectal mucosal healing.

Similar to their importance in UC pathogenesis, dendritic cells and T cells play critical roles in driving AD immunopathology (Bieber 2008, Weidinger 2016). In AD, skin-resident dendritic cells readily engulf foreign antigens and allergens that have penetrated the perturbed dermal barrier, and traffic to the lymph nodes, where they activate and polarize naïve T cells (Bieber 2011). Once activated, T cells exit lymphoid organs, migrate to the skin, and secrete inflammatory cytokines and chemokines. Activated T cells can directly drive skin inflammation, or recruit other immune cells, including eosinophils and mast cells, that further contribute to the inflammatory processes.

Trafficking of dendritic cells, T cells, and eosinophils have all been shown to be modulated in-part by functional antagonism of $S1P_1$. In addition to the effect of reducing circulating lymphocytes described above, $S1P_1$ has been shown to modulate the trafficking of dendritic cells towards draining lymph nodes (Kleuser 2013, Japtok 2014) and the egress of eosinophils from the bone marrow (Sugita 2010). The role of $S1P_1$ functional antagonism in the immune cells implicated in AD pathogenesis, and therefore the potential to reduce skin inflammation, supports the development of etrasimod as a potential therapeutic for AD.

Refer to the latest Investigator's Brochure (IB) for a complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects.

1.3. Benefit and Risk Assessment

Etrasimod has been found to be safe and well-tolerated in approximately 281 subjects that have been dosed with the investigational drug. [redacted]

Etrasimod has already demonstrated beneficial effects in another autoimmune inflammatory disease, UC, in a Phase 2 study (Study APD334-003) with 1 and 2 mg etrasimod dosed once daily and the Open-Label Extension (Study APD334-005) with an etrasimod 2 mg dose administered once daily for up to 46 weeks.

There have been no clinically significant safety concerns in clinical studies with etrasimod to date. However, macular edema, liver enzyme elevations, and dyspnea have been reported with fingolimod, one of the currently licensed S1P receptor modulators (GILENYA 2010). It is believed that the non-selectivity (ie, activity at all 5 S1P receptors) of this first-generation S1P receptor modulator contributes to many of these adverse events (AEs) (Peyrin-Biroulet 2017). Given the putative association between receptor activation and AEs, development of etrasimod, as a next-generation S1P receptor modulator, has focused on optimizing selectivity for those receptors associated with clinical benefit ($S1P_{1,4,5}$) and avoidance of the receptors that initiate downstream signaling events believed to be connected to AEs ($S1P_{2,3}$).

[redacted]

The S1P receptor modulator class of drugs are also associated with an expected, on-target effect of reducing heart rate (HR) upon first dosing. This chronotropic reaction is caused by agonism of $S1P_1$ in cardiac tissue, which activates G protein-coupled inwardly rectifying potassium channels. $S1P_1$-mediated HR reduction is maximal on the first day of dosing, with recovery thereafter (Camm 2014). Cardiac events have been rare, asymptomatic, and transient with etrasimod. [redacted] Vital signs will be monitored closely during the study and direct observation will be performed during the period after the subject receives the Day 1 dose in the Double-Blind and Open-Label Extension periods and also at treatment re-initiation after a defined period of treatment interruption.

Based on the preclinical and clinical data generated from etrasimod studies along with the precautions outlined above, the favorable benefit/risk assessment justifies the further development of etrasimod in subjects with AD with this Phase 2 study.

Further description of expected benefits, identified and potential risks, and the reference safety information (RSI) for etrasimod are provided in the current version of the IB.

2. OBJECTIVES

Primary Objective

- To assess the efficacy of etrasimod monotherapy (1 or 2 mg) in subjects with moderate-to-severe AD during the Double-Blind Treatment Period.

Safety Objective

- To assess the safety and tolerability of etrasimod monotherapy (1 or 2 mg) in subjects with moderate-to-severe AD during the Double-Blind Treatment Period.

Open-Label Extension Objective

- To assess the long-term safety, tolerability, and efficacy of etrasimod monotherapy (2 mg) in subjects with moderate-to-severe AD.

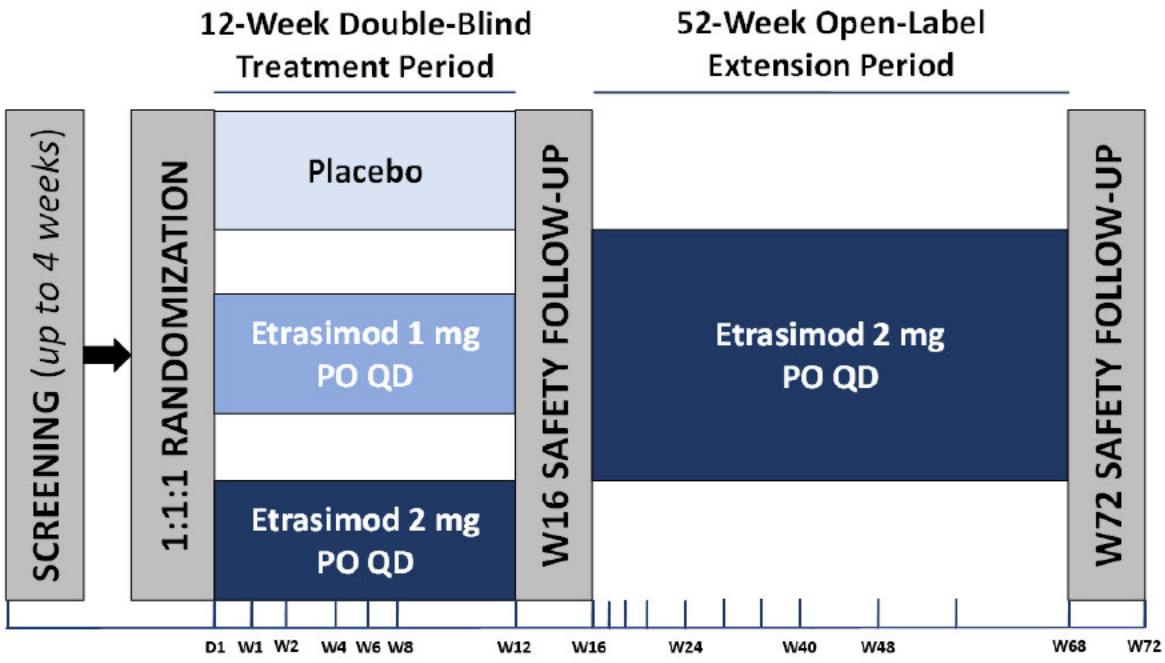
3. STUDY DESIGN

3.1. Overall Design

This Phase 2, multicenter, randomized, double-blind, placebo-controlled study in adult subjects with moderate-to-severe AD whose disease is not adequately controlled with topical therapies, or for whom those therapies are not advisable, is designed to evaluate the safety and efficacy of etrasimod monotherapy compared with placebo. The study includes multiple periods: up to a 4-week Screening Period (to determine subject eligibility); a 12-week Double-Blind Treatment Period with a 4-week Safety Follow-Up Period following the last dose of double-blinded study treatment; and eligible subjects may enter a 52-week Open-Label Extension Period also followed by a 4-week Safety Follow-Up Period after the last dose of study treatment (Figure 1). Subjects with chronic AD defined by Hanifin and Rajka criteria ([redacted]) that has been present for at least 1 year despite optimized skin care (ie, use of emollients, avoidance of irritants) will be equally randomized (1:1:1 ratio) to receive etrasimod 1 or 2 mg or placebo.

Randomization will be stratified by validated Investigator's Global Assessment (vIGA) score at Baseline (3 versus 4) and region (as appropriate). Subjects will receive etrasimod 1 or 2 mg or placebo orally once daily in a double-blind manner for 12 weeks. During the Open-Label Extension Period, all eligible subjects will receive etrasimod 2 mg orally, once daily. The application of topical moisturizers will be required at least once daily for at least 1 week prior to randomization and throughout the study without change (ie, type, frequency, application). [redacted] Rescue therapy will be permitted for uncontrolled symptoms at the discretion of the investigator based on an exacerbation of disease severity or subject self-reporting of worsened symptoms.

Figure 1: Study Design



D, day; PO, oral; QD, once daily; W, week

3.2. Discussion and Rationale for Study Design

This Phase 2 study will be a randomized, double-blind, placebo-controlled, efficacy and safety study that is intended to support the development of etrasimod for the treatment of moderate-to-severe AD. The subjects will be those with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications, or for whom topical treatment is medically inadvisable despite optimized skin care.

This study will assess etrasimod monotherapy compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study since it will provide the most robust assessment of the efficacy and safety of etrasimod. The 12-week treatment duration was selected to ensure that etrasimod could reach its maximal efficacy with some maintenance of effect while minimizing the time that a subject may be on placebo treatment. As this is a placebo-controlled study, the duration is limited, although rescue therapy is permitted for intractable symptoms, at the investigator's discretion. Regardless of the dose or treatment to which subjects are randomized in the Double-Blind Treatment Period, eligible subjects may continue into the Open-Label Extension Period with etrasimod 2 mg once daily for up to 52 weeks if continuation eligibility criteria are fulfilled. The Open-Label Extension is designed to allow subjects to continue etrasimod therapy and to assess long-term safety and tolerability of 2 mg once daily dosing as a chronic therapy.

[redacted]

Efficacy will be evaluated by changes in AD severity using the Eczema Area and Severity Index (EASI), vIGA, SCORing Atopic Dermatitis (SCORAD), and affected body surface area (BSA). To best understand the potential dose-dependent efficacy of etrasimod, the primary endpoint will be the percent change in EASI from Baseline to end of the Double-Blind Treatment Period (Week 12).

Additionally, because patient-reported outcomes (PROs) can provide subject perspectives on aspects of their disease conditions and overall health status, several PROs will be explored in this study. The pruritus numeric rating scale (NRS) will be collected by each subject on a daily basis and recorded in a diary with a 24-hour recall period. The pruritus NRS may also be assessed at the study visits. To capture important symptoms of AD and subject responses to therapy, other well used instruments such as the Patient Global Assessment (PGA), Dermatology Life Quality Index (DLQI), and Patient Oriented Eczema Measure (POEM) will be assessed at study visits. Sleep and itch will also be monitored as part of the SCORAD.

[redacted]

3.3. End of Study

Primary Completion: The date on which the last subject was examined or received an intervention to collect final data for the primary endpoint. In this study, this date is defined as when the last subject has completed assessments for Week 12.

End of Study: The end of the study is defined as the date of the last visit of the last subject in the study globally.

