Statistical Analysis Plan

Arena Pharmaceuticals, Inc.
Protocol Number: APD334-201

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

Version 3.0
Date: 05 November 2021

Document History

Version	Approval Date	Changes
Version 1	07 October 2020	
Version 2.0	22 June 2021	Section 5G: Inclusion of Post Hoc Analysis Set for the DB Treatment Period Inclusion of Post Hoc Analysis Section (Section 12) A Analysis using the post hoc analysis set B Additional exploratory endpoints C Additional sensitivity analyses [redacted]
Version 3.0	05 November 2021	Updated OLE baseline definition Included additional subgroup analysis for EASI-75 and vIGA in the Post Hoc Analysis Section (Section 12) Change AEs of Special Interest to Targeted Medical Events

Statistical Analysis Plan Signature Page

Final Statistical Analysis Plan v3.0 (dated 05 Nov 2021) for protocol APD334-201.

	Name	Signature	Date
Author:	[redacted]	[redacted]	2021 | 16:21:01 EDT
Position:	Biostatistician		
Company:	IQVIA Biotech		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name		
Approved By:	[redacted]	[redacted]	ov-2021 | 12:40:06 PDT
Position:	Associate Dire		
Company:	Arena Pharmaceuticals		
Approved By:	[redacted]	[redacted]	v-2021 | 12:55:12 PDT
Position:	VP, Biostatisti		
Company:	Arena Pharmaceuticals		

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[redacted]

1. Introduction

This statistical analysis plan (SAP) describes the statistical rationale, methods, rules and conventions to be used in the presentation and analysis of efficacy, safety, and [redacted] data for Protocol APD334-201. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This Statistical Analysis Plan (SAP) is based on study Protocol Amendment 1.0, dated 19 August 2019.

This SAP provides additional details concerning the statistical analyses outlined in the protocol and reflects any changes to the protocol from any amendments. This plan will not repeat all the definitions given in the protocol but will provide further details of the summaries and analyses planned therein.

This plan will cover the analyses for: 1) the primary database lock after the completion of the Double-Blind (DB) Treatment Period; 2) the final database lock after the completion of the Open-Label Extension (OLE) Period. The plan will be finalized before the time of primary database lock and treatment unblinding. After that, the SAP may be amended to accommodate ad hoc analyses before the final database lock. Ad hoc analyses will be labeled as such on the output and identified in the Clinical Study Report.

2. Protocol Objectives

A. Primary Objective

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

B. Safety Objective

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

C. 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 Endpoints

A. Primary Efficacy Endpoint

Percent change in Eczema Area and Severity Index (EASI) from Baseline to Week 12.

B. 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 achieving a validated Investigator's Global Assessment (vIGA) of 0 or 1 (on a 5-point scale) and a reduction from Baseline of ≥ 2 points at Week 12.

C. Secondary Efficacy Endpoints

- Percent change in weekly peak pruritus numeric rating scale (NRS) from an itch daily diary from Baseline to Week 12.
- Proportion of subjects with improvement (reduction) in weekly 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 body surface area (BSA) AD involvement total and for each body region from Baseline to Week 12.

D. Exploratory Efficacy Endpoints

- Change in Dermatology Life Quality Index (DLQI) from Baseline to Week 12.
- Change in Patient Oriented Eczema Measure (POEM) from Baseline to Week 12.
- Percent change in SCORing Atopic Dermatitis (SCORAD), total and by symptom (severity, and subjective symptoms), from Baseline to Week 12.

[redacted]

[redacted]

E. Open Label Extension Efficacy Endpoints

These efficacy outcomes will be measured at scheduled visits up to 52 weeks: EASI, vIGA, SCORAD, BSA, pruritus NRS, POEM, DLQI, and Patient Global Assessment (PGA).

Dichotomous response outcomes derived from specific scores will also be assessed.

F. Safety Endpoints

- Incidence and severity of adverse events (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. [redacted].
- [redacted]
- Physical examination findings.
- Other safety endpoints ([redacted] ophthalmoscopy [redacted]).

4. Study Design

A. Design Overview

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 DB Treatment Period with a 4-week Safety Follow-Up (SFU) Period following the last dose of double-blind study treatment; and eligible subjects may enter a 52-week OLE Period also followed by a 4-week Safety Follow-Up Period.

Randomization will be stratified by vIGA score at Baseline (3 versus 4) and region [redacted] Subjects will receive etrasimod 1 or 2 mg or placebo orally once daily in a double-blinded manner for 12 weeks. During the OLE 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 (i.e., 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.

B. Study Population

Subjects with chronic AD defined by Hanifin and Rajka criteria ([redacted]) that has been present for at least 1 year despite optimized skin care (i.e., use of emollients, avoidance of irritants) whose disease is not adequately controlled with topical therapies, or for whom those therapies are not advisable.

C. Sample Size Determination

It is assumed that the percent change in EASI from Baseline to Week 12 will be normally distributed with an estimated standard deviation (SD) of 41%. 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. This sample size also accounts for an estimated drop-out rate up to 25%.

D. Treatment Randomization

Randomization will be stratified by vIGA score at Baseline (3 versus 4) and region [redacted]

E. Assessment Schedule

For the statistical analysis, DB Treatment Period will include 12 weeks treatment and 4 weeks safety follow-up; OLE Period will include 52 weeks treatment and 4 weeks safety follow-up. The date at which the subject is randomized will be referred to as the "Baseline/Day 1". Subjects will be requested to attend the following scheduled visits for the DB Treatment Period from their Baseline/Day 1 visit: Week 1, 2, 4, 6, 8, 12 and Week 16/SFU visit. For the OLE Period, Week 16 (this will be same as Week 16 in the DB Treatment Period), Week 17, 18, 20, 24, 28, 32, 40, 48, 56, 68, and Week 72/ SFU. The acceptable visit window for scheduled visits for the DB Treatment Period including Week 16, and Week 17 and 18 in OLE Period is ± 3 days, for all the other OLE visits, the scheduled visit window is ± 7 days. Visits that subjects make to the clinic outside the visit window are recorded as unscheduled visits.

Please refer to protocol [redacted] for details.

5. General Analytical Considerations

A. Data Sources and General Rules

Data are recorded on electronic case report form (eCRF) 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. Laboratory data, [redacted] blood samples and [redacted] data are collected separately by the selected vendors. Section 14 of the protocol provides additional details regarding data handling and record keeping.

