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Statistical Analysis Plan

Study Title:	**A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 24-Week Study, with a 28-Week Open-Label Extension, to Assess the Safety and Efficacy of Etrasimod in Subjects with Moderate-to-Severe Alopecia Areata**
Protocol Number and Version:	**APD334-205 (C5041008) Amendment 2.0 (United States) / Amendment 2.1 (Canada), dated 25 May 2021**
Product:	**Etrasimod (APD334 [PF-07915503])**
Sponsor:	**Arena Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.** **6154 Nancy Ridge Drive** **San Diego, California** **USA, 92121**
Date:	**22-Feb-2023**
Version:	**Final v2.0**
Prepared by:	PPD

STATISTICAL ANALYSIS PLAN REVISION SUMMARY			
Version	**Version Date**	**Author**	**Summary of Changes**
Final 1.0	30-Nov-2022	PPD	Initial version
Final 2.0	22-Feb-2023	PPD	Added Sections 11.6 and 11.7; Updated List of Abbreviations and Appendix 3.

This statistical analysis plan will be reviewed and revised as needed. The most recent approved version will replace the previous version in place.

Statistical Analysis Plan Signature Page

Final Statistical Analysis Plan v2.0 (dated 22-Feb-2023) for protocol APD334-205.

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Approval(s):

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.

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ABBREVIATIONS

AA	Alopecia Areata
AAIC	finite-sample corrected Akaike Information Criteria
AA-QLI	Alopecia Areata Quality of Life Index
AASIS	Alopecia Areata Symptom Impact Scale
AE	Adverse Event
ALC	Absolute Lymphocyte Count
AR (1)	Autoregressive (order 1)
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BMI	Body Mass Index
DB	Double-Blind
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
bpm	beats per minute
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ET	Early Termination
FAS	Full Analysis Set
FEF 25-75	Forced Expiratory Flow at 25% to 75%
FEV_1	Forced Expiratory Volume at 1 second
FVC	Forced Vital Capacity
FCS	Fully Conditional Specification
HR	Heart Rate
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
OC	Observed Case
OLE	Open-Label Extension
PDMP	Protocol Deviations Management Plan
PFT	Pulmonary Function Test
PK	Pharmacokinetic
PMM	Predictive Mean Matching
PP	Per Protocol
PPS	Per Protocol Set
PT	Preferred Term
QT	QT interval
QTcF	Fridericia's correction Formula for QT interval
RR	RR interval
S1P	Sphingosine 1-phosphate

SAE	Serious Adverse Event
SAF	Safety Set
SALT I	Severity of Alopecia Tool I
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System®
SD	Standard Deviation
SFU	Safety Follow-Up
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLC	Total Lung Capacity
TLF	Tables, Listings, and Figures
UN	Unstructured
WHO-DD	World Health Organization Drug Dictionary
WOCF	Worst Observation Carried Forward

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical rationale, methods, rules, and conventions to be used in the presentation and analysis of safety and efficacy for protocol APD334-205. The analyses described in the SAP are based upon the protocol amendment 2.0 (United States)/ amendment 2.1 (Canada) dated 25-May-2021.

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 covers 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. Post hoc analyses may be performed and labeled as such on the output and may be included in the Clinical Study Report (CSR) and identified as such in the CSR.

The mock table, listing, and figure (TLF) shells are prepared in a separate file based on this analysis plan. Upon approval of the SAP, some updates (including but not limited to titles, footnotes, headings and re-numbering of tables) on TLF shells are allowed without a SAP amendment as long as the updates within TLF shells do not conflict with the contents of the SAP.