4. STUDY POPULATION

4.1. Inclusion Criteria – Double-Blind Treatment Period

Subjects must meet ALL of the following inclusion criteria to be eligible for enrollment into the study:

1. Men or women between ≥ 18 and ≤ 70 years of age at the time of informed consent.
2. Chronic AD, defined by Hanifin and Rajka criteria ([redacted]), that has been present for at least 1 year prior to the Screening Visit.
3. EASI ≥ 12 at the Screening Visit and ≥ 16 at the Baseline Visit.
4. vIGA score ≥ 3 (on the 0 to 4 vIGA scale, in which 3 = moderate and 4 = severe) involvement at the Screening and Baseline visits.
5. BSA ≥ 10% of AD involvement at the Screening and Baseline visits.
6. Recent history (within 6 months prior to the Screening Visit) of inadequate response to treatment with topical medications, or when topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks), which can be documented by medical records or by the history provided to the investigator by the subject despite optimized skin care (ie, avoidance of irritants, use of emollients).
7. Willing to apply a dose of topical emollient/moisturizer at least once daily for ≥ 1 week prior to the Baseline Visit and willing to continue daily application over the course of the study without change (ie, type, frequency, application).
8. Willing and able to comply with all clinic visits and study-related procedures and understand and complete study-related questionnaires.
9. Provide signed informed consent prior to conducting any procedures.

4.2. Exclusion Criteria – Double-Blind Treatment Period

Subjects will be excluded from the study if they meet ANY of the following exclusion criteria.

[redacted]

[redacted]

3. Phototherapy for AD or artificial tanning (beds, booths, or lamps) within 4 weeks prior to Screening or during Screening.
4. Presence of skin comorbidities that will interfere with study assessments of the underlying disease.

[redacted]

[redacted]

[redacted]

[redacted]

5. SUBJECT ACTIVITIES AND RESTRICTIONS

For dosing requirements, including holding the dose prior to the study visit on study visit days, see Dosage and Administration, Section 6.3. Rescue therapies and prohibited medications/procedures are located in Section 6.8.2 and Section 6.8.3, respectively.

Optimized skin care is expected to be followed prior to and maintained throughout the study as per current guidelines and recommendations for AD (Eichenfield 2014, Eichenfield 2017). Subjects are expected to continue their usual skin care routine and basic skin care regimen without notable changes for the course of the study treatment and follow-up periods. This includes frequency and length of showering or bathing, including bleach baths, the use of emollients, topical anesthetics, antihistamines, and topical and systemic anti-infective medications.

Subjects must be willing to apply topical emollient or moisturizer at least once daily for ≥ 1 week prior to the Baseline Visit and willing to continue daily application over the course of the study without change (ie, type, frequency, application).

On visit days during the study, subjects should not apply any topical emollient or moisturizer prior to attending clinic and completing their visit. Study treatment should also be held the day of clinic visits. Subjects will take their daily dose at the study site on study visit days.

6. STUDY TREATMENT

Study treatments used in this study include the pharmaceutical form of the active substance being tested (test product) and the placebo being used as a reference.

6.1. Study Treatment(s) Administered

Study treatment(s) for the Double-Blind Treatment Period are listed in Table 1. During the Open-Label Extension Period, all eligible subjects will receive 2 mg etrasimod.

Table 1: Study Treatment(s)

Study Treatment	Dose	Mode of Administration	Frequency	Formulation
Etrasimod	1 mg	Oral	Once daily	Tablet
Etrasimod	2 mg	Oral	Once daily	Tablet
Placebo	NA	Oral	Once daily	Tablet

NA, not applicable

6.2. Identity of Study Treatment

6.2.1. Etrasimod

The active pharmaceutical ingredient in etrasimod tablets is APD334 [redacted] APD334 [redacted] is manufactured, packaged, tested, and released in compliance with current Good Manufacturing Practice.

Etrasimod tablet drug product is a blue, round, biconvex, plain, immediate-release, film-coated tablet. Etrasimod tablets are composed of APD334 [redacted] and is supplied in the dosage strength (based on etrasimod free acid content) of 1 and 2 mg.

6.2.2. Placebo

The placebo tablet formulation is composed of excipients [redacted] The placebo drug product is manufactured, packaged, tested, and released in compliance with current Good Manufacturing Practice.

6.3. Dosage and Administration

One tablet (etrasimod 1 or 2 mg or placebo) is to be taken once daily with water (either with or without food) at approximately the same time each day, preferably in the morning. On study visit days, subjects should wait to take their assigned dose until after [redacted] blood samples have been drawn and after all pre-dose assessments and procedures have been

completed. Subjects will take their daily dose at the study site on study visit days. The time of [redacted] sample collection and subsequent dosing should be documented.

6.3.1. Instructions for Missed Dose(s)

Subjects should be instructed that if they forget to take a dose, they can take the dose within 8 hours of the normal dosing time; otherwise, they should take their next dose at the regular time on the following day. If the subject vomits the tablet, he/she should be instructed not to take another tablet on the same day, but to take the next dose at the regular time on the following day. Subjects should be instructed to contact the investigator if they miss more than 2 consecutive doses.

6.3.2. Dose Interruptions

If the investigator deems it necessary to withhold study treatment, temporary withholding is permitted for up to 3 days without obtaining prior approval from the Sponsor. If study treatment interruption ≥ 7 days is required for a medical reason, the investigator must contact the medical monitor as soon as this is anticipated.

The procedure for first-dose cardiac monitoring as outlined in Section 10.5.7.4 should be performed and/or discussed with the medical monitor any time a subject misses a study treatment as follows:

- ≥ 2 consecutive days within the first week of study treatment
- ≥ 7 consecutive days after the first week of study treatment

If these doses of study treatment are missed, subjects must contact the Investigator to discuss treatment re-initiation and are required to return to the study site before taking their next dose of study treatment. The subject must take the next dose of study treatment at the study site, and the in-clinic cardiac monitoring as outlined in Section 10.5.7.4 should be performed.

6.4. Method of Assigning Subjects to Treatment

For the Double-Blind Treatment Period, subjects will be centrally assigned to randomized study treatment using an Interactive Web Response System (IWRS). Details of the randomization methodology are provided in the statistical analysis plan (SAP).

During the Open-Label Extension Period, all eligible subjects will receive the same treatment (no randomization).

6.5. Selection and Timing of Dose for Each Subject

Subjects will self-administer 1 tablet once daily (with water, either with or without food). The tablet should be taken at approximately the same time each day, preferably in the morning. On visit days during the study, subjects should not apply any topical emollient or moisturizer prior to attending clinic and completing their visit. Additionally, on study visit days, subjects should wait and take their dose at the study site after blood draws [redacted] and after all pre-dose assessments have been completed.

6.6. Blinding

This study includes a Double-Blind Treatment Period with limited access to the randomization code. The investigational drug and placebo tablets are identical in physical appearance. The treatment each subject receives will not be disclosed to the investigator, study site staff, subject, Sponsor personnel involved with the conduct of the study (with the exception of the clinical supply staff and designated safety staff), or study vendors. The IWRS will hold treatment codes for study treatment.

The IWRS will be programmed with blind-breaking instructions. In the case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted based upon medical necessity. Subject safety must always be the first consideration in making such a determination. If a subject's treatment assignment is unblinded, the medical monitor or Sponsor delegate must be notified within 24 hours after breaking the blind. The date and reason the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

Unblinding may occur after all subjects have completed the Double-Blind Treatment Period, including the Safety Follow-Up Visit.

6.7. Treatment Compliance

The investigator is responsible for ensuring that subjects are correctly instructed on how to take their study treatment and that each subject is fully compliant with their assigned treatment regimen. Subject compliance will be based on tablet counts at specified study visits (Section 7.4 and Appendix 1; Table 8 and Table 9).

6.8. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine that a subject receives from Day 1 through the end of study must be recorded along with the following:

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

The medical monitor should be contacted if there are any questions regarding concomitant therapy.

6.8.1. Required Concomitant Therapy

Subjects are required to apply topical moisturizers at least once daily for at least 1 week before randomization and throughout the study without change (ie, type, frequency, application). Topical moisturizers are generally permitted, except for new prescription moisturizers or moisturizers containing additives (including ceramide, hyaluronic acid, urea, or filaggrin degradation products) during the Screening Period or during the study. Subjects may continue using stable doses of such moisturizers if initiated before the Screening Visit.

6.8.2. Allowed Concomitant Therapy and Rescue Therapy

If medically necessary due to intolerable symptoms, rescue therapy will be permitted at the discretion of the investigator based on disease worsening as evaluated by the investigator (ie, increased EASI or BSA), or as reported by the subject (ie, worse itch). Optimized skin care is expected to be followed prior to and maintained throughout the study as per current guidelines and recommendations for AD (eg, avoidance of irritants).

Whenever possible during the Double-Blind Treatment Period, rescue therapies should be withheld for at least 4 weeks from the start of the study treatment. If possible, investigators should attempt to limit initial rescue therapy to topical medications as a first line treatment for AD and AD flares according to current guidelines and recommendations (Eichenfield 2014, Eichenfield 2017). Primarily topical medium potency corticosteroids such as triamcinolone acetonide 0.1% and fluocinolone acetonide 0.025% should be used, and applied to problem areas only, in conjunction with oral antihistamines, if needed. Topical calcineurin inhibitors may also be applied to problem areas if additional therapy is required for intractable symptoms. Only when symptoms continue to persist are systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine) recommended for rescue therapy.

If a subject receives rescue therapy with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs, study treatment will need to be immediately discontinued. After treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the investigator and the medical monitor, but no sooner than 5 half-lives after the last dose of systemic rescue medication.

Rescue therapies and the indication and details (ie, name, dose, frequency of administration, strength, duration of use) will be recorded in the subject's chart and eCRF, if applicable. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this purpose, if necessary.

During the Open-Label Extension Period, after 12 weeks (Week 28), topical corticosteroids and calcineurin inhibitors can be used, and details regarding therapy (ie, name, dose, frequency of administration, strength, duration of use) should be recorded.

6.8.3. Prohibited Concomitant Therapy and Procedures

[redacted]

The following medications or procedures are excluded from the Double-Blind and Open-Label Extension Periods of the study:

- [redacted]
- [redacted] If these medications are initiated,

then study treatment must be interrupted and potentially terminated. See rescue therapy (Section 6.8.2)

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Phototherapy and/or ultraviolet light/tanning
- Initiation during the Screening Period of prescription emollients or moisturizers [redacted]
- Any change in emollients or moisturizers (ie, type, frequency, application) within 1 week prior to Baseline and throughout the course of the Study
- [redacted]
- [redacted]
- [redacted]

[redacted]

For concomitant procedures:

- Subjects should not undergo major elective surgery while on study treatment during the Double-Blind Treatment Period. During the Open-Label Extension Period, discuss first with the medical monitor
- Subjects may not donate blood during the study and for 4 weeks after the last dose of study treatment

- Subjects may not donate sperm, or oocytes during the study and for 4 weeks after the last dose of study treatment

7. STUDY TREATMENT AND MATERIALS MANAGEMENT

7.1. Packaging and Labeling

Tablets are packaged in induction-sealed, high-density polyethylene bottles with child-resistant screw caps and desiccant canisters. Each bottle will be labeled as required per country requirements.