Statistical analysis will be performed following IQVIA Biotech standard operating procedures and on the IQVIA Biotech computer network. All statistical analysis will be performed using SAS Version 9.4 with program code prepared specifically for the project by qualified IQVIA Biotech statisticians and SAS programmers.

All observed and derived variables (e.g., change from baseline, percentage change from baseline, and response status) that are analyzed or summarized will be listed by subject. Descriptive statistics will provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include number of subjects, mean, SD median, minimum, and maximum.

B. Definition of Baseline and Study Day

Study day will be defined separately for the DB Treatment Period and OLE Period. For all subjects, Day 1 is the date of first study drug administration in the DB Treatment Period. This will be referred to as the **Overall Day 1**. For those enrolling into the OLE Period, an **OLE Day 1** will be additionally defined as the date of the first study drug administration in the OLE Period at Week 16.

Study day will be calculated relative to the date of Overall Day 1.

Similarly, Baseline will be defined separately for DB Treatment Period and OLE Period as follows:

- DB Treatment Period: baseline will be defined as the last available measurement prior to the first dose of the study drug in DB Treatment Period. Specifically, for vital signs (resting heat rate (HR), blood pressure (BP), body temperature, and respiratory rate) and [redacted], the Day 1 pre-randomization assessments will be used as baseline measurements. The lowest pre-dose HR measurement will be used for comparison to the post-dose HR measurement. This will be referred to as the **DB baseline**.

- OLE Period: for those enrolling into the OLE Period, an **OLE baseline** will be additionally defined as the last pre-dose measurement at Week 16at Week 16.

Change from baseline is defined for both DB Treatment Period and OLE Period as the post-baseline value minus the baseline value unless otherwise specified. Percent change from baseline is calculated as follows: Percent change = (Change from baseline / Baseline) x 100.

C. Analysis Visit Window

Efficacy and safety endpoints will be analyzed according to their windowed visits defined by actual overall study day (i.e. calculated relative to first dose date in the DB Treatment Period). If more than one visit occurs within a single visit window, then the analysis will take the one closest to the target day. If the 2 visits are equidistant from the target day, the later visit will be used. Some efficacy or safety data are not scheduled to be assessed at each post-baseline visit. If the assessment date is not in the analysis visit window, the analysis will take the post-baseline scheduled visit closest to the assessment date. If there are 2 scheduled visits equidistant from the assessment date, the later visit will be used. The below table provides details of each analysis visit window.

[redacted]

[redacted]

D. Covariate Adjustment in Primary Analysis

The primary efficacy analyses will adjust for baseline EASI score, baseline vIGA score (3 versus 4) and region [redacted] Key secondary analyses will adjust for baseline vIGA score (3 versus 4) and region [redacted] as described in Section 8 Efficacy Analyses below.

E. Interim Analyses

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

F. Multiple Comparisons and Multiplicity

For DB Treatment Period: 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.

For the OLE Period: no formal statistical testing will be performed. Only descriptive statistics will be provided.

G. Analysis Sets

The following analysis sets will be defined for the DB Treatment Period and OLE Period separately:

Table 2 Analysis Sets

Analysis Set	Description
DB Treatment Period	
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 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 (PPS)	The PPS consists of all subjects in the FAS who adhere to the protocol. The PPS 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. Specific reasons for warranting exclusion from this analysis set will be documented prior to database lock and may include, but are not limited to: • Not meeting critical inclusion/exclusion criteria • Study treatment noncompliance • Receiving incorrect study treatment • Missing more than a defined number of visits while still on study • Chronic prohibited medication use while on study treatment
Treatment Completer Set (TCS)	The TCS includes subjects in EASI or vIGA specific mFAS who have completed 12 weeks of study treatment in DB Treatment Period.
Safety Set (SAF)	The SAF includes all randomized subjects who received at least 1 dose of study treatment.
[redacted]	[redacted]
Post Hoc Analyses Set (PHAS)	The PHAS excludes 9 subjects from the Full Analyses Set in the 2 mg treatment group with unwarranted dose interruption due to lymphocyte decrease between week 4 and 12
OLE Period	
OLE Safety Set (OLE SAF)	The OLE SAF includes all subjects who enrolled in the OLE Period and received at least one dose of etrasimod. All safety

	and efficacy analysis in the OLE Period will be performed over OLE SAF. For the analyses of efficacy endpoints, subjects will further be required to have at least one efficacy measurement in the OLE Period. Therefore, efficacy evaluable set is endpoint specific.
[redacted]	[redacted]

H. Missing Data

In order to analyze primary and secondary efficacy endpoints at Week 12 in the FAS, the handling of missing data and rescue medication uses are specified in Section 8.B - 8.C. No imputation will be implemented for exploratory efficacy and safety endpoints. The handling of missing reporting information for safety assessments are specified in Section 9.

I. Data Display Characteristics

Data displays produced for this study will include three types - summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the eCRF or derived for each subject. In general, they will be ordered by treatment, subject number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject (e.g., further ordering by lab test names in the lab listings).

Summary tables will display summary statistics calculated for each of the treatment groups, unless described otherwise in following sections.

The Standard Display of table, listings, and figures (TLFs) and Precision of Data Displayed are documented in the appendix of SAP TLF Shell.

6. Subject Characteristics

Subject characteristics will be summarized overall and by treatment group for FAS, SAF, and PPS in the DB Treatment Period. Subject characteristics will be further summarized overall and by DB treatment group for OLE SAF in the OLE Period.

A. Demographics and Baseline Characteristics

- Age (years)
- Sex
- Race
- Ethnicity
- Region
- Weight (kg)
- Height (cm)
- Body mass index BMI (kg/m^2)
- Baseline EASI score
- Baseline vIGA
- Baseline percent BSA AD involvement
- Baseline SCORAD total score
- Baseline peak pruritus NRS score from daily diary

B. Medical History/Atopic Dermatitis History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 23.0 March 2020) and summarized by system organ class (SOC) and preferred term (PT).