The statistical analysis of the following data will be described in separate SAPs:

- Serum biomarkers data
- Holter monitoring data
- Pharmacokinetic data, including summary of plasma concentration, steady-state analysis, and exposure-response relationship analysis

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To assess the safety and efficacy of etrasimod monotherapy (2 mg and 3 mg) in subjects with moderate-to-severe alopecia areata (AA) during the Double-Blind (DB) Treatment Period

2.1.2 Secondary Objectives

- To assess the long-term safety and efficacy of etrasimod monotherapy (2 mg and 3 mg) in subjects with moderate-to-severe AA
- To determine the plasma concentration of etrasimod 2 mg and 3 mg in subjects with moderate-to-severe AA

2.2 Endpoints

2.2.1 Double-Blind Treatment Period

2.2.1.1 Primary Efficacy Endpoint

- Percent change from Baseline in Severity of Alopecia Tool I [SALT I] at Week 24

2.2.1.2 Secondary Efficacy Endpoints

- Change from Baseline in SALT I at Week 24
- Proportion of subjects achieving a ≥ 30% improvement from Baseline in SALT I at Week 24
- Proportion of subjects achieving a ≥ 50% improvement from Baseline in SALT I at Week 24
- Proportion of subjects achieving a ≥ 75% improvement from Baseline in SALT I at Week 24

2.2.1.3 Exploratory Efficacy Endpoints

- Percent change from Baseline in SALT I over time
- Change from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 30% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 50% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 75% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 90% improvement from Baseline in SALT I at Week 24
- Change from Baseline in Alopecia Areata Symptom Impact Scale (AASIS) at Week 24

- Change from Baseline in Alopecia Areata-Related Quality of Life Index (AA-QLI) at Week 24
- Change from Baseline in serum biomarkers at Week 24*
- Percent change from Baseline in peripheral lymphocyte counts at Week 24
- Percent change from Baseline in SALT I at Week 24 as assessed by blinded central review
- Change from Baseline in SALT I at Week 24 as assessed by blinded central review
- Proportion of subjects achieving a ≥ 30% improvement from Baseline in SALT I at Week 24 as assessed by blinded central review
- Proportion of subjects achieving a ≥ 50% improvement from Baseline in SALT I at Week 24 as assessed by blinded central review
- Proportion of subjects achieving a ≥ 75% improvement from Baseline in SALT I at Week 24 as assessed by blinded central review
- Proportion of subjects achieving a ≥ 90% improvement from Baseline in SALT I at Week 24 as assessed by blinded central review

* The statistical analysis to be performed for these endpoints will be described in a separated SAP (refer to Section 1)

2.2.1.4 Safety Endpoints

- Incidence and severity of adverse events (AEs) throughout the DB Treatment Period
- Incidence and severity of laboratory abnormalities and change from Baseline in laboratory values (to include hematology, serum chemistry, coagulation, and urinalysis) at Weeks 1 (Cohort 2 only), 2, 4, 8, 12, 16, 20, and 24
- Incidence of clinically significant vital sign abnormalities and changes from Baseline at 1-, 2-, 3-, and 4-hour post-dose on Day 1 as well as Weeks 1 (Cohort 2 only), 2, 4, 8, 12, 16, 20, and 24
- Electrocardiograms (ECG) at 4-hour post-dose on Day 1 as well as Weeks 12 and 24
- Holter Monitoring on Day 1 (Cohort 2 only) and Week 1 (Cohort 2 only)*
- Physical examination findings (abnormalities will be recorded and summarized as medical history or AEs, as applicable)

* The statistical analysis to be performed for these endpoints will be described in a separated SAP (refer to Section 1)

2.2.1.5 Pharmacokinetic Endpoints

- Plasma concentrations of etrasimod from samples collected prior to dosing and 4 hours (± 15 minutes) postdose (after ECG) on Day 1*
- Plasma concentrations of etrasimod from samples collected prior to dosing (trough; within 60 minutes prior to dosing) at Weeks 1 (Cohort 2 only), 2, 4, 8, 12, 16, 20, and 24 *

* The statistical analysis to be performed for these endpoints will be described in a separated SAP (refer to Section 1)