7.2. Storage and Handling

[redacted]

7.3. Preparation

No preparation by study site personnel is required.

7.4. Accountability

At specified study visits, previously dispensed study treatment tablets will be collected by the investigator or qualified staff to assess subject compliance (Appendix 1; Table 8 and Table 9).

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of study treatment tablets. To ensure adequate records, all drug supplies will be accounted for in the drug accountability inventory forms and will be monitored by counting of unused study treatment tablets.

7.5. Retention and Disposal

All study treatment will be reconciled by the study monitor and unused study treatment will be returned or destroyed according to applicable country regulations. On-site destruction following all local regulations and in accordance with applicable site standard operating procedures (SOPs) is permitted. Prior to any action being taken with study treatment, the investigator will contact the Sponsor (or contract research organization [CRO] for approval of such action). Final reconciliation will be performed at study completion.

8. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

8.1. Discontinuation of Study Treatment

A subject's treatment with study drug may be discontinued for any of the following reasons:

- AE
- Death
- Pregnancy (Section 10.5.9)
- Protocol deviation
- Physician decision
- Withdrawal by subject
- Lost to follow-up
- Study terminated by Sponsor
- Criteria met from cardiac heart rate monitoring to discontinue study treatment (Section 10.5.7.4)
- Other

8.2. Discontinuation from the Study

Subjects may discontinue from the study at any time for any of the following reasons:

- AE
- Death
- Pregnancy (Section 10.5.9)
- Protocol deviation
- Physician decision
- Withdrawal by subject
- Lost to follow-up
- Study terminated by Sponsor
- Criteria met from cardiac heart rate monitoring to discontinue study treatment (Section 10.5.7.4)
- Other

A subject may elect to discontinue study participation at any time for any reason without prejudice to their future medical care by the physician or at the institution. Subjects who discontinue study treatment during the Double-Blind Study Period but who consent to remain in the study will continue to comply with study visits and assessments.

If a subject withdraws consent, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. The investigator should make a reasonable attempt to document the specific reason why consent was withdrawn.

An end of treatment (EoT) visit should be completed within 1 week of when study treatment has been terminated and a Safety Follow-Up Visit 4 weeks after the last dose of study treatment. Whenever possible, subjects should continue on study even when study treatment has been discontinued during the Double-Blind Treatment Period.

8.3. Lost to Follow-Up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and cannot be contacted by the study site.

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (this would include telephone calls and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.4. Premature Termination of the Study or Study Site

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Upon request of Health Authorities

The Sponsor will notify the investigator if the study is placed on hold or if the Sponsor decides to discontinue the study. Health authorities and (Independent Ethics Committee[s]) IECs/ (Institutional Review Board[s]) IRBs will be informed about the termination of the study in accordance with applicable regulations.

The Sponsor has the right to replace a study site at any time. Reasons for replacing a study site may include, but are not limited to:

- Excessively slow recruitment

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP)

9. STUDY PERIODS

9.1. Screening and Eligibility

Subjects must sign the informed consent before any study-specific procedure can be performed. The Screening Period will last up to 4 weeks. A summary of Screening and enrollment events is provided in the [redacted]. Inclusion and exclusion criteria are listed in Section 4.1 and Section 4.2, respectively. Eligible subjects who have met all inclusion/exclusion criteria requirements may be randomized into the study.

Eligibility for the Open-Label Extension Period will be assessed at the Week 16 visit (coincides with the Double-Blind Treatment Period Safety Follow-Up Visit) and are defined in Section 4.3.

9.1.1. Discontinuation of AD Medications

[redacted]

As per eligibility criteria (Section 4.2), previous use of systemic medications for AD must be at least 4 weeks prior to Screening, dupilumab at least 8 weeks prior to Screening, and other biologic agents within 5 half-lives (if known) or 16 weeks prior to Screening, whichever is longer.

9.2. Treatment and Safety Follow-Up Periods

Subjects who complete all screening requirements and remain eligible for the study will be randomized to receive etrasimod 1 or 2 mg or placebo orally once daily in the Double-Blind Treatment Period. Subjects will continue to receive study treatment for 12 weeks. Eligible subjects may receive open-label treatment with etrasimod 2 mg for up to 52 weeks following completion of all Double-Blind Treatment Period assessments, including the Safety Follow-Up Visit (Week 16). Subjects will self-administer study treatment, except on study visit days. Study visits and assessments will be conducted according to the [redacted].

Safety Follow-Up Visits are scheduled 4 weeks after last dose of study treatment in both the Double-Blind Treatment and Open-Label Extension Periods.

9.2.1. Double-Blind Treatment Period: Week 0/Day 1 (Pre-Randomization)

[redacted]

[redacted]

Women of childbearing potential will have a urine pregnancy test prior to randomization (Section 10.2.6).

Subjects who continue to meet all eligibility criteria will be randomized as outlined in Section 6.4.

9.2.2. Double-Blind Treatment Period: Randomization (Study Day 1)

Randomization may occur on Day 1 after all eligibility criteria have been confirmed. It is recommended that procedures are performed in a consistent order and at approximately the same time of day for each visit. [redacted] The recommended sequence of events is as follows:

- Questionnaire administration
- AE review
- Vital signs (performed with subject in the seated position)
- [redacted]
- Physical examination including disease severity assessments
- Blood sample collection for laboratory tests and [redacted]

Day 1 pre-randomization vital signs (resting HR, BP, body temperature, and respiratory rate) will be used as baseline measurements. The lowest pre-dose HR measurement will be used for comparison to the post-dose HR measurement. See Section 10.5.7.4 for detailed guidance on cardiac monitoring following administration of the first dose and subject discharge criteria post-dose.

After dosing on Day 1:

- [redacted]
- [redacted]

[redacted]

9.2.3. Additional Study Visits (After Day 1)

The recommended sequence of events presented for Day 1 (Section 9.2.2) should be followed for subsequent visits during the Double-Blind Treatment Period, where applicable, with study treatment being administered after blood sample collection.

9.2.4. Double-Blind Treatment Period Safety Follow-Up Visit

Subjects who complete the Double-Blind Treatment Period will return for a Safety Follow-Up Visit 4 weeks after the last dose of study treatment (Week 16). Visit assessments are detailed in the [redacted].

Subjects who terminate the study treatment early in the Double-Blind Treatment Period, should have an EoT Visit (Section 9.3) and a Safety Follow-Up Visit 4 weeks after the last dose of study treatment.

For subjects that have discontinued study treatment prior to Week 12 or are determined ineligible for the Open-Label Extension Period (Section 9.2.5), Week 16 will be the End of Study Visit (Section 9.4). Whenever possible, visits should be scheduled on the Weeks designated in the [redacted].

9.2.5. Open-Label Extension (Week 16-Week 68)

For subjects that remain on study treatment at Week 12, eligibility into the Open-Label Extension Period will be determined at Week 16 (coincides with the Double-Blind Treatment Period Safety Follow-Up Visit [Section 9.2.4]).

For eligible subjects that continue into the Open-Label Extension Period, following the administration of etrasimod 2 mg, a cardiac monitoring investigation will be performed [redacted] as outlined in Section 10.5.7.4.

If by approximately Week 28, within the Open-Label Extension Period, the subject has achieved suboptimal benefit from etrasimod treatment, both subjects and investigators should discuss the subject's continued participation in the study.

The recommended sequence of events presented for Double-Blind Treatment Period Day 1 (Section 9.2.2) should be followed for visits during the Open-Label Extension Period, where applicable, with study treatment being administered after blood sample collection.

9.2.6. Open-Label Extension Period Safety Follow-Up Visit

Subjects who complete the Open-Label Extension Period will return for a Safety Follow-Up Visit 4 weeks after the last dose of study treatment (Week 72). Visit assessments are detailed in the [redacted].

Subjects who terminate the study treatment early in the Open-Label Extension Period, should have an EoT Visit (Section 9.3) and a Safety Follow-Up Visit 4 weeks after the last dose of study treatment.

The Open-Label Extension Period Safety Follow-Up Visit will also be the End of Study Visit (Section 9.4).

9.3. Early Study Treatment Termination

Subjects who stop taking their study treatment before the end of the Double-Blind Treatment or Open-Label Extension Periods will return to the study site for an EoT Visit within 1 week of the last study treatment administration. Subjects who stop taking their study treatment before the end of the Double-Blind Treatment Period are not eligible to participate in the Open-Label Extension Period. Visit assessments are detailed in the [redacted]. Study site staff will work with subjects who withdraw early to obtain as much follow-up data as possible. Lymphocyte counts should be monitored until returned to approximately baseline or stable. In the Double-Blind Treatment Period, whenever possible, subjects should continue in the study even if study treatment has been discontinued. Subjects who discontinue study treatment, but who consent to remain in the study will continue to comply with study visits and assessments.

9.4. End of Study Visit

The End of Study Visit for an individual subject is defined as the date of the final study contact (eg, Safety Follow-Up Visit) when assessments or procedures are done.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1. Subject Informed Consent

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activities are performed.

10.2. Screening and Eligibility

Subject eligibility will be assessed based on protocol inclusion and exclusion criteria. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. Screening procedures must be completed within 4 weeks prior to receiving the first dose of study treatment (Appendix 1; Table 8).

Additional eligibility assessment will be performed at Week 16 to determine eligibility to continue into the Open-Label Extension Period, as outlined in Section 4.3.

10.2.1. Rescreening

If a subject fails ≥ 1 screening laboratory (or other) assessment criteria, the assessment(s) may be repeated once at the discretion of the investigator, and the subject may be enrolled if criteria are then met, provided the assessments are completed within the Screening Period. Any rescreening laboratory assessments beyond 1 time will need to be discussed with the medical monitor before proceeding. If a subject fails screening, then 1 re-screening attempt during a new Screening Period may be made, if appropriate. Each subject must be reconsented prior to each screening attempt.

10.2.2. Demography and Other Subject Characteristics

Demographics including year of birth, sex at birth, Hispanic ethnicity, and race as described by the subject, will be collected at Screening.

10.2.3. Medical History/Atopic Dermatitis History

A complete medical history of each subject will be collected and documented during Screening to determine subject eligibility. The history should include illnesses, hospitalizations, and participation in other investigational drug studies.

The diagnosis of AD by Hanifin and Rajka criteria ([redacted]) will be recorded, and the duration of AD.