The following will be summarized for AD history:

- Time since AD diagnosis in years, calculated as the year of screening minus the year of first AD diagnosis
- Time since AD symptom in years, calculated as the year of screening minus year of first AD symptom
- Number of exacerbations in the last 12 months
- Hospitalization for complications of AD or side effects of treatment (Y, N)
- Prior use of AD therapy (Y, N), including phototherapy, biologics, Janus Kinase (JAK) inhibitors and other immunosuppressants
- Participation in prior dermatology clinical studies (Y, N)

7. Subject Accountability

A. Disposition

Subject disposition in the whole study (DB Treatment Period and OLE Period) will be summarized using frequency counts and percentages, including: subjects

who were screened, randomized, enrolled into OLE Period, completed treatment in DB Treatment Period, completed treatment in the DB Treatment Period and OLE Period, discontinued treatment (overall and by reason of discontinuation) and discontinued study (overall and by reason of discontinuation). Screen failures will be summarized for overall only and by reason of screen failure.

B. Analysis Set Inclusions

The numbers and percentages of FAS subjects included in SAF, any mFAS, PPS, TCS, [redacted] will be presented for each treatment group and overall. Reasons for exclusion from the PPS will be summarized.

C. Protocol Deviations

The major protocol deviations will be summarized for each category by treatment group and all protocol deviations will be presented in a by-subject listing. The protocol deviations that lead to subjects being excluded from PPS will also presented in the listing.

8. Efficacy Analyses

A. Efficacy Outcomes

- **EASI** is a validated scoring system that grades the severity and extent of AD. It is a composite index with scores ranging from 0 to 72. Percent change (0 -100) in EASI from Baseline to Week 12 is the primary efficacy endpoint.
- **vIGA** is a 5-point scale to measure disease severity: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; and 4 = severe.
- **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. BSA is described below in BSA AD section. 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 total score is calculated as: A/5 + 7B/2 + C where the maximum is 103.

- **Pruritus NRS** is a simple assessment tool of the intensity of pruritus (itch) from 0 to 10 with 0 being "no itch" and 10 being "the worst itch imaginable." Both maximum/peak and average NRS scores will be assessed.

  In a daily diary, subjects are asked to rate their worst itch and itch on average over the previous 24 hours. The weekly average NRS (peak and average) will be analyzed as efficacy endpoints, and derived as per the following schedule and rule:

  - For DB Treatment Period: Baseline (Day 1), Week 1 (Day 2 to 8), Week 2 (Day 9 to 15), Week 3 (Day 16 to 22)…Week 12 (Day 79 to 85)… and Week 16 (Day 107 to Day 113 or Day of Week 16 visit whichever comes first for subjects enrolled into OLE Period).
  - For OLE Period: Week 17 (Day of week 16 visit +1 to Day 120), Week 18 (Day 121 to 127), Week 19 (Day 128 to 134)…Week 28 (Day 191 +).
  - Subjects must complete at least 3 NRS entries to calculate the weekly average. The weekly average will be considered missing if more than 4 entries are missing for that weekly interval. The baseline for the analysis of diary data is Day 1.

  At each scheduled office visit, the subject is asked to rate their worst itch and itch on average in the past 7 days and these are recorded as office based peak and average NRS.

- **BSA AD** will be assessed for each region of the body and combined. The region percent affected BSA is the affected percentage (0-100) at each body region. The total percent affected BSA is the sum of multiplying region percent affected BSA by the multiplication factor with a maximum of 100.

Body Region	**Multiplication Factor**
Head and Neck	9%
Upper Limbs (right)	9%
Upper Limbs (left)	9%
Lower Limbs (right)	18%
Lower Limbs (left)	18%
Anterior Trunk	18%
Back	18%
Genitals	1%

- **PGA** includes 2 questions **for wellness and appearance.** Subjects will rate their overall well-being based on a 5-point Likert scale from poor to excellent. Response choices are: 'Poor', 'Fair', 'Good', 'Very Good,' or 'Excellent'.

- **POEM** consists of 7 questions asking patients to rank how many days over the past 7 days they have experienced specific AD-related symptoms. Each of the seven questions carries equal weight and is scored from 0 to 4 as follows:

No days	Scored 0
1-2 days	Scored 1
3-4 days	Scored 2
5-6 days	Scored 3
Every day	Scored 4

The scores from the 7 questions are added up to give an overall POEM score (0-28). 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'.

- **DLQI** is a 10-item patient-reported outcome (PRO) measure that assesses the extent to which the skin condition has affected the subject's quality of life over the past week, including 6 domains (daily activities, personal relationships, symptoms and feelings, leisure, work/school, and treatment). Total score (0-30) will be calculated as the sum of 10 questions with each ranging from 0 to 3. The scoring of each answer is as follows:

Very much	Scored 3
A lot	Scored 2
A little	Scored 1
Not at all	Scored 0
Not relevant	Scored 0
Question unanswered	Scored 0

Question 7	Question 7A	Score
Yes	Any response	3
No	A lot	2
No	A little	1
No	Not at all	0
Not relevant	Any response	0

If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30. If two or more questions are left unanswered the total DLQI score is missing. If question 7 is answered 'yes' or 'not relevant', then the answer of 7a will be ignored.

B. Primary Efficacy Outcome Analysis

The primary endpoint of percentage change in EASI from Baseline to Week 12 will be analyzed based on the FAS using an analysis of covariance (ANCOVA) model. The ANCOVA model will include treatment group as factors, Baseline EASI score and the two randomization factors of baseline vIGA (3 versus 4) and

region [redacted] as covariates. 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 (FCS) method and predictive mean matching (PMM) for EASI scores (Heitjan 1991, van Buuren 2007). The rescue medications considered for the purposes of efficacy analysis will include topical and systemic corticosteroids used during the DB Treatment Period of the study.

For MI, 100 imputation models will be generated, including treatment, baseline vIGA (3 versus 4), region [redacted] baseline EASI score, and EASI scores at the previous scheduled visits. Percent change in EASI at Week 12 will be derived from the imputed EASI values.

[redacted]

Multiple results of ANCOVA (least square [LS] means and LS mean difference between etrasimod and placebo) for each MI dataset will be combined and reported along with 95% CI and p-value and using Rubin's method ([redacted]).

All subjects are required to have a baseline EASI score upon randomization. In the unlikely event that a subject is missing baseline EASI, the baseline value will be imputed first using the above covariates. The imputation model will be modified as appropriate based on the actual data.