2.2.2 Open-Label Extension Period

2.2.2.1 Exploratory Efficacy Endpoints

- Change and percent change from Baseline in SALT I at Weeks 25, 28, 36, 44, and 52
- Change from Baseline in AASIS at Weeks 36 and 52
- Change from Baseline in AA-QLI at Weeks 36 and 52
- Percent change from Baseline in peripheral lymphocyte counts at Weeks 25, 28, 36, 44, and 52
- Proportion of subjects achieving a ≥ 30% improvement from Baseline in SALT I at Weeks 25, 28, 36, 44, and 52
- Proportion of subjects achieving a ≥ 50% improvement from Baseline in SALT I at Weeks 25, 28, 36, 44, and 52
- Proportion of subjects achieving a ≥ 75% improvement from Baseline in SALT I at Weeks 25, 28, 36, 44, and 52
- Proportion of subjects achieving a ≥ 90% improvement from Baseline in SALT I at Weeks 25, 28, 36, 44, and 52

2.2.2.2 Safety Endpoints

- Incidence and severity of AEs throughout the OLE Period
- Incidence and severity of laboratory abnormalities and change from Baseline in laboratory values (to include hematology, serum chemistry, coagulation, and urinalysis) at Weeks 25, 28, 36, 44, and 52
- Incidence of clinically significant vital sign abnormalities and changes from Baseline at

1-, 2-, 3-, and 4-hour post-dose on Week 24 as well as Weeks 25, 28, 36, 44, and 52

- ECG at 4-hour post-dose on Week 24 as well as Weeks 36, 44, and 52
- Holter Monitoring at Weeks 24 and 25 as well as any time a subject escalates from 2 mg to 3 mg etrasimod*
- Physical examination findings (abnormalities will be recorded and summarized as AEs)

* The statistical analysis to be performed for these endpoints will be described in a separated SAP (refer to Section 1)

2.2.2.3 Pharmacokinetic Endpoints

- Plasma concentrations of etrasimod from samples collected prior to dosing and 4 hours (± 15 minutes) postdose (after ECG) on Week 24*
- Plasma concentrations of etrasimod from samples collected prior to dosing (trough; within 60 minutes prior to dosing) at Weeks 25, 28, 36, and 44*
- Plasma concentrations of etrasimod will be assessed from samples collected anytime at Week 52 or at the Early Termination (ET) visit, and the follow-up visits, as applicable*

* The statistical analysis to be performed for these endpoints will be described in a separated SAP (refer to Section 1)

3 STUDY DESIGN

3.1 Design Overview

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of etrasimod 2 mg and 3 mg, once daily for up to 52 weeks in subjects with moderate-to-severe AA. The study includes multiple periods: a ≤ 4-week Screening Period (to determine subject eligibility), a 24-week DB Treatment Period, a 28-week OLE Period, and a 4-week Safety Follow-Up (SFU) Period for a maximum total study duration of 60 weeks.

This study will include approximately 78 subjects (36 in Cohort 1 and 42 in Cohort 2 as described below) with moderate-to-severe AA with current episode of hair loss for ≥ 6 months but < 8 years in Cohort 1 and hair loss for ≥ 6 months and < 5 years in Cohort 2 (current episode must also be relatively stable during the last 6 months with no significant regrowth).