10.2.4. Prior and Ongoing Therapies

Prior therapies related to the treatment of AD will be collected during Screening. Documentation should include the rationale for prior treatment failure. All ongoing medications will be recorded at Screening and updated as needed throughout the entire study.

10.2.5. Social History

A social history including the amount and duration of tobacco and alcohol use will be collected at Screening.

A standard urine drug screen will be performed. Subjects who test positive will be assessed for eligibility in study participation by the investigator.

10.2.6. Pregnancy Testing

A serum pregnancy test for β-hCG will be performed at Screening to determine eligibility for women of childbearing potential. Post-screening, a urine pregnancy test will be performed on women of childbearing potential on Day 1 pre-randomization and at specified study visits before in-clinic study treatment administration, as indicated in the [redacted]. Home pregnancy tests may be required at [redacted]. A positive urine pregnancy test must be confirmed with a follow-up serum β-hCG pregnancy test. If at any point there is a case of a positive urine β-hCG test, the subject will have study treatment interrupted and a serum sample will be obtained and submitted to the central laboratory for β-hCG testing. If the serum test confirms positive, the subject will be discontinued from the study treatment and all the necessary follow up will be conducted as per Section 10.5.9. If the serum test is negative, the subject may resume study treatment.

Negative pregnancy test results must be documented for all women of childbearing potential prior to dosing at applicable study visits. Women who are surgically sterile or who are postmenopausal are not considered to be of childbearing potential. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

10.2.7. Active Infections or Live Vaccines

Given the mechanism of action of etrasimod and the known pharmacodynamic effect of lymphocyte lowering, subjects with known active infections will be excluded from the study. Live vaccinations cannot be administered within 4 weeks of Screening, during Screening, during the Treatment Periods with study treatment, or 2 weeks after treatment completion.

10.2.7.1. Known Active Infections

Subjects with known active bacterial, viral, fungal, mycobacterial infection, or other infection (including TB or atypical mycobacterial disease) or any major episode of infection that required hospitalization or treatment with IV antibiotics within 4 weeks of Screening or during Screening, or oral antibiotics within 2 weeks prior to Screening will be excluded from the study. Superficial fungal infection of the nail bed will be allowed.

10.2.7.2. Known or Suspected Immunodeficiencies

[redacted]

10.3. Efficacy Assessments

Multiple parameters will be collected during the study to assess efficacy/effectiveness of etrasimod including measures of AD severity, and patient-reported measures of AD symptoms and quality of life. Questionnaires and PRO assessments should be administered prior to obtaining investigator assessments, safety and laboratory assessments, and study treatment administration. Refer to the study manual for instructions on the administration and use of all patient-reported instruments (including POEM and DLQI).

Wherever possible, to maintain consistency, the same individual at the site should administer the investigator assessments for the duration of the study.

10.3.1. Eczema Area and Severity Index

The EASI is a validated scoring system that grades the severity and extent of AD (Tofte 1998, Hanifin 2001). EASI is the core outcome measure for the clinical signs of AD, which has been used extensively in clinical studies. The EASI is a composite index with scores ranging from 0 to 72. The EASI scoring assessment multiplies the percentage of the affected area in 4 specific disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification), which will each be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe).

The EASI Area Score is documented for 4 regions of the body. Region 1: head and neck; Region 2: trunk (including genital area); Region 3: upper limbs; and Region 4: lower limbs (including buttocks), with the area of AD involvement assessed as a percentage by body area and

converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

The EASI will be collected at time points according to the [redacted].

10.3.2. SCORing Atopic Dermatitis

The SCORAD is a validated measure of the extent and severity of AD. There are 3 components to the assessment: A = extent or affected BSA, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the subject or relative on a Visual Analogue Scale, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C where the maximum is 103 (European-Task-Force-on-Atopic-Dermatitis 1993).

The SCORAD will be performed at time points according to the [redacted].

10.3.3. Validated Investigator's Global Assessment

The vIGA scale for AD is a 5-point scale to measure disease severity. The IGA score is selected using descriptors that best describe the overall appearance of skin lesions at a given time point using the following scoring: 0 = clear (no inflammatory signs of AD); 1 = almost clear (barely perceptible erythema and papulation); 2 = mild (slight but definite erythema and papulation); 3 = moderate (clearly perceptible erythema and papulation); and 4 = severe (marked erythema papulation) (vIGA-AD™ 2017).The vIGA will be performed at time points according to the [redacted].

10.3.4. Atopic Dermatitis Body Surface Area Involvement

Body surface area affected by AD will be assessed for each section of the body. The possible highest score for each region is: head and neck (9%), anterior trunk (18%), back (18%), upper limbs (18%), lower limbs (36%), and genitals (1%) and will be reported as a percentage of all major body sections combined.

The BSA assessment will be performed at time points according to the [redacted].

10.3.5. Patient-Reported Outcomes

10.3.5.1. Pruritus Numeric Rating Scale

The pruritus NRS is a simple assessment tool that subjects will use to report the intensity of their pruritus (itch). The scale for the pruritus NRS is from 0 to 10 with 0 being "no itch" and 10 being "the worst itch imaginable."

At Baseline and subsequent visits, subjects will be asked to rate the intensity of their itch (maximum/peak and average) over the previous 7 days. Subjects will also be asked to rate their average itch intensity over the previous 24 hours and their maximum itch intensity in a daily diary (Stander 2013, PruritusResources 2019).

The pruritus NRS will be assessed at time points according to the [redacted].

10.3.5.2. Dermatology Life Quality Index

The DLQI is a validated 10-item questionnaire designed to measure the impact of skin disease on the quality of life (QoL) of an affected individual (Finlay 1994). The format is a simple response to 10 items, which assess QoL over the past week. For each item, the scale is rated as follows: 0 = "not at all"; 1 = "a little"; 2 = "a lot"; 3 = "very much," with an overall scoring system of 0 to 30; a high score is indicative of a poor QoL. For general inflammatory skin conditions a change in DLQI score of at least 4 points is considered clinically important (Basra 2015).

The DLQI will be assessed at time points according to the [redacted].

10.3.5.3. Patient Global Assessment of Disease

Two questions will be included for subjects to rate their disease and their disease severity.

Subjects will rate their overall well-being based on a 5-point Likert scale from poor to excellent. Subjects will be asked, "Considering all the ways in which your eczema affects you, indicate how well you are doing." Response choices are: 'Poor', 'Fair', 'Good', 'Very Good,' or 'Excellent'.

Subjects will also be asked to best describe the overall appearance of skin lesions at a given time point using the vIGA scale (Section 10.3.3). The vIGA scale has been adapted for patients to complete. The scale has been modified for easier understanding for subjects, to exclude medical terminology (eg, lichenification has been adapted to thickening and erythema to redness).

Subjects will complete these assessments at time points according to the [redacted].

10.3.5.4. Patient Oriented Eczema Measure

The Patient Oriented Eczema Measure (POEM) is a patient-derived validated tool used for monitoring atopic eczema severity. The POEM consists of 7 questions asking patients to rank how many days over the past 7 days they have experienced specific AD-related symptoms (UON 2004, Charman 2013).

Each of the seven questions carries equal weight and is scored from 0 to 4 as follows: No days = 0; 1-2 days = 1; 3-4 days = 2; 5-6 days = 3; Every day = 4. The scores from the 7 questions are added up to give an overall POEM score. An overall POEM score of 0-2 = 'clear/almost clear', 3–7 = 'mild', 8–16 = 'moderate', 17–24 = 'severe', and 25–28 = 'very severe atopic eczema'.

Subjects will complete these assessments at time points according to the [redacted].

[redacted]

10.5. Safety Assessments

Planned time points for all safety assessments are provided in the [redacted].

10.5.1. Vital Signs

Resting vital sign measurements will be made with the subject in the seated position and include HR, BP, body temperature, respiratory rate. Vital signs will be measured prior to any blood draws that occur at the same study visit or overlapping time point.

10.5.2. Physical Examinations

A complete physical examination will be performed as indicated in the [redacted]. A focused physical examination will be performed at all other study visits to assess body systems related to specific areas of complaint (old and new) and for AD severity.

Genitourinary and breast exams may be performed as necessary for assessment of AD severity as needed. Symptom-directed physical examinations may be performed at the investigator's discretion at any time during the study.

The full physical examination includes the following assessments:

- General inspection
- Head/ears/eyes/nose/throat examination
- Neck
- Cardiac examination
- Auscultation of lungs
- Abdominal examination
- Neurological assessment
- Musculoskeletal assessment
- Full skin assessments

[redacted]

10.5.4. Clinical Laboratory Assessments

Details regarding clinical laboratory sample collection, preparation, and shipment are provided in the laboratory manual by the central laboratory. All laboratory assessments required by the protocol will be performed by a central laboratory unless otherwise stated. See information on the grading and management of laboratory abnormalities according to assessed severity provided in Appendix 2 and Appendix 3. See Table 3 for the list of clinical laboratory tests to be performed and the [redacted] for timing and frequency for each test.

Clinical safety laboratory tests should be completed pre-dose. The investigator must review the laboratory report, document the review, and record any clinically relevant changes on the AE section of the eCRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 30 days after the last dose of study treatment, should be repeated until the

values return to normal or baseline or are no longer considered clinically significant by the investigator. If such values do not return to normal or baseline, or otherwise resolve to a non-clinically significant value within a reasonable period of time, as judged by the investigator, the etiology should be identified, and the Sponsor should be notified. Relevant local laboratory results and non-protocol specified assessments that are performed at a local laboratory and result in a change in subject management or are considered clinically significant by the investigator (eg, AE or dose modification) should be recorded in the eCRF.

Information on the grading and management of laboratory abnormalities according to assessed severity is provided in Appendix 2 and Appendix 3.