In addition to the primary method for handling missing data and rescue medication use in the FAS, the following sensitivity analyses will be performed using alternative methods and/or in alternative analysis set:

- FAS, MI tipping point analysis

  A tipping point analysis (Carpenter and Kenward 2013) will be performed to investigate the robustness of departures from the missing at random (MAR) assumption in the MI model by applying a specified sequence of shift parameters that modify the imputed EASI values, as follows:

  - Missing EASI values will be imputed 100 times, following the MI method described above, with adjustment to the imputed EASI by shift

parameter S_1=0.5 in both etrasimod groups. A positive adjustment assumes a worsened outcome. The adjusted EASI value will be capped at 72. Imputed percent change in EASI will be derived accordingly. The MNAR statement with the ADJUST option in PROC MI will be used to apply the shift parameter.

- Each of the 100 completed datasets applying the shift parameters will be analyzed using an ANCOVA model as described above. The results from the 100 completed datasets will be combined for inference using PROC MIANALYZE.

- Repeat the above steps, with adjustment by shift parameter S_2=1.0 in both etrasimod groups. Repeat the process for the following pre-specified shift parameters: 0.5, 1.0, 1.5, 2.0…71.5, 72

- The shift parameters that result in a reversed study conclusion (i.e., p-value increases from <0.05 to ≥0.05) will be indicated.

- mFAS, using OC (observed data regardless of rescue medication uses and without imputation)

  EASI values 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, baseline EASI and baseline vIGA (3 versus 4) and region [redacted] as covariates. An unstructured (UN) covariance matrix will be specified for the MMRM model. If the model does not converge using an unstructured covariance matrix, an auto-regressive AR(1) structure will be tested. If AR(1) fails to converge, a compound symmetric structure will be used. LS means and LS mean differences at each visit between treatment groups with p-values and corresponding 95% CIs will be reported.

The same ANCOVA model as described above for the primary analysis will be performed, using the following:

- Last Observation Carried Forward (LOCF): The primary endpoint will be analyzed in the modified FAS (mFAS), with assessments after the first use of rescue medication set to missing. All missing data will be imputed using post-baseline LOCF method.
- Worst Case Carried Forward (WCCF): The primary endpoint will be analyzed in the mFAS, with assessments after the first use of rescue medication set to missing. All missing data will be imputed using post-baseline WCRF method.
- Observed Cases (OC) in mFAS: observed data analyses in mFAS, regardless of rescue medication uses and without missing data imputation,

will be performed using a mixed effects model with repeated measures (MMRM) including all scheduled visits up to Week 12.

- OC in Per Protocol Set (PPS): observed data analysis will be performed among PPS, regardless of rescue medication uses and without missing data imputation.
- OC in treatment completers (TCS): observed data analysis will be performed among mFAS subjects who have completed 12 weeks of study treatment, regardless of rescue medication uses and without missing data imputation.

C. Key Secondary Efficacy Outcome Analyses

The two proportion-based key secondary endpoints (EASI-75 at Week 12 and vIGA response status at Week 12) will be analyzed in the FAS using the Cochran-Mantel-Haenszel method (CMH) adjusted for randomization stratification factors of baseline vIGA score (3 versus 4) and region [redacted] Missing data will be imputed in the FAS using the NRI method: missing dichotomous response status at Week 12 (including those after use of rescue medication) will be imputed using the non-responder imputation (NRI) method, ie, "non-responders" or "failure" for missing response. The number, percentage of subjects achieving the goal and Clopper-Pearson exact 95% confidence intervals will be reported. The differences in proportion between treatment groups, along with p-values and the 95% CIs will also be reported.

The following sensitivity analyses will be performed:

- FAS, MI

  Missing Week 12 EASI-75 response status will be derived based on the multiple imputed datasets for EASI values as described above. The same CMH test will then be performed for EASI-75 and combined using Rubin's method. Combined proportion along with the 95% CI, and p-value will be reported.

- mFAS, using OC (observed data regardless of rescue medication uses and without imputation)

  Response endpoint at Week 12 will be analyzed using a logistic regression model including treatment group as factor, Baseline EASI score and the two randomization factors of baseline vIGA (3 versus 4) and region [redacted] as covariates. Odds ratio of etrasimod versus placebo along with the p-value and 95% CI will be reported.

The same CMH test as described above will be performed for the key secondary endpoints, using the following:

- PPS, using OC
- TCS, using OC

D. Other Secondary Efficacy Outcome Analyses

Secondary efficacy endpoints will be analyzed using the below methods:

- Longitudinal continuous variables (percent change in weekly peak pruritus NRS, change and percentage change in %BSA) measured at visits (weeks) up to Week 12 will be analyzed with a MMRM model based on FAS using observed data. The MMRM model will include treatment group, visit (week), and interaction of treatment-by-visit (week) as factors, and baseline measure and randomization stratification factors as covariates. An unstructured covariance matrix will be specified for the MMRM model. If the model does not converge using an unstructured covariance matrix, an auto-regressive AR(1) structure will be tested. If AR(1) fails to converge, a compound symmetric structure will be used. LS means at visit (week) and LS mean differences at visit (week) between treatment group with p-values and corresponding 95% CIs will be reported.