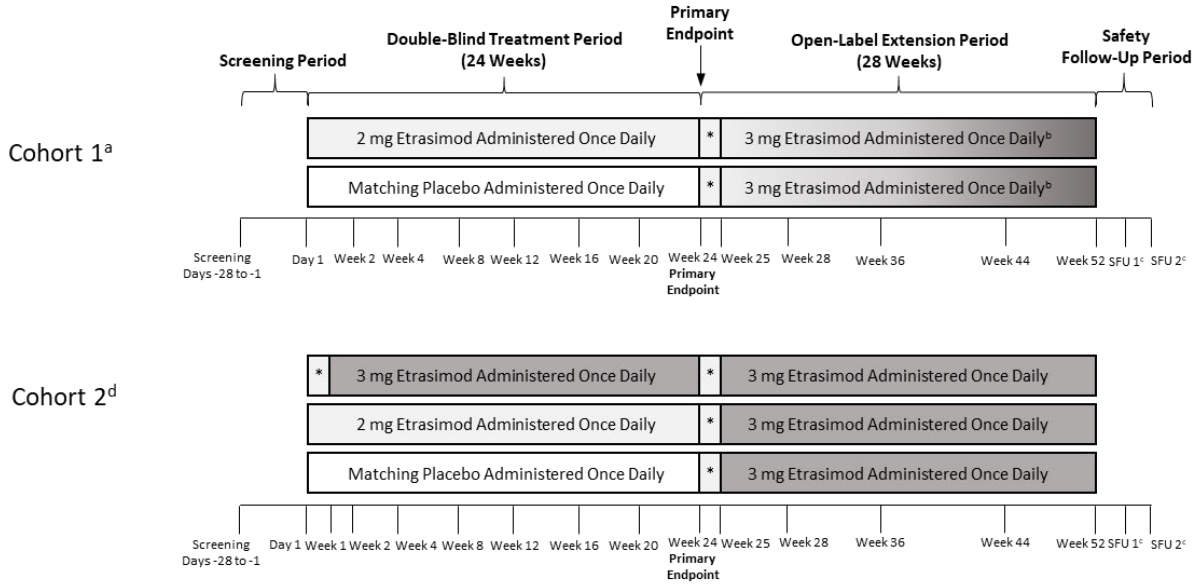
Subjects will be separated into 2 cohorts as follows:

Cohort 1: All subjects (approximately 36 subjects) enrolled under the original protocol, and Amendments 0.1, 0.2, 1.0, and 1.1.

Subjects will be randomized in a 2:1 ratio to receive etrasimod 2 mg or placebo orally, once daily. Randomization is stratified by SALT I score (< 100, 100) at Day 1/Baseline. Subjects will complete the DB Treatment Period per their original randomization assignment. Subjects who have entered the OLE Period prior to Amendments 2.0 and 2.1 implementation will transition to 3 mg once daily at their next study visit. Subjects who have not entered the OLE Period prior to Amendments 2.0 and 2.1 implementation will receive etrasimod 2 mg from the Week 24 visit to the Week 25 visit and will transition at the Week 25 visit to etrasimod 3 mg orally, once daily for the remainder of the OLE Period. Of note, subjects already in the OLE Period at the time of Amendments 2.0 and 2.1 implementation may be allowed to continue on etrasimod 2 mg at the Investigator's discretion provided that they have achieved a SALT I score ≤ 20.

Cohort 2: All subjects (approximately 42 subjects) enrolled under protocol Amendments 2.0 and 2.1. Subjects will be randomized in a 4:1:2 ratio to receive etrasimod 3 mg, etrasimod 2 mg, or placebo orally, once daily, in a double-blind manner for the 24-week DB Treatment Period. Randomization will be stratified by SALT I score (< 50, ≥ 50) at Day 1/Baseline. During the DB Treatment Period, subjects assigned to etrasimod 3 mg will receive etrasimod 2 mg orally, once daily from Day 1 to the Week 1 visit and will transition at the Week 1 visit to etrasimod 3 mg orally, once daily for the remainder of the DB Treatment Period. During the OLE Period, all subjects will receive etrasimod 2 mg orally, once daily from the Week 24 visit to the Week 25 visit. At the Week 25 visit all subjects will transition to 3 mg orally, once daily for the remainder of the OLE Period.

Figure 1: Schematic Diagram of Study Design



[a] Randomized 2:1 (etrasimod 2 mg:placebo) in the Double-Blind Treatment Period.

[b] Subjects entering the Open-Label Extension Period (Week 24 visit) before implementation of Amendments 2.0 and 2.1 will transition to 3 mg once daily at their next study visit (refer to Section 10.5.7.5 and Appendix 1 of the protocol for additional information on Holter monitoring). Subjects entering the Open-Label Extension Period (Week 24 visit) after implementation of Amendments 2.0 and 2.1 will receive etrasimod 2 mg from the Week 24 visit to the Week 25 visit and will transition to etrasimod 3 mg at the Week 25 visit. Of note, subjects already in the Open-Label Extension Period at the time of Amendments 2.0 and 2.1 implementation may be allowed to continue on etrasimod 2 mg at the Investigator's discretion provided that they have achieved a SALT I score ≤ 20.