Table 3: Clinical Laboratory Tests

Infectious Disease	**Drugs of Abuse**
Human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody (with reflex PCR) TB with interferon-gamma release assay (IGRA; preferably, QuantiFERON-TB Gold In-Tube).	Urine drug screen: amphetamine, cocaine, methamphetamine, methylenedioxymethamphetamine, or phencyclidine
Pregnancy Testing	**Coagulation**
Serum pregnancy test human chorionic gonadotropin (β-hCG- [only for females of child-bearing potential with positive urine β-hCG]) Urine β-hCG (only for females of child-bearing potential)	Prothrombin time (PT) Activated partial thromboplastin time (PTT) International Normalized Ratio (INR)
Urinalysis	**Hematology**
Appearance Bilirubin Color Glucose Ketones Microscopic examination of sediment Nitrite Occult blood pH Protein Specific gravity Urobilinogen	Hematocrit Hemoglobin Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential [redacted]
Serum Chemistry	
Albumin Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Creatinine with eGFR by CKD-EPI Creatine kinase Gamma-glutamyl transferase (GGT) Glucose Lactate dehydrogenase (LDH)	Lipase Magnesium Phosphorus Potassium Sodium Thyroid-stimulating hormone (TSH) with reflex free T4 and free T3 if abnormal Total bilirubin Direct bilirubin Total cholesterol Total protein Triglycerides Uric acid
Other Tests	
[redacted]	

[redacted]

Screening/Baseline Assessment:

The initial eye examination will include:

- Ophthalmologic history

- Best corrected visual acuity measurement (autorefraction, using Snellen chart internationally)
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- [redacted]
- Retinal photographs should be taken
- Ophthalmic findings should be recorded

Post-Screening/Post-Baseline Assessments:

At the scheduled ophthalmology visit, the eye examination will include:

- Ophthalmic history
- Best corrected visual acuity measurement
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- [redacted]
- Retinal photographs should be taken
- Ophthalmic findings should be recorded

Additional testing at the visits should be performed as deemed clinically necessary. Subjects experiencing unexpected ophthalmic symptoms without a known suspected etiology or experiencing a relevant ophthalmic AE may need to have repeat ophthalmoscopy [redacted] testing performed. Guidance on clinical monitoring of ophthalmic symptoms is provided in Section 10.5.7.6.

10.5.7. Safety Monitoring Guidance

10.5.7.1. Drug Induced Liver Injury

Based on United States Food and Drug Administration guidance (FDA 2009) for drug induced liver injury, discontinuation of study treatment should be considered if any of the following occur:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for > 2 weeks
- ALT or AST > 3 × ULN **and** Total Bilirubin > 2 × ULN, or international normalized ratio > 1.5
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Information on the grading and management of laboratory abnormalities according to assessment severity is provided in Appendix 2 and Appendix 3, respectively.

[redacted]

10.5.7.3. Guidance on Monitoring Subjects for Infections

[redacted]

Therefore, investigators and subjects should be vigilant in monitoring for signs and symptoms of infections during the trial and after discontinuation of study treatment. Subjects should be instructed to promptly report to their treating physicians and investigator any signs and symptoms of infection (eg, fever, visualized red or swollen body parts). All infections that develop during the study will be reported as AEs on the respective eCRF pages (Appendix 2).

All infections that develop during the study will be reported as AEs on the respective eCRF pages. In the case of suspected or confirmed serious or atypical infection that is considered related to study treatment, study treatment interruption should be considered, and the Investigator should inform the medical monitor of any such cases. The elimination half-life of approximately 33 hours allows washout of etrasimod within a week.

Additional evaluations will be performed at the discretion of the Investigator and/or specialist consultants.

[redacted]

All radiologic images (eg, magnetic resonance imaging, computer tomography, x-rays) and diagnostic laboratory test results performed by local laboratories/facilities should be retained as source documents by study sites and made available upon request by the Sponsor for central adjudication as needed. All infections that develop during the study will be reported as AEs on the respective eCRF pages.

The Investigator should consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof (eg, antiviral treatment for herpes simplex or zoster) and may consult with infectious disease experts, as appropriate.

[redacted]

[redacted]

[redacted]

10.5.7.6. Ophthalmic Symptom Monitoring

[redacted]

Subjects experiencing unexpected ophthalmic symptoms, including blurred vision, decreased visual acuity, or other clinically significant ocular adverse events, without a known/suspected etiology may need to have repeat ophthalmoscopy [redacted] testing performed. [redacted]

Unscheduled ophthalmology visits in case of any visual complaint: If, during the study, there are complaints of decreased vision or identification of worsening visual acuity (equal to or more than 2 lines on a standard eye chart using best corrected vision) then an unscheduled ophthalmic examination should be performed.

At an unscheduled ophthalmology visit, the eye examination will include:

- Best corrected visual acuity measurement
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- [redacted]

[redacted] These subjects must be followed up monthly with ophthalmologic evaluations until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than 3 months). These evaluations will include repeat best-corrected visual acuity, fundus examination, [redacted]. If the subject does not show definite signs of improvement on examination by specialist testing [redacted] 6-8 weeks after interruption of study treatment, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated.

[redacted]

10.5.8. Adverse Events

10.5.8.1. Definitions

10.5.8.1.1. Adverse Event

An AE is any untoward medical occurrence that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs can include, but are not limited to, any of the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant disease or accidents
- Clinically relevant adverse changes in laboratory parameters over the course of the study
- Pre-existing conditions that worsen in severity, increase in frequency, or have new signs/symptoms

Information on the grading and management of laboratory abnormalities according to assessment severity is provided in Appendix 2 and Appendix 3, respectively.

10.5.8.1.2. Serious Adverse Event

An AE should be classified as a serious adverse event (SAE) if it meets 1 of the following criteria:

Fatal:	The AE resulted in death.
Life-threatening:	The AE placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this definition.
Disabling/ incapacitating:	The AE resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the study treatment before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

10.5.8.1.3. Adverse Drug Reaction

An adverse drug reaction (ADR) in the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, is any noxious and unintended response to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

10.5.8.1.4. Events of Interest

Based on the mechanism of action of etrasimod and prior experience with other agents acting via a similar mechanism, as well as known comorbid conditions with AD, potential events of interest may be identified. In addition to appropriate reporting of these events as an AE or an SAE, supplementary detailed information may be collected.

10.5.8.1.5. Severity

The severity of each AE will be assessed at the onset by a nurse/or physician. When recording the outcome of the AE, the maximum severity of the AE experienced will also be recorded. The severity of each AE will be graded according to the Common Terminology Criteria for Adverse Events:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Grade 4	Life-threatening consequences, urgent intervention indicated.
Grade 5	Death related to an AE.

Additional information on CTCAE grading of AEs is provided in Appendix 2.

10.5.8.1.6. Relationship

The investigator is obligated to assess the relationship between the study treatment and each occurrence of each AE. The AE relationship to study treatment must be characterized as 1 of the following categories:

Not Related:	The AE does not follow a reasonable temporal sequence from administration of the drug, does not abate upon discontinuation of the drug, does not follow a known or hypothesized cause-effect relationship, and (if applicable) does not reappear when the drug is reintroduced, furthermore, there may exist a clear alternative medical

	explanation (e.g., underlying disease state) or association with study procedure or study conduct.
Unlikely Related:	The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
Probably Related:	The AE follows a reasonable temporal sequence from administration of the drug and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
Related:	The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study treatment administration should be considered and investigated. The investigator should consult the IB and the Product Information of marketed products within the drug class, when applicable. For each AE, the investigator must document in the medical notes that he/she has reviewed the AE and has provided an assessment of causality. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor; however, the investigator should always make an initial assessment of causality for every event before the initial transmission of the SAE to the Sponsor. The investigator may change his/her opinion of causality based on subsequent receipt of information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.5.8.2. Eliciting, Recording, and Reporting Adverse Events

10.5.8.2.1. Eliciting Adverse Events

Subjects will be instructed that they may report AEs at any time. An open-ended or nondirected method of questioning should be used at each study visit to elicit the reporting of AEs.

10.5.8.2.2. Recording Adverse Events

The AE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent) and continues up to 30 days after the last study treatment administration. If an AE is not resolved or stabilized by this time, the Sponsor in consultation with the investigator will decide whether to continue to monitor the AE or closeout the event in the database if no further follow-up is necessary.

Any SAE suspected to be related to the study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration.

Investigator and study personnel will record all AEs and SAEs whether received through an unsolicited report by a subject, elicited during subject questioning, discovered during physical

examination, laboratory testing, and/or other means by recording them on the eCRF and SAE Report Form, as appropriate. The following information should be recorded on the AE eCRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

For SAEs, events occurring secondary to the primary event should be described on the eCRF in the narrative description field.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the eCRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

10.5.8.2.3. Diagnosis Versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

10.5.8.3. Reporting Serious Adverse Events

All SAEs are subject to reporting requirements.

10.5.8.3.1. Serious Adverse Events

All SAEs, whether or not considered related to study treatment, must be reported to the Sponsor Contact **within 24 hours of becoming aware of the event.** Enter the SAE information on the eCRF, and send other available pertinent information (eg, hospital records, laboratory results) to the designated Sponsor contact:

IQVIA Pharmacovigilance

[redacted]

If additional follow-up information is required or becomes available for a previously reported SAE, entry of the new information on the eCRF should be completed **within 24 hours of awareness.**

Elective hospitalization and/or surgery for clearly preexisting conditions (eg, a surgery that has been scheduled prior to the subject's entry into the study) will not be reported as an SAE. All other hospitalizations, including elective hospitalizations for any condition that was not preexisting, will be reported as an SAE.

Any SAE that is ongoing when the subject completes the study or discontinues the study will be followed by the investigator until the event resolves, stabilizes or returns to baseline status.

10.5.8.3.2. Serious, Unexpected Adverse Drug Reactions

All ADRs that are both serious and unexpected are subject to expedited reporting to regulatory agencies. An unexpected ADR is one for which the nature or severity is not consistent with information in the relevant source documents.

The following documents or circumstances will be used to determine whether an AE/ADR is expected:

1. For a medicinal product not yet approved for marketing in a country, the RSI of the company's IB will serve as the source document in that country.
2. Reports that add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the RSI of the IB would be considered "unexpected."

10.5.9. Pregnancy

If at any point any pregnancy test is confirmed positive, the subject will be withdrawn from the study treatment.

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment and until 30 days after the last dose.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE; however, to fulfill regulatory requirements, any pregnancy and/or pregnancy outcome should be reported via the Pregnancy Report Form to the designated Sponsor Contact **within 24 hours of awareness.**

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported as such even if outside the SAE reporting period.

10.6. Procedures for Overdose

See the IB for additional information.

There is no established overdose threshold for this clinical study, nor is there any recommended specific treatment for an overdose but to provide supportive care if clinically indicated.

In the event of a suspected overdose, the investigator and/or treating physician should:

1. Closely monitor the subject for any AE/SAE and laboratory abnormalities and provide supportive care.

2. Contact the medical monitor immediately.
3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study treatment, if possible, and if requested by the medical monitor.
4. Document the total quantity of the excess dose, taking into consideration the duration of the overdose in the eCRF and the time frame.

Subjects who overdose will be counseled on correct dosing and administration of study treatment. Decisions regarding study discontinuation, dose interruptions, or dose modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the subject.

[redacted]

11. PLANNED STATISTICAL METHODS

11.1. General Considerations

Statistical considerations will be discussed in Sections 11.2 to 11.8 for the Double-Blind Treatment Period, and in Section 11.9 for the Open-Label Extension Period. Details regarding the statistical analyses will be provided in the SAP, which will be finalized prior to database lock of the Double-Blind portion of the study.

Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

11.2. Determination of Sample Size

It is assumed that the percent change in EASI from Baseline to Week 12 will be normally distributed with a SD of 41%. Assuming a 1:1:1 randomization, 120 subjects (40 subjects each in 1 mg etrasimod, 2 mg etrasimod, or placebo groups) is sufficient to achieve at least 90% power to detect a difference of 35% in EASI from Baseline to Week 12 between each of the etrasimod treatment groups and placebo by a 2-sample t-test using a 1-sided significance level of 0.025 with estimated SD at 41%. This sample size also accounts for an estimated drop-out rate up to 25%.

11.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined (Table 7).

Table 7: Analysis Sets

Analysis Set	Description
Full Analysis Set (FAS)	The FAS includes all randomized subjects, irrespective of whether they received any study treatment.
Modified Full Analysis Set (mFAS)	The mFAS population consists of all randomized subjects who received at least 1 dose of study treatment, have a baseline measurement, and have at least 1 post-randomization measurement. The mFAS is endpoint specific, therefore subjects included in the analysis set for 1 endpoint may differ from another endpoint, based on the baseline and post-baseline data.
Per Protocol Set	The Per Protocol Set consists of all subjects in the FAS population who adhere to the protocol. The Per Protocol Set will be used in sensitivity analyses of the primary and key secondary endpoints to evaluate the influence of major protocol violators and protocol deviators on the primary results. Subjects may be excluded from this population if they violate the eligibility criteria or significantly deviate from the study plan. Specific reasons for warranting exclusion from this population will be documented prior to database lock and may include, but are not limited to, study treatment noncompliance, receiving incorrect study treatment, missing more than a defined number of visits while still on study,

Analysis Set	Description
	and chronic prohibited medication use while on study treatment. The statistical analysis plan, which will be finalized prior to database lock, will be the final documentation for the Per Protocol Set definition.
Safety Set	The Safety Set includes all randomized subjects who received at least 1 dose of study treatment.
[redacted]	[redacted]

11.4. Missing Data

11.4.1. Primary Methods of Handling Missing Data and Rescue Medication Uses

In order to analyze primary and secondary efficacy endpoints at Week 12 in the Full Analysis Set (FAS), handling missing data and rescue mediation uses are specified as following.

For the primary endpoint of percentage change in EASI from Baseline to Week 12, EASI scores after rescue medication use will be set to missing. All missing EASI scores at scheduled visits up to Week 12 will be imputed using a multiple imputation (MI) technique with a fully conditional specification method and predictive mean matching for EASI scores (Heitjan 1991, van Buuren 2007). Detailed MI model descriptions and analysis procedures will be specified in the SAP.

For analysis of dichotomous endpoints (eg, 75% reduction in EASI [EASI-75], vIGA 0 to 1) at Week 12, all subjects in the FAS will be included in the analyses. Subjects in any of the following cases will be considered as "non-responders" or "failure":

- Use rescue medications during treatment;
- Prematurely discontinue from study due to any reason prior to Week 12; or
- With missing data at Week 12 for any reason.

11.4.2. Sensitivity Analyses

In addition to the primary methods for handling missing data and rescue medication use in the FAS described in Section 11.4.1, the following sensitivity analyses will be performed for the primary and key secondary endpoints using alternative methods to handle missing data and rescue medication use, and/or in alternative analysis populations:

- For the MI analysis of percentage of change in EASI from Baseline to Week 12, data missing at random within each treatment group will be investigated using tipping point analysis method ([redacted]).
- Percentage of change in EASI from Baseline to Week 12 will be analyzed in the modified Full Analysis Set (mFAS), data will be set to missing after rescue medication uses; all missing data will be imputed using post-baseline last observation carried forward method.

- Percentage of change in EASI from Baseline to Week 12 will be analyzed in the mFAS set, data will be set to missing after rescue medication uses; all missing data will be imputed using post-baseline worst-case-carry-forward method.
- Proportion of subjects achieved EASI-75 response at Week 12 will be analyzed in the mFAS set using EASI scores imputed by the MI method discussed in Section 11.4.1.
- Observed data analyses in mFAS set, regardless of rescue medication uses and without missing data imputation:
  - For longitudinal continuous variables (eg, percentage of change in EASI from Baseline to Week 12), mixed effects model with repeated measures (MMRM) analysis will be performed and by visit results will be reported;
  - For longitudinal dichotomous measures (eg, EASI-75, vIGA 0 to 1), logistic regression analysis will be performed by visit.
- Completers analyses of primary and secondary endpoints for subjects who complete 12 weeks of study treatment.
- Analyses of primary and key secondary endpoints in the Per Protocol set.

11.5. Efficacy Analyses

The primary endpoint of percentage change in EASI from Baseline to Week 12 will be analyzed in the FAS and using MI procedure with analysis of covariance (ANCOVA) model. The ANCOVA model will include treatment group as factor, Baseline EASI score and randomization factor as covariates. Multiple results of ANCOVA (least square [LS] means and LS mean difference from placebo) for each MI dataset will be analyzed and reported along with 95% confidence interval (CI) and p-value using Rubin's method ([redacted]).

Proportion-based key secondary endpoints (eg, EASI-75, vIGA 0 to 1) at Week 12 will be analyzed in the FAS using the Cochran-Mantel-Haenszel method adjusted for randomization stratification factor. The number and percentage of subjects achieving the goal and the difference in proportion between treatment groups achieving the goal, along with p-value and the 95% CIs will be reported.

Other secondary endpoints (listed in Section 11.5.4) will be analyzed using the following methods in general and specific details will be discussed in the SAP.

- Longitudinal continuous variables measured at scheduled visits up to Week 12 will be analyzed using a MMRM model. The MMRM model will include treatment group, visit, and interaction of treatment-by-visit as factors, and baseline measure and randomization stratification factor as covariates. An unstructured covariance matrix will be specified for the MMRM model. LS means at visit and LS mean differences between treatment group with p-values and corresponding 95% CIs will be reported. This method will also be applied to other score based or continuous measures.
- Longitudinal dichotomous measures at scheduled visits will be analyzed using a logistic regression model. The model will include treatment group as a factor, Baseline EASI score and randomization stratification factor as covariates. The odds ratios and 95% CIs, and associated p-value will be reported.

Analysis methods for exploratory endpoints will be described in the SAP.

In addition to between group analyses on the primary and secondary endpoints, dose response of key efficacy measures for the 2 etrasimod doses and placebo will be assessed as exploratory using appropriate analysis models, which will be specified in the SAP.

Efficacy data will be analyzed by randomized treatment, while safety data will be analyzed by actual treatment.

11.5.1. Endpoint Definitions

Efficacy will be assessed by changes in AD severity using EASI, vIGA, SCORAD, and BSA. Symptoms of itch will be assessed using the pruritus NRS. Patient-reported outcomes will also be assessed using the DLQI, POEM, and PGA.

The following definitions will be used to assess efficacy outcomes:

11.5.2. Primary Efficacy Endpoint

- Percent change in EASI from Baseline to Week 12.

11.5.3. Key Secondary Efficacy Endpoints

- Proportion of subjects achieving EASI-75, defined as a 75% reduction of EASI from Baseline to Week 12.
- Proportion of subjects with a vIGA 0 to 1 (on a 5-point scale) score and a reduction from Baseline of ≥ 2 points at Week 12.

11.5.4. Secondary Efficacy Endpoints

- Percent change in peak pruritus NRS from an itch daily diary from Baseline to Week 12.
- Proportion of subjects with improvement (reduction) in peak pruritus NRS ≥ 3 from an itch daily diary from Baseline to Week 12.
- Proportion of subjects achieving EASI-50, defined as a ≥ 50% reduction of EASI from Baseline to Week 12.
- Proportion of subjects achieving EASI-90, defined as a ≥ 90% reduction of EASI from Baseline to Week 12.
- Change and percentage change in percent BSA AD involvement from Baseline to Week 12.

11.5.5. Exploratory Efficacy Endpoints

- Change in DLQI from Baseline to Week 12.
- Change in POEM from Baseline to Week 12.
- Percent change in SCORAD from Baseline to Week 12.

[redacted]

11.5.6. Efficacy assessment during open-label extension:

These efficacy outcomes will be measured at scheduled visits up to 52 weeks: EASI, vIGA, SCORAD, BSA, Pruritus NRS, POEM, DLQI, and PGA. Dichotomous response outcomes derived from specific scores will be assessed.

[redacted]

11.5.8. Subgroup Analyses

- Sex (male, female)
- Race (white, non-white)
- Age (≤ or > median)
- Baseline vIGA (3 or 4)
- Baseline EASI score (≤ or > median)
- Baseline percent BSA AD involvement (≤ or > median)

11.6. Testing Strategy

No formal testing strategy or adjustments of the Type I error will be employed for the primary and key secondary endpoints. Estimates and CIs for treatment groups and from pairwise comparisons will be reported in an exploratory manner.

11.7. Interim Analysis

No formal interim analysis of efficacy is planned. Periodic blinded assessments of the assumption regarding the SD of the percentage change in EASI from Baseline to Week 12 may be conducted. The planned sample size will not be reduced as a result of the SD assessments.

11.8. Safety Analyses

A detailed description of all safety analyses will be provided in the SAP.

11.8.1. Safety Endpoints

- Incidence and severity of AEs.
- Incidence and severity of laboratory abnormalities and change from Baseline in laboratory values (to include hematology, serum chemistry, coagulation, and urinalysis).
- Incidence of clinically significant vital sign abnormalities and changes from Baseline. May include [redacted] post-first-dose.
- ECGs.
- Physical examination findings.

11.8.2. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities.

For each treatment group, the proportion of subjects with treatment-emergent AEs (TEAEs) will be summarized overall, by severity, and by relationship to study treatment. SAEs will also be summarized by treatment group. A TEAE is defined as:

- An AE that occurs after initiation of study treatment that was not present at the time of treatment start.
- An AE that increases in severity after the initiation of study treatment, if the event was present at the time of treatment start.

Any AE occurring before the first dose of study treatment will be summarized separately.

11.8.3. Extent of Exposure

The duration of time on study and time on study treatment will be summarized for each treatment using descriptive statistics. The number of subjects on study treatment for certain time intervals will also be summarized. The total subject-years and total subject-years on study will also be included in this summary.

11.8.4. Clinical Laboratory Parameters

Laboratory parameters will be summarized by treatment group at each scheduled assessment time point using descriptive statistics. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together.

Individual subject values will be listed and values outside of the standard reference range will be noted. Shift tables and analyses of changes from Baseline will be produced.