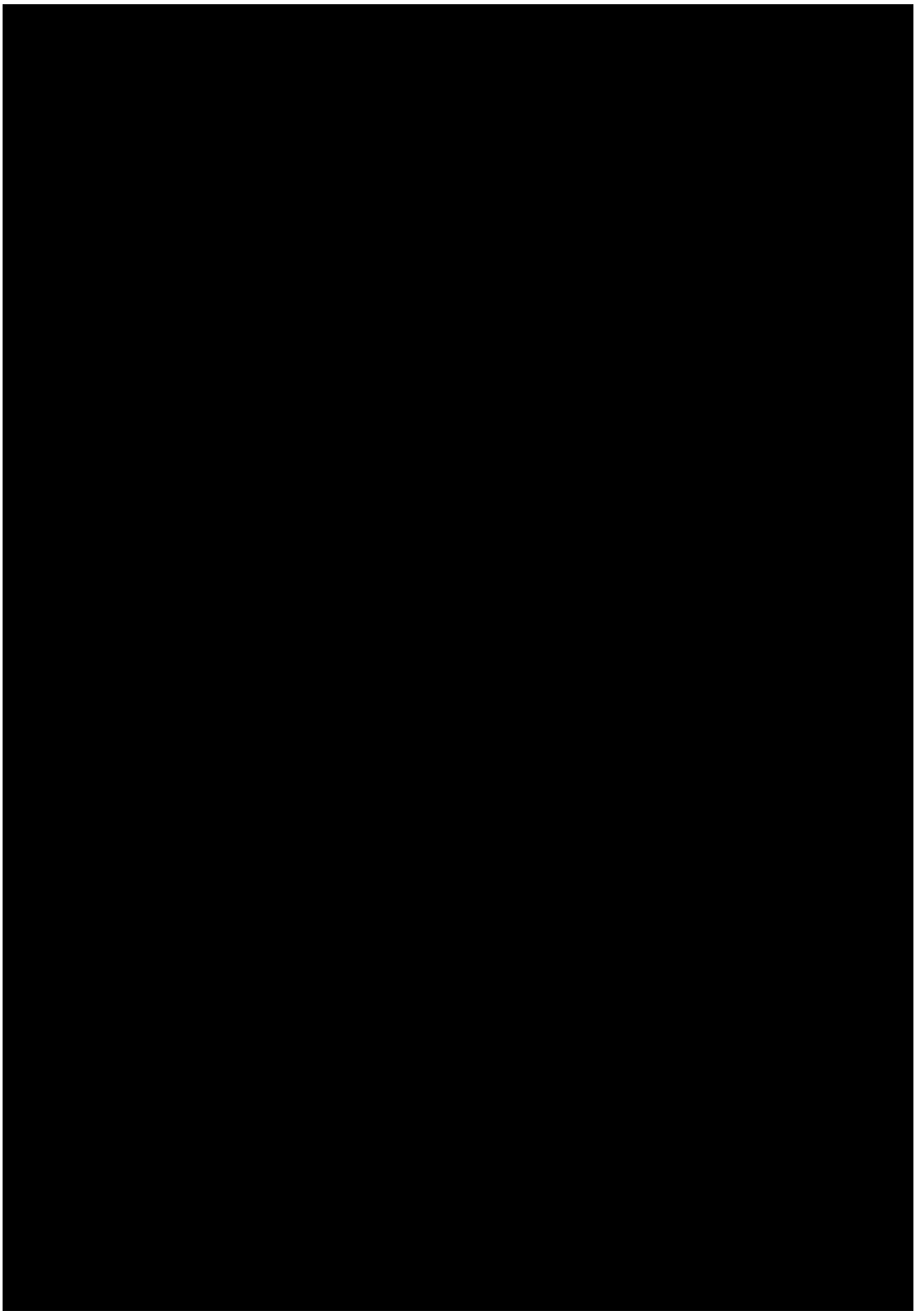
- Dichotomous measures (weekly peak NRS $\geq$ 3 reduction, EASI-50, and EASI-90) at Week 12 will be analyzed in the same way as for the key secondary endpoints based on FAS with CMH method adjusted for randomization stratification factors of baseline vIGA score (3 versus 4) and region [redacted] Missing data (including those after use of rescue medication) will be handled by NRI method. The number, percentage of subjects achieving the goal and Clopper-Pearson exact 95% confidence intervals will be reported. The differences in proportion between treatment groups, along with p-values and the 95% CIs will also be reported. Weekly peak NRS $\geq$ 3 reduction will be assessed among the subset of subjects whose baseline peak NRS is $\geq$ 3.

Sensitivity analyses will be performed in the PPS and TCS using observed data.

E. Exploratory Efficacy Outcome Analysis

Below exploratory endpoints will be analyzed in a similar manner as the secondary continuous variables with the MMRM model based on FAS using observed data.

- Change in DLQI from Baseline to Week 12.
- Change in POEM from Baseline to Week 12.
- Percent change in SCORAD total and individual symptom scores from Baseline to Week 12.



The primary and sensitivity analysis for all efficacy endpoints are summarized in **Table 3**.

Table 3 Summary of Efficacy Analyses

Efficacy Endpoint	Primary Analysis	Sensitivity Analysis
DB Treatment Period		
Primary		
• Percent change in EASI from Baseline to Week 12	• FAS, MI (ANCOVA)	• #1 FAS, MI tipping point analysis (ANCOVA) • #2 mFAS, MI (ANCOVA) • #3 mFAS, LOCF (ANCOVA) • #4 mFAS, WCCF (ANCOVA) • #5 mFAS, OC (MMRM) • #6 PPS, OC (ANCOVA) • #7 TCS, OC (ANCOVA)
Key Secondary		
• EASI-75 at Week 12 • vIGA response at Week 12	• FAS, NRI (CMH)	• #1 FAS, MI (CMH), (EASI-75 only) • #2 mFAS, NRI (CMH) • #3 mFAS, OC (Logistic regression) • #4 PPS, OC (CMH) • #5 TCS, OC (CMH)
Other Secondary		
• Percent change in peak pruritus NRS from diary from Baseline to Week 12. • Change and percentage change in percent BSA (total and 8 body regions) from Baseline to Week 12 (no sensitivity analysis for individual body regions).	• FAS, OC (MMRM)	• #1 PPS, OC (MMRM) • #2 TCS, OC (MMRM)
• Peak pruritus NRS ≥ 3 reduction from Baseline to Week 12. • EASI-50 at Week 12. • EASI-90 at Week 12.	• FAS, NRI (CMH)	• #1 PPS, OC (CMH) • #2 TCS, OC (CMH)
Exploratory		
• Change in DLQI from Baseline to Week 12. • Change in POEM from Baseline to Week 12. • Percent change in SCORAD (total, 6 severity/intensity symptoms, and 2 subjective	• FAS, OC (MMRM)	N/A

symptoms) from Baseline to Week 12. [redacted]		
[redacted]	[redacted]	N/A
[redacted]	[redacted]	N/A
OLE Period		
• EASI • vIGA • SCORAD • NRS • BSA • DLQI • POEM • PGA	• OLE SAF, OC	N/A

DB=Double Blind; OLE=Open-Label Extension.
FAS=Full Analysis Set; mFAS=modified Full Analysis Set; PPS=Per Protocol Set; TCS=Treatment Completer Set; SAF=Safety Analysis Set.
MI=Multiple Imputation; NRI=non-responder imputation; LOCF =Last Observation Carried Forward; WCCF=Worst Case Carried Forward; OC= Observed Case.
EASI=Eczema Area and Severity Index; vIGA= validated Investigator's Global Assessment; DLQI= Dermatology Life Quality Index; POEM= Patient-Oriented Eczema Measure; SCORAD= SCORing Atopic Dermatitis; PGA= Patient Global Assessment.
CMH=Cochran-Mantel-Haenszel; NRS= Numerical Rating Scale; BSA=Body Surface Area; ANCOVA=Analysis of Covariance; MMRM=Mixed Model with Repeated Measures.