[c] SFU 1 and SFU 2 are to be conducted 2 and 4 weeks (± 3 days) after last dose of study drug, respectively.

[d] Randomized 4:1:2 (etrasimod 3 mg:etrasimod 2 mg:placebo) in the Double-Blind Treatment Period.

* Subjects will initiate treatment on 2 mg etrasimod for 1 week prior to starting 3 mg.

Note: A visit window of ± 1 day is permitted for the Week 1 and Week 25 visits and ± 3 days for the Week 2, 4, 8, 12, 16, 20, 24, 28, 36, 44, and 52 visits. Subjects who discontinue treatment prematurely, regardless of the reason, should be instructed to return for an ET visit within 1 week of when the last dose of study drug was taken, and to return for the Safety Follow-Up visits 2 weeks and 4 weeks (± 3 days) after the last dose of study drug.

Note: Refer to Section 6.3.2 of the protocol for information on re-initiation of treatment after dose interruptions ET, early termination; N, number (of subjects); SFU, Safety Follow-Up

3.2 Sample Size

Subjects will be randomized as follows:

- Cohort 1: ~36 subjects in 2:1 randomization ratio (~24 subjects to etrasimod 2 mg and ~12 subjects to placebo)
- Cohort 2: ~42 subjects with SALT I < 95 at Baseline in 4:1:2 randomization ratio (~24 subjects to etrasimod 3 mg, ~6 subjects to etrasimod 2 mg, and ~12 subjects to placebo)

Assuming a 15% drop-out rate from the study over 24 weeks, at least 35 treatment completers (20 subjects to etrasimod 3 mg, 5 subjects to etrasimod 2 mg, and 10 subjects to placebo from Cohort 2; plus subjects from Cohort 1 with SALT I < 95 at Baseline) at Week 24 will provide at least 80% and 47% power to detect a treatment difference of 20% for etrasimod 3 mg and etrasimod 2 mg from placebo, respectively, in the percent change from Baseline in SALT I at Week 24 by a 2-sample t-test using a 2-sided significance test level of 0.05 and common standard deviation (SD) of 17.8%.

3.3 Treatment Randomization and Unblinding Procedures

Under protocol amendments 1.0 and 1.1 (Cohort 1), randomization will take place at the Day 1 visit prior to first dosing. Subjects who complete all Screening requirements and remain eligible for the study will be randomized in a 2:1 ratio to receive etrasimod 2 mg or placebo orally once daily for 24 weeks in the DB Treatment Period. The randomization will be stratified by SALT I score (< 100, 100) at Day 1/Baseline.

Subjects enrolled during Amendment 2.0 and later (Cohort 2) who complete all Screening requirements and remain eligible for the study will be randomized in a 4:1:2 ratio to receive etrasimod 3 mg, etrasimod 2 mg, or placebo orally once daily for 24 weeks in the Double-Blind Treatment Period.

This study includes a DB Treatment Period with limited access to the randomization code. The Unblinding Plan documents the procedure for unblinding.

After completing the 24-week DB Treatment Period, eligibility for participation in the OLE Period will be determined. All eligible subjects in Cohort 1 will receive etrasimod 2 mg orally, for at least 1 week during the OLE Period. Subjects in Cohort 1 will transition to 3 mg at the Week 25 visit or at their next OLE study visit after the implementation of Amendments 2.0 and 2.1. Subjects in Cohort 2 will receive etrasimod 2 mg orally, once daily for 1 week during the OLE Period and then transition to etrasimod 3 mg orally, once daily for the remainder of the OLE Period. Subjects from Cohort 1 who are already in the OLE Period at the time of Amendments 2.0 and 2.1 implementation may be allowed to continue on etrasimod 2 mg at the Investigator's discretion provided that they have achieved a SALT I score ≤ 20.