[redacted]

11.8.6. Vital Signs

Descriptive statistics for vital signs (BP, HR, respirations, body temperature) will be presented by treatment group. The change from Baseline for each of the vital signs and ECG parameters will be summarized. Incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

11.8.7. Physical Examination

Clinically significant physical examination abnormalities will be included in medical history or recorded and summarized as an AE.

11.9. Statistical Considerations for the Open-Label Extension Period

The objectives of the Open-Label Extension Period are to evaluate long-term safety, tolerability, and efficacy up to 52 weeks for eligible subjects who complete the 12-week Double-Blind Treatment Period and the Safety Follow-Up Visit 4 weeks after last dose of study treatment. All subjects will receive 2 mg etrasimod treatment during Open-Label Extension Period.

No pair-wise comparison will be performed. Only descriptive statistics will be provided and details will be discussed in the SAP.

Analysis sets: all safety outcomes will be analyzed in Safety Set which includes all subjects who receive at least 1 dose of etrasimod. Efficacy outcomes will be summarized in efficacy evaluable set which includes subjects who receive at least 1 dose of etrasimod and have at least 1 efficacy measurement during the Open-Label Extension Period; therefore, efficacy evaluable set is endpoint specific.

Baseline for the Open-Label Extension Period is defined as the last measurement prior to the first etrasimod dose started at Week 16.

Safety analyses will follow general considerations in Sections 11.8.1 to11.8.7 with following exceptions:

- 1 treatment group in the Open-Label Extension Period and 3 subgroups in the Double-Blind Treatment Period will be analyzed
- the Open-Label Extension Period visits will follow Table 9 in Appendix 1

- change from baseline will be analyzed on change from Double-Blind Treatment Period baseline, and change from Open-Label Extension Period baseline, respectively

Efficacy outcomes will be measured at scheduled visits in the Open-Label Extension Period: EASI, vIGA, SCORAD, BSA, Pruritus NRS, POEM, DLQI, and PGA (Table 9 of Appendix 1). Dichotomous response outcomes derived from specific scores will be assessed. Continuous variables will be summarized by visit using the number of observations, mean, SD, median, minimum, and maximum; and categorical variables will be summarized by visit using frequency counts and percentages, with following considerations.

- 1 treatment group in the Open-Label Extension Period and 3 subgroups in the Double-Blind Treatment Period will be analyzed
- change from baseline in continuous variables will be analyzed on change from Double-Blind Treatment Period baseline, and change from Open-Label Extension Period baseline, respectively
- subgroup analyses of main efficacy outcomes will be performed in, but not limited to, the following categories:
  - Week 12 EASI-75 responders versus non-responders
  - Week 12 vIGA responders versus non-responders (responder is defined as vIGA 0 to 1 [on a 5-point scale] score and a reduction from Double-Blind Treatment Period Baseline of ≥ 2 points)
  - EASI score at Double-Blind Treatment Period baseline (≤ or > median)
  - Percent BSA AD involvement at Double-Blind Treatment Period baseline (≤ or > median)

12. ETHICAL CONSIDERATIONS

12.1. Ethical Conduct of the Study

This study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP, ICH guidelines, other applicable regulatory requirements (eg, local requirements), the study protocol, and where applicable, Sponsor and/or CRO SOPs.

12.2. Institutional Review Board or Independent Ethics Committee Approval

Before initiating a study, the investigator must have written and dated approval from the IRB/IEC for the study protocol, written informed consent form (ICF), subject recruitment materials and procedures (eg, advertisements or websites), and any other written information to be provided to subjects. Approval from the committee must be documented in a letter to the investigator specifying the protocol number, protocol version, documents reviewed, and the date on which the committee met and granted approval.

All documents subject to review during the study, including any modifications made to the protocol after receipt of IRB/IEC approval, must also be submitted to the committee for approval prior to implementation. The investigator must also provide periodic reports as required and promptly report important safety information (ie, SAEs) and protocol violations, as appropriate, to the IRB/IEC.

As part of the investigator's written application to the IRB/IEC, the investigator should provide the committee with a current copy of the IB. If the IB is updated during the study, the investigator should supply an updated copy to the committee.

12.3. Informed Consent and Assent

The investigator will fully inform the subject of all pertinent aspects of the study, including the approval of the study by the IRB/IEC. Before informed consent/assent may be obtained, the investigator should provide the subject ample time and opportunity to inquire about details of the study and to decide whether to participate.

Prior to a subject's participation in the study, the IRB/IEC-approved ICF must be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF or study materials to be available and/or supplied to subjects should receive the IRB/IEC's approval in advance of use. The subject will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

12.4. Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is provided from the Sponsor.

Prior to study participation, the investigator shall inform the subject that the monitor(s), auditor(s), IRB/IEC, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, and that, by signing a written ICF, the subject is authorizing such access.

In addition, prior to study participation, the subject must be informed that the records identifying the subject will not be made publicly available; if the results of the study are published, the subject's identity will remain confidential.

12.5. Protocol Compliance

The investigator/institution will conduct the study in compliance with the protocol agreed to by the Sponsor and regulatory authorities (if applicable) and that was approved by the IRB/IEC. The investigator/institution and the Sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The investigator should not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and prior review and documented approval from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazard(s) to study subjects or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of telephone number).

When an important deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the medical monitor for the study. Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the subject's participation and/or the assessment of safety or efficacy in the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reported by investigator or site delegate to the IRB/IEC and regulatory authorities, as applicable, prior to implementation.

The investigator should document and explain any deviation from the approved protocol.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance and quality control systems shall be implemented and maintained with written SOPs to ensure that the study is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control shall be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

An agreement must be secured from all involved parties to ensure direct access to all study-related sites, source documents, and reports for the purpose of monitoring and auditing by the Sponsor and inspection by regulatory authorities.

13.1. Training of Study Site Personnel

Prior to study activities being initiated at the study site, the Sponsor or designee will train study site personnel on the protocol and applicable procedures. Training should be documented.

Note: If new study site personnel are assigned to the study after the initial training, study sites should contact the study monitor to coordinate training. Qualified study personnel may conduct training, as appropriate. Training of new study personnel should also be documented.

13.2. Monitoring

Study site monitoring is conducted to ensure the study is progressing as expected, the rights and well-being of human subjects are protected, the reported study data are accurate, complete, and verifiable, and the conduct of the study is in compliance with the currently approved protocol, with GCP and with applicable regulatory requirements. Protocol deviations identified will be documented.

Details of study site monitoring are documented in the study Clinical Monitoring Plan or similar document. The Clinical Monitoring Plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed (eg, targeted and/or risk based), and the distribution of monitoring reports. Monitoring may include a study site selection visit, which may be conducted in person or via communication media (eg, teleconference, online meeting) or may be waived in accordance with policy and procedures being followed for the study, if appropriate. Monitoring will include a study site initiation visit, interim monitoring visit(s), and a study site closeout visit. An interim monitoring visit may be combined with a closeout visit, if applicable.

13.3. Audit

Audits of vendors contracted by Arena for this study may be performed. Audits of participating study investigator sites may also be performed independently of, and separately from, routine monitoring to evaluate clinical study conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Management

14.1.1. Case Report Forms

An eCRF must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to the Sponsor and regulatory authorities, as applicable.

The documentation related to the validation of the eCRFs will be maintained in the Trial Master File. The Trial Master File will be maintained by the CRO and the Sponsor.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by study site personnel. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All changed information, including the date and person performing the corrections, will be available via the audit trail, which will be part of the electronic data capture system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness and acceptability by Sponsor personnel (or their representatives). The Sponsor (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to the eCRFs as evidence thereof.

14.1.2. Source Documents

Per regulatory requirements, the investigator or designee will maintain accurate and up-to-date study documentation, including source documentation for each study subject. Source documents are defined as original documents, data, and records. These may include, but are not limited to, hospital records, clinical and office charts, laboratory data/information, subject electronic diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments (eg, ECGs, X-rays). Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) and will provide direct access to the source data.

14.2. Study Documentation and Records Retention

The investigator and study staff have the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by the Sponsor, representatives of the Sponsor, the IRB/IEC, and regulatory authorities (ie, FDA or international regulatory authorities) at any time, and should consist of the following elements:

- Subject files: containing the completed eCRFs (if applicable), supporting source documentation including medical records, laboratory data, and signed ICFs.

- Regulatory files: containing the protocol with all amendments and Investigator signature pages, copies of all other regulatory documentation, all correspondence between the study site and the IRB/IEC and Sponsor, and drug accountability files, including a complete account of the receipt, dispensation, return, and disposition of the study treatment.

Records will be available for 2 years after marketing application approval, or if the application is not approved or never submitted, 2 years after the last shipment and delivery of the study treatment and the appropriate competent regulatory authorities are notified. The Sponsor will provide written notification when it is appropriate for the investigator to discard the study-specific documents referenced above.

During the record retention period, the investigator or designee must inform the Sponsor or designee (eg, CRO) of the location of study documentation. During or after the record retention period, the investigator or designee must inform and seek the Sponsor's approval in the following circumstances:

- If the custody of documentation needs to be transferred or moved to another location.
- If the investigator is unable to retain documentation for the specified period.

The Sponsor retains the right to utilize a document storage location/facility other than the one suggested by the investigator.

14.3. Clinical Study Report

Whether the study is completed or prematurely terminated, a clinical study report will be prepared and provided to the regulatory agencies according to applicable regulatory requirement(s).

14.4. Disclosure of Study Results

The Sponsor will post the results of the study in a publicly accessible database in accordance with the applicable laws and regulations.

15. RESPONSIBILITIES

15.1. Investigator Responsibilities

The investigator must comply with this protocol and the conduct of all study procedures. The investigator will disclose to the Sponsor sufficient, accurate, financial information to allow the Sponsor to submit accurate disclosure statements to the US FDA per 21 Code of Federal Regulations (CFR) Part 54 (Financial Disclosure by Clinical Investigators). The investigator is responsible for compliance with applicable sections of 21 CFR Part 312, Subpart D, (*Responsibilities of Investigators*) and other ICH GCP requirements, federal, and local laws, applicable to conducting drug studies.

The investigator is responsible for ensuring an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of 21 CFR Part 50, obtain the informed consent of each human subject to whom the study treatment is administered.

15.2. Sponsor Responsibilities

The Sponsor is responsible for compliance with applicable sections of 21 CFR Part 312, Subpart D (*Responsibilities of Sponsors*). The Sponsor is responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the Investigational New Drug (IND) application, maintaining an effective IND with respect to the investigations, and ensuring the FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

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APPENDIX 2: GRADING OF CLINICAL AND LABORATORY ADVERSE EVENTS

All clinical and clinically significant laboratory abnormalities will be graded according to the CTCAE Scale for Severity of Adverse Events and Laboratory Abnormalities (available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf).