F. OLE Period Efficacy Analysis

The following endpoints will be assessed in the OLE Period:

- Continuous variables: observed value and change (percent) from Baseline in EASI, SCORAD, BSA, pruritus NRS, POEM, DLQI, and PGA
- Dichotomous variables: EASI-75, vIGA

The above variables will be summarized by visit using descriptive statistics based on the applicable analysis set, with following considerations:

- Only observed cases will be used with no imputation of missing data
- Summaries will be provided for 1 treatment group ("Total") in OLE Period and also by orignal treatment groups ("Etrasimod 1mg" , "Etrasimod 2mg" and "Placebo") in DB Treatment Period
- Change from baseline in continuous variables will be analyzed on change from DB baseline and change from OLE baseline, respectively

For OLE Period, subgroup analyses of main efficacy outcomes (EASI, vIGA, NRS, BSA) will be performed in the following categories:

- Week 12 EASI-75 responders versus non-responders
- Week 12 vIGA responders versus non-responders
- EASI score at DB baseline (≤ or > median)
- Percent BSA AD involvement at DB baseline (≤ or > median)

G. Efficacy Analysis on Subgroups of Subjects

Subgroup analyses of primary and key secondary endpoints for the DB Treatment Period will be conducted for each of the following groups:

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

9. Safety Analyses

Safety analyses will use data from the SAF for DB Treatment Period and OLE Safety Set for OLE Period. For the DB Treatment Period, summary will be done on the 3 treatment groups; for the OLE Period, summary will be done on 1 treatment group in the OLE Period and 3 subgroups in the DB Treatment Period. Week 16 is the last

scheduled visit in DB Treatment Period and first scheduled visit in OLE Period. Overall (DB + OLE) summaries will be provided as detailed below.

A. Exposure and Compliance

The following exposure and compliance parameters will be defined and summarized for DB treatment and OLE Periods separately, and for overall using descriptive statistics:

- The duration (days) on study, defined as date of last study visit minus date of first dose of study treatment plus 1. Total subject-years of duration on study will be summarized.

- The time (days) on study treatment, defined as date of last dose of study treatment minus date of first dose of study treatment plus 1. Total subject-years of time on study treatment will be summarized. The overall time on study treatment will be the sum of days a subject on treatment during DB and OLE periods.

- Total number of tablets taken, defined as total number of tablets dispensed minus total number of tablets returned. Unreturned bottles will be assumed unused and will be included as 0 tablets in amount taken.

- Percent compliance will be calculated for the DB Treatment Period, OLE Period and study overall as the number of tablets taken divided by the expected number of tablets (days on study treatment × 1 tablet/day), expressed as a percentage.

- Subject compliance is defined as 80% - 120% (inclusive) in percent compliance. If the percentage of study medication compliance is unknown, the subject is assumed to be non-compliant with study medication.

- Number and percent of subjects that have dose interruptions, as well as those with dose interruptions due to AEs

B. Prior and Concomitant Medication/Therapy and Rescue Therapy

Prior and concomitant medications will be coded using the WHODrug Version 01 March 2020 (Global, B3 format).

Prior (with start and stop dates prior to first dose of study drug) and concomitant (ongoing or with stop dates on or after first dose of study drug) medications will be presented in a by-subject listing. Rescue therapy medications will be presented in a separate listing. Non-drug treatment for AD will be presented in a separate listing.

For the determination of prior vs concomitant medications/therapies, the following rules regarding the stop date will be applied and Baseline below refers to baseline in DB Treatment Period:

- If only year was recorded, and it is before Baseline, it is a prior medication; if year is same or after Baseline, it is assumed to be a concomitant medication.
- If day is missing, but month and year are before Baseline, it is a prior medication; if month and year are the same as Baseline, it is assumed to be a concomitant medication; if month and year are after Baseline, it is a concomitant medication.
- If start date is after Baseline, it is a concomitant medication regardless.
- All medications that start in the OLE Period are considered as concomitant.

Prior medications/therapies for DB Treatment Period will be summarized by treatment using WHO Drug Dictionary (WHO-DD) Anatomical-Therapeutic-Chemical (ATC) classification and preferred term (PT). The highest available level of ATC among ATC 1-4 will be presented. For example, if ATC 1, ATC 2 and ATC 3 are available, the summary table and subject listing will present ATC 3. Concomitant medications/therapies will be summarized for DB Treatment Period, OLE Period and overall using ATC and PT.

C. Adverse Events

All AEs will be coded using MedDRA Version 23.0 March 2020. A treatment-emergent AE (TEAE) is defined as:

- Any reported AE that occurs after initiation of study treatment that was not present at the time of treatment start.
- All AEs that occur in the OLE Period are considered as TEAEs.

For the determination of TEAEs, the following rules regarding the partial start date will be applied and Baseline below refers to baseline in DB Treatment Period:

- If only the year was recorded, and it is before Baseline, it is a non-TEAE; if year is the same or after Baseline, it is assumed to be a TEAE.
- If the day is missing, but month and year are before Baseline, it is a non-TEAE; if the month and year are the same as Baseline, it is assumed to be a TEAE; if the month and year are after Baseline, it is a TEAE.
- If start date is after Baseline, it is a TEAE regardless.

If the relationship to treatment is missing, the event will be conservatively considered as being related to study drug. If the severity is missing, a separate

category of missing severity will be included in the summary table, and no imputation of severity will be performed.