3.4 Schedule of Events

For the statistical analysis, DB Treatment Period will include 24 weeks treatment; OLE Period will include 28 weeks treatment and 4 weeks SFU. The date at which the subject is randomized will be referred to as the "Day 1/Baseline". Subjects will be requested to attend the following scheduled visits for the DB Treatment Period from their Day 1/Baseline visit: Weeks 1, 2, 4, 8, 12, 16, 20, 24 visits as applicable (Week 1 visit is applicable to Cohort 2 only). For the OLE Period, subjects will attend scheduled visits at Week 24 (this will be same as Week 24 in the DB Treatment Period), and Weeks 25, 28, 36, 44, and 52. Subjects who terminate the study drug early in the DB Treatment Period or OLE Period should have SFU Visits 2 weeks and 4 weeks after the last dose of study drug. Visits subjects make to the clinic outside the visit window are recorded as unscheduled visits. Refer to Schedules of Assessments (Appendix 1 and Appendix 2 in the protocol) for more details.

4 GENERAL CONSIDERATIONS

Formats and layouts of TLF will be provided in a separate document (output general layout is described in Appendix **3**).

An analysis of efficacy and safety data will be performed after all subjects have completed or early terminated from the 24-week DB Treatment Period. A final analysis of efficacy and safety data will be performed once all subjects completed or early terminated from the study.

4.1 Baseline

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

Double-Blind Treatment Period

The Study Baseline or DB Treatment Period Baseline (DB Baseline) will be defined as the last non-missing assessment prior to the first study treatment dose (including unscheduled assessments). If the last non-missing assessment is performed on the same date as the first study treatment and time is not available, the assessment will be considered as baseline, except for adverse events and medications starting on the first study treatment dose date which will be considered post-baseline.

Open-Label Extension Period

The OLE Period Baseline (OLE Baseline) will be defined as the last non-missing assessment prior to the first etrasimod dose started at Week 24 for subjects who received placebo during the DB Treatment Period. For subjects who were on etrasimod in the DB Treatment Period, the OLE Baseline will be taken from the DB Baseline.

Change from Baseline will be 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 will be calculated as follows:

Percent change from Baseline (%) = (Change from Baseline / Baseline) x 100.

Percent change from Baseline will be missing in situation where Baseline value equals to 0.

4.2 Reference Start Date, Study Day, and Period Day

Study Day will be calculated as follows and will be used to show start/end day of assessments or events:

Study Day = (Date of event – Date of first dose) + 1 if date of event is on or after the date of first dose of study treatment

= (Date of event – Date of first dose) if date of event is before the date of first dose of study treatment.

Period Day will be calculated as follows for each study period separately:

Period Day for DB Treatment Period = (Date of event – Date of first dose of study treatment during the DB Treatment Period) + 1 if date of event is on or after the date of first dose of study treatment during the DB Treatment Period

= (Date of event – Date of first dose of study treatment during the DB Treatment Period) if date of event is before the date of first dose of study treatment during the DB Treatment Period

Period Day for OLE Period = (Date of event – Date of first dose of study treatment during the OLE Period) + 1.

In the situation where the date of event is partially or completely missing, the Study Day and corresponding Period Day will be missing.

4.3 Windowing Conventions

When available, visits will be analyzed as scheduled (refer to protocol Appendices 1 and 2). ET and/or unscheduled/retest measurements will only be included if a scheduled measurement is not available, and the ET or unscheduled/retest measurement falls within the analysis visit windows as described in Table 1.

If there is more than one retest, unscheduled or ET assessment for a given analysis visit, the assessment closest to the target day will be retained for data summary of that visit; if there are 2

observations with equal distance to the target day, then the later one will be retained. All data from scheduled, retest, unscheduled, and ET visit assessments will be listed.