Examples of CTCAE terms and grading are provided for clinical adverse events in Table 10 and for laboratory abnormalities in Table 11.

Table 10: Example of CTCAE Terms and Grading for Clinical Adverse Events

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	–	–
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing.					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self-care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways.					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self-care ADL	–	–
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	–
Definition: A disorder characterized by visual perception of unclear or fuzzy images.					

ADL, activities of daily life; CTCAE, Common Terminology Criteria for Adverse Events

Table 11: Example of CTCAE Terms and Grading for Laboratory Abnormalities [redacted]

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Alanine aminotransferase increased	> ULN-3.0 × ULN if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal	> 3.0-5.0 × ULN if baseline was normal; > 3.0-5.0 × baseline if baseline was abnormal	> 5.0-20.0 × ULN if baseline was normal; > 5.0-20.0 × baseline if baseline was abnormal	> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal	–
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen. **Navigational Note**: Also consider Hepatobiliary disorders: Hepatic failure					
Aspartate aminotransferase increased	> ULN-3.0 × ULN if baseline was normal; 1.5-3.0 × baseline if baseline was abnormal	> 3.0-5.0 × ULN if baseline was normal; > 3.0-5.0 × baseline if baseline was abnormal	> 5.0-20.0 × ULN if baseline was normal; > 5.0-20.0 × baseline if baseline was abnormal	> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal	–
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen. **Navigational Note**: Also consider Hepatobiliary disorders: Hepatic failure					
Forced expiratory volume decreased	FEV_1% (percentages of observed FEV_1 and FVC related to their respective predicted values) 99-70% predicted	FEV_1 60%-69%	50%-59%	≤ 49%	–
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds. **Navigational Note**: Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
Vital capacity abnormal	90%-75% of predicted value	< 75%-50% of predicted value; limiting instrumental ADL	< 50% of predicted value; limiting self-care ADL	–	–
Definition: A finding based on [redacted] test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value. **Navigational Note**: Also consider Investigations: Forced Expiratory Volume; Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
Carbon monoxide diffusing capacity decreased	3-5 units below LLN; for follow-up, a decrease of 3-5 units (mL/min/mm Hg) below the baseline value; asymptomatic and intervention not indicated	6-8 units below LLN; for follow-up, an asymptomatic decrease of > 5-8 units (mL/min/mm Hg) below the baseline value; symptomatic and intervention not indicated	Asymptomatic decrease of > 8 units drop; > 5 units drop along with the presence of pulmonary symptoms (eg, > Grade 2 hypoxia or > Grade 2 dyspnea); intervention indicated	–	–
Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide. **Navigational Note**: Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					

ADL, activities of daily life; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity; LLN, lower limit of normal; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; ULN, upper limit of normal

APPENDIX 3: GUIDANCE FOR THE MANAGEMENT OF CLINICAL AND LABORATORY ADVERSE EVENTS

Clinical AEs and abnormal results of laboratory tests and safety assessments considered to be an AE by the Investigator should be graded according to the severity scale of the CTCAE.

Uniform guidance for the management of AEs is provided in Figure 2.

Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before study treatment discontinuation, unless such a delay is not consistent with good medical practice.

A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new AE grade.

Study treatment may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 creatinine kinase after strenuous exercise, or triglyceride elevation that is non-fasting or that can be medically managed) or a clinical event considered unrelated to investigational product.

Any questions regarding adverse event management should be directed to the medical monitor.

APPENDIX 5: INVESTIGATOR SIGNATURE

Study title: A Multicenter, Randomized, Double-Blinded, Placebo-Controlled 16-Week Study (with a 52-Week Open-Label Extension) to Assess the Safety and Efficacy of Etrasimod in Subjects with Moderate-to-Severe Atopic Dermatitis

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Investigator Signature	**Date**

Investigator Name and Credentials - Printed
Institution Name - Printed

APPENDIX 6: SPONSOR SIGNATURE

Study title: A Multicenter, Randomized, Double-Blinded, Placebo-Controlled 16-Week Study (with a 52-Week Open-Label Extension) to Assess the Safety and Efficacy of Etrasimod in Subjects with Moderate-to-Severe Atopic Dermatitis

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[redacted]
Executive Vice President, Head of Research and Development
Arena Pharmaceuticals, Inc.

[redacted]

[redacted]
Date

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Meaning: Author Approval
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UserName: [redacted]
Title: EVP, R&D & CMO
Date: Tuesday, 20 August 2019, 11:58 AM Pacific Daylight Time
Meaning: Approval
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CLINICAL STUDY PROTOCOL

SUMMARY OF CHANGES

Protocol title:	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled 16-Week Study (with a 52-Week Open-Label Extension) to Assess the Safety and Efficacy of Etrasimod in Subjects with Moderate-to-Severe Atopic Dermatitis
Protocol number:	APD334-201
Version:	Amendment 1.0, dated 19 August 2019
Replaces version:	Original, dated 29 April 2019

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 1.0, 19 August 2019

Overall Rationale for the Amendment

The overall rationale for the changes implemented in this protocol amendment were to provide operational clarifications and instructions to the clinical sites and investigators. In addition, further information is provided to investigators on monitoring patient safety. Minor editorial and document formatting revisions were also made for consistency.

Summary of Changes

Section No (s). and Name (s)	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions for consistency, these include: Etrasimod referred to as "investigational drug" and etrasimod/placebo referred to as "study treatment."	Minor changes to improve consistency, clarity, and flow of the document. These changes are considered minor and therefore have not been summarized.
1.3. Benefit and Risk Assessment	[redacted]	Updated and/or new text is more descriptive and provides background information. New text describes inclusion and exclusion criteria implemented in this study and includes more detail on measures taken to promote cardiac safety.

Section No (s). and Name (s)	Description of Change	Brief Rationale
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Multiple sections: 5. Subject Activities and Restrictions; 6.5. Selection and Timing of Dose for Each Subject; Appendix 1 Schedule of Assessments: Table 8 Double-Blind Treatment Period and Table 9 Open-Label Extension Period	Added: "On visit days during the study, subjects should not apply any topical emollient or moisturizer prior to attending clinic and completing their visit."	Provides additional information and clarity on what subjects should do on visit days with regard to application of topical emollients or moisturizers.

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5. Subject Activities and Restrictions	Added information regarding what subjects should do on visit days: "Study treatment should also be held the day of clinic visits. Subjects will take their daily dose at the study site on study visit days."	For clarification of timing of study treatment administration on clinic visit days.
6.3.2. Dose Interruptions [redacted]	Added to 6.3.2: "If these doses of study treatment are missed, subjects must contact the Investigator to discuss treatment re-initiation and are required to return to the study site before taking their next dose of study treatment. The subject must take the next dose of study treatment at the study site, and the in-clinic cardiac monitoring as outlined in Section 10.5.7.4 should be performed." [redacted]	Clarification and further investigator instruction regarding the study treatment re-initiation process.
6.8.3. Prohibited Concomitant Therapy and Procedures	Updated to allow use of topical corticosteroids as needed during the Open-Label Extension Period.	For clarification in this section as Section 6.8.2 already indicates that after 12 weeks (Week 28), topical corticosteroids and calcineurin inhibitors can be used during the Open-Label Extension Period.
9.2.4. Double-Blind Treatment Period Safety Follow-Up Visit	Added: "Whenever possible, visits should be scheduled on the Weeks designated in the [redacted].	Clarification regarding scheduling of study visits.
9.2.5. Open-Label Extension (Week 16-Week 68)	Added: "If by approximately Week 28, within the Open-Label Extension Period, the subject has achieved suboptimal benefit from etrasimod treatment, both subjects and investigators should discuss the subject's continued participation in the study."	Sponsor decision that subjects without benefit from study treatment should discuss discontinuing participation in the Open-Label Extension Period of the study.
10.3. Efficacy Assessments	Added: "Wherever possible, to maintain consistency, the same individual at the site should administer the investigator assessments for the duration of the study."	Clarification regarding procedures for obtaining investigator assessments.

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10.3.5.1. Pruritus Numeric Rating Scale	Updated text such that at study visits subjects will be asked to rate their itch intensity from the previous 7 days, not just the past day.	Corrected a typographical error.
10.3.5.3. Patient Global Assessment of Disease	Adapted the patient completed- vIGA scale to more understandable terminology and included text to explain this modification. Edited text as follows: "Subjects will also be asked to best describe the overall appearance of skin lesions at a given time point using the vIGA scale (Section 10.3.3). The vIGA scale has been adapted for patients to complete. The scale has been modified for easier understanding for subjects, to exclude medical terminology (eg, lichenification has been adapted to thickening and erythema to redness). ~~the following scoring: 0 = clear (no inflammatory signs of AD); 1 = almost clear (perceptual erythema and papulation); 2 = mild (mild erythema and papulation); 3 = moderate (moderate erythema and papulation); and 4 = severe (severe erythema papulation).~~"	Clarification of study assessments to be completed by study subjects. Medical language was translated to more understandable terminology.
10.3.5.4. Patient Oriented Eczema Measure	New section added (Section 10.3.5.4.) to describe Patient Oriented Eczema Measure.	Description of assessment tool was inadvertently omitted in the original protocol.
[redacted]	[redacted]	Clarification of investigator responsibilities, given that ECGs will be centrally read as well.
Table 3: Clinical Laboratory Tests	Updated test to confirm hepatitis C virus from reflex RIBA to reflex PCR.	Sponsor decision to use updated confirmatory testing method.
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Section No (s). and Name (s)	Description of Change	Brief Rationale
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Section No (s). and Name (s)	Description of Change	Brief Rationale
10.5.7.3. Guidance on Monitoring Subjects for Infections	New section added.	This section has been added to provide Investigators with information on monitoring subjects for infections throughout the study and the appropriate steps to take. Specific guidance is given regarding signs and symptoms of infections and progressive multifocal leukoencephalopathy.
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11.3. Analysis Sets	Provided another example of specific reasons for warranting exclusion from the per protocol set to include, chronic usage of prohibited medication while on study treatment.	New text further defines the Per Protocol Set to be used for analysis.

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12.3. Informed Consent and Assent	Deleted: "If a subject is unable to read, an impartial witness will be present during the entire informed consent discussion."	Not applicable in this study where subjects must be able to read in order to complete patient assessment tools throughout the study.
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[redacted]	[redacted]	[redacted]

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Appendix 2: Grading of Clinical and Laboratory Adverse Events	New appendix added and referenced throughout main body of protocol.	Appendix added as a reference for investigators to assess clinical and laboratory adverse events.
Appendix 3: Guidance for the Management of Clinical and Laboratory Adverse Events	New appendix added and referenced throughout main body of protocol.	Appendix added as a reference for investigators to manage clinical and laboratory adverse events.
[redacted]	[redacted]	[redacted]