AE profile will be provided (for DB Treatment Period, OLE Period, and overall), by treatment group and overall as follows:

- All AEs
- Non-TEAEs (for DB Treatment Period and overall)
- All TEAEs
- Serious AEs
- Non-Serious TEAEs
- TEAEs leading to study treatment discontinuation
- TEAEs leading to study treatment interruptions
- TEAEs related to study treatment. This will include TEAEs with a drug relationship of "Probably Related" and "Related"

Summaries of the incidence of TEAEs (for DB Treatment Period, OLE Period, and overall), will be displayed by treatment according to the following:

- TEAEs by SOC in alphabetical order and PT in descending order of frequency (in etrasimod 2mg, etrasimod 1mg, and then placebo)
- SAEs by SOC and PT
- TEAEs by SOC, PT, and maximum Common Terminology Criteria for Adverse Events (CTCAE) severity
- TEAEs by SOC, PT, and maximum relationship to the study treatment
- Non-serious TEAE by SOC and PT

Targeted Medical Events by PT and Category will be summarized for DB Treatment Period, OLE Period, and overall.

All AEs will be presented in a by-treatment, and by-subject listing, for the DB treatment and OLE Periods separately, detailing the verbatim term given by the investigator, the PT, SOC, onset date, end date, CTCAE grade, outcome, relationship to study treatment, action taken with study drug, other action taken, seriousness and criteria for seriousness. SAEs and AEs leading to study treatment discontinuation will also be presented in a separate listing.

D. Clinical Laboratory Results

Laboratory parameters from the central laboratory will be summarized by treatment group at each scheduled assessment time point. For continuous lab parameters (hematology, serum chemistry, coagulation, and urinalysis), absolute values and change from Baseline will be summarized using descriptive statistics. For the OLE Period, change from Baseline will be calculated for the DB baseline and OLE baseline separately. Associated laboratory parameters (e.g., hepatic

enzymes, renal function, and hematology) will be grouped and presented together.

Changes from Baseline in the out of reference range abnormality flags will also be summarized using shift tables at each post-Baseline visit.

Data listings by-treatment and by-subject will be provided for all laboratory parameters reported in the standard units provided by the central laboratory. Lab values outside of the standard reference range will be noted.

Local laboratory assessments will be displayed in a separate listing. Pregnancy test results will be listed.

E. Vital Signs

Descriptive statistics for absolute values and change from Baseline in vital signs (BP, HR, respirations, body temperature) will be presented by treatment group. For OLE Period, change from Baseline will be calculated for the DB baseline and OLE baseline separately.

At baseline and week 16, descriptive statistics for pre-dose measurements and change of vital signs values will be presented by treatment group [redacted] after treatment initiation. [redacted]

[redacted]

[redacted]

[redacted]

G. Physical Examination

Clinically significant physical examination abnormalities will be included in medical history or recorded and summarized as an AE. The abnormal physical examination findings will be presented in a subject listing.

[redacted]

[redacted]

[redacted]

10. Other Assessments

[redacted]

[redacted]

[redacted]

[redacted]

11. Changes in Planned Analyses from the Protocol

A. Pairwise Correlation Coefficient among Efficacy Endpoints

Pairwise Pearson's correlation test will be performed for the following continuous efficacy endpoints for DB Treatment Period using FAS, observed cases. Pearson correlation coefficient and the corresponding p value will be presented.

- Percent change in EASI from Baseline to Week 12
- Percent change in diary based weekly peak NRS from Baseline to Week 12
- Change in %BSA total score from Baseline to Week 12
- Change in DLQI total score from Baseline to Week 12
- Change in POEM from Baseline to Week 12
- Change in SCORAD total score from Baseline to Week 12
- [redacted]

Pairwise association test stratified by region and baseline vIGA will be performed for DB Treatment Period using FAS, observed cases using CMH test for the following binary endpoints:

- EASI -50/75/90 from Baseline to Week 12
- vIGA response from Baseline to Week 12
- Diary based weekly peak NRS >=3 points reduction from Baseline to Week 12

B. COVID-19 Related Analysis Changes

In order to describe the impact of COVID-19 on current study, the following disposition events if any will be summarized:

- Subjects discontinued from the treatment/study as a result of a positive COVID-19 diagnosis under AE category.
- Subjects withdrawn due to COVID-19 pandemic. This is due to other reasons such as site closure, travel restrictions, fear of infection, etc. that are not related to COVID-19 diagnosis.

COVID-19 related protocol deviations will also be identified.

The above COVID-19 (including protocol deviation, treatment/study discontinuation and diagnosis of COVID-19) will be flagged at subject-level in corresponding data listings. Also, all COVID-19 related symptoms and confirmed cases occur during the study will be reported as AEs and included in the summaries. Subjects with study visits altered (including home visit, phone visits, etc) and missed due to COVID-19 will also be recorded in the database.

12. Post Hoc Analyses

A. Analyses with the Post Hoc Analysis Set

A post hoc analyses set (PHAS) will be defined by excluding 9 subjects [redacted] from the full analysis set in the 2mg etrasimod group. The efficacy of treatment in these subjects were impacted by unwarranted dose interruption between week 4 and 8. The following analysis will be repeated using the post hoc analysis set:

- The primary outcome (percentage change in EASI from Baseline to Week 12) will be analyzed using the same ANCOVA and MMRM model described in section 8 (subsection B).
- EASI-75 and VIGA response rate (i.e. proportion of subjects achieving a validated Investigator's Global Assessment (vIGA) of 0 or 1 (on a 5-point scale) and a reduction from Baseline of ≥ 2 points) will be analyzed using the same CMH analysis described in section 8 (subsection C).
- Percentage in weekly peak NRS will be analyzed with the same MMRM model described in section 8 (subsection D).
- Weekly peak pruritus NRS with ≥ 3 and ≥ 4 reduction will also be analyzed with the same CMH analysis described in section 8 (subsection C).

B. Additional Exploratory Outcomes

The following additional outcomes will be explored:

- Proportion of subjects achieving an improvement (reduction) of ≥ 4 points in POEM from Baseline to Week 12.
- Proportion of subjects achieving an improvement (reduction) of ≥ 4 points in DLQI from Baseline to Week 12.
- Proportion of subjects achieving an improvement (increase) of ≥ 2 points in PGA from Baseline to Week 12.
- Proportion of subjects achieving an improvement (reduction) of ≥ 3 points in office based peak pruritis from Baseline through Week 12
- Proportion of subjects achieving an improvement (reduction) of ≥ 4 points in office based peak pruritis from Baseline through Week 12

The above outcomes will be analyzed in the FAS and the PHAS using the Cochran-Mantel-Haenszel method (CMH) adjusted for randomization stratification factors of baseline vIGA score (3 versus 4) and region [redacted]. Missing data will be imputed using the NRI method. The number, percentage of subjects achieving each outcome and Clopper-Pearson exact 95% confidence intervals will be reported. The differences in proportion between treatment groups, along with p-values and the 95% CIs will also be reported.

C. Sensitivity Analysis for Percent Change in EASI

Additional sensitivity analysis for percent change in EASI will be performed with observed cases in the FAS using the MMRM model described in section 8 (subsection B)

D. Additional Subgroup Analyses for EASI-75 and vIGA

Prior Systemic Failure Subject (Yes, No)

Prior Systemic Failure Subject are subjects who previously had ineffective/intolerant therapy in oral steroid, oral JAK and Dupilumab, or other conventional Systemic therapy:

- 15 subjects in the 2mg etrasimod group: [redacted]
- 3 subjects in the 1mg etrasimod group: [redacted]
- 10 subjects in the placebo group: [redacted]

EASI-75 and vIGA response rate by visit will be analyzed for the subgroups of Prior Systemic Failure Subject (Yes, No) and using the same CMH analysis described in section 8 (subsection C).

13.References

Carpenter, J. R. and Kenward, M. G. (2013), Multiple Imputation and Its Application, New York: John Wiley & Sons.

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Ruberg SJ. Dose Response Studies. II. Analysis and Interpretation. J Biopharm Stat 5(1), 15-42 (1995).

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Appendix 1

[redacted]

[redacted]

[redacted]

[redacted]

B. Summary of Plasma Concentrations

Concentrations below the limit of quantification (BLQ) will be assigned a numerical value of zero for the calculation of descriptive statistics and plotting of concentrations. For geometric mean and geometric %CV, the zero values will be excluded.

Individual subject etrasimod plasma concentrations will be presented in the data listings (showing treatment received, sex, age, scheduled nominal time, and actual time) and also summarized using descriptive statistics (n, mean, SD, % Coefficient of Variance [CV], geometric mean, geometric %CV, minimum, median, and maximum) for each scheduled visit, as following:

- For timepoints in the DB Treatment Period (Baseline/Day 1 to Week 16), by actual treatment received in DB Treatment Period
- For timepoints in OLE Period (Week 16 to Week 72), by actual treatment received in DB Treatment Period and overall

Mean (SD) plasma concentrations will be plotted versus scheduled nominal time from start of treatment on both linear and semilogarithmic scales according to the above summaries.

Individual subject plasma concentrations will be plotted (in both linear and semilogarithmic scales) versus actual time from start of treatment, for timepoints in DB Treatment Period (Baseline/Day 1 to Week 16) and for timelines in OLE Period (Week 16 to 72), separately.

C. Steady-State (SS) Concentration Analysis

[redacted]

Steady-state (SS) concentration will be assessed for the DB Treatment Period and OLE Period separately. Individual subject SS pre-dose (trough) plasma concentrations will be averaged across ($C_{ss,avg\ trough}$) across the timeframe shown by the statistical model to be steady state; for the DB portion, out to a maximum timeframe of 12 weeks, and in the OLE out to a maximum of 68 weeks. Only C_{trough} values in the range of steady state will be averaged into $C_{ss,avg,trough}$.. Individual SS pre-dose concentrations will be included in the data listings and summarized using descriptive statistics as described above for DB Treatment Period and for OLE Period separately (except with respect to scheduled nominal time which is not applicable).

Box plots of SS pre-dose (trough) plasma concentrations will be plotted versus scheduled nominal time for each scheduled nominal visit, by treatment received in DB Treatment Period and overall.

Box plot of $C_{ss,avg\ trough}$ will be plotted by treatment received in DB Treatment Period and overall.

Scatter plot matrices, stratified by treatment, of individual subject $C_{ss,avg\ trough}$ values versus baseline body weight and age will also be plotted, and showing correlation coefficient (Spearman's rank correlation coefficient) and p-value.

Etrasimod plasma steady-state will be determined by regressing trough (pre-dose) concentration values over time for the DB Treatment Period (Baseline/Day 1 to Week 16) and OLE Period (Week 16 to Week 72) separately and the resultant slope will be tested for its difference from zero. For each treatment period, a set of data ranged by weeks will be fitted using a mixed effect model with Treatment group (for DB Treatment Period) and week (as a continuous covariate) as fixed effect terms and subject as a random effect term. Steady state is estimated to be achieved as the earliest week included in the analysis when the 90% CI of the slope includes 0.

D. Exposure-Response Relationship Analysis

To explore potential etrasimod plasma exposure-response relationships, the following will be generated, and Baseline below refers to DB Baseline:

- Scatter plot matrix of individual subject change from baseline in EASI Score at Week 12 values versus corresponding individual subject pre-dose (trough) concentrations at Week 12, and showing correlation coefficient r- and p-value (Spearman's rank correlation coefficient). The same approach will also be used to generate another set of similar scatter plots but using instead

individual subject $C_{ss,avg\ trough}$ concentrations (rather than Week 12 predose concentrations).

[redacted]

[redacted]

- Overlay plot showing profiles of mean (SD) heart rate absolute change from baseline (first dose cardiac monitoring) and mean (SD) plasma concentration versus scheduled nominal time from start of treatment for Day 1 will be plotted by DB treatment. A similar set of overlay plots will also be generated instead using mean (SD) heart rate (beats/min) and mean (SD) heart rate percent change from baseline values (ECG data).

- Overlay plot showing profiles of mean (SD) heart rate absolute change from baseline (first dose cardiac monitoring) and mean (SD) plasma concentration versus scheduled nominal time from start of treatment for Week 16 will be plotted by DB treatment. A similar set of overlay plots will also be generated instead using mean (SD) heart rate (beats/min) and mean (SD) heart rate percent change from baseline values (ECG data).

- A scatterplot of individual heart rate versus individual etrasimod plasma concentration from start of treatment for Day 1 and all scheduled nominal time by DB treatment, depicting regression relationship, will be generated; treatment groups will be denoted using different symbols but a single regression presented.