Table 1: Analysis Visit Windows

Analysis Visit	Target Study Day	Visit Window (Period Day)
DB Treatment Period		
DB Baseline	1	Refer to DB Treatment Period Baseline definition in Section 4.1
Week 1 (Cohort 2 only)	Day 8	Post first dose – Day 11
Week 2	Day 15	Cohort 1: Post first dose – Day 21 Cohort 2: Day 12 – Day 21
Week 4	Day 29	Day 22 – Day 42
Week 8	Day 57	Day 43 – Day 70
Week 12	Day 85	Day 71 – Day 98
Week 16	Day 113	Day 99 – Day 126
Week 20	Day 141	Day 127– Day 154
Week 24*	Day 169	Day 155 – (Last treatment day + 6) in DB period for subjects never treated in OLE; Day 155 – Pre first dose in OLE for subjects treated in OLE
OLE Period **		
OLE Baseline	OLE Day 1	Refer to OLE Period Baseline definition in Section 4.1
Week 25	OLE Day 8	Post first dose in OLE – OLE Day 18
Week 28	OLE Day 29	OLE Day 19 – OLE Day 56
Week 36	OLE Day 85	OLE Day 57 – OLE Day 112
Week 44	OLE Day 141	OLE Day 113 – OLE Day 168
Week 52	OLE Day 197	OLE Day 169 – (Last treatment day + 6)
Safety Follow-up 1	Last treatment day + 14 days (± 3 days)	(Last treatment day +7) – (Last treatment day + 21 days)
Safety Follow-up 2	Last treatment day + 28 days (± 3 days)	(Last treatment day + 22 days) - (Last contact day)

DB = Double-Blind; OLE = Open-Label Extension; SFU = Safety Follow-Up
* Week 24 is the last scheduled visit in DB Treatment Period and first scheduled visit in OLE Period.
** The days are Period Day (refer to Section 4.2) in the OLE Period.

4.4 Descriptive Statistics

All continuous variables will be summarized by presenting the number of subjects, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages. Summary tables will be presented by treatment and visit, when applicable.

4.5 Handling of Retests, Unscheduled Visits, and Early Termination Data

Retests measurements, unscheduled measurements, and ET visit assessments will be included in analysis and summarized via analysis visit windowing according to the windowing conventions in Section 4.3.

4.6 Software Version

All analyses will be performed using SAS® software Version 9.4.

5 STATISTICAL CONSIDERATIONS

5.1 Analysis Sets

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

Table 2. Summary of Analysis Sets

Analysis Set	Description
DB Treatment Period	
Randomized Set	The Randomized Set includes all randomized subjects, irrespective of whether they received any study drug. All subjects will be analyzed according to the treatment group to which they were randomized.
Full Analysis Set (FAS)	The FAS includes all randomized subjects with a SALT I < 95 at Baseline who received at least one dose of study drug. The FAS will be used for the primary analysis of the primary efficacy endpoint and main analysis of the secondary, exploratory, and other efficacy endpoints. All subjects will be analyzed according to the treatment group to which they were randomized.
Modified Full Analysis Set (mFAS)	The mFAS consists of all randomized subjects with a SALT I < 95 at Baseline who received at least 1 dose of study drug, 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. The mFAS will be used for sensitivity analyses for the primary and secondary endpoints in SALT I. All subjects will be analyzed according to the treatment group to which they were randomized.

Analysis Set	Description
Per Protocol Set (PPS)	The PPS consists of all subjects in the FAS with no major protocol deviations (PD) potentially having an impact on the SALT I-related primary and secondary efficacy endpoints (refer to Sections 7.2 and 10.1). The PPS will be used for sensitivity analyses for the primary and secondary efficacy endpoints in SALT I to evaluate the influence of major PD potentially having an impact on the efficacy endpoints. All subjects will be analyzed according to the treatment group to which they were randomized.
Safety Set (SAF)	The SAF consists of all randomized subjects who received at least 1 dose of study drug. All safety analysis in the DB Treatment Period will be performed using SAF. All subjects will be analyzed according to the actual treatment they received. In case a subject received more than one actual treatment, the first treatment received will be used for the safety analysis.
OLE Period	
OLE Safety Set (OLE SAF)	The OLE SAF includes all subjects who received at least one dose of study drug in the OLE Period. All safety analysis in the OLE Period will be performed using OLE SAF. All subjects will be analyzed according to the actual treatment they received. In case a subject received more than one actual treatment, the first treatment received will be used for the safety analysis.
OLE Full Analysis Set (OLE FAS)	The OLE FAS includes all subjects with a SALT I < 95 at Baseline who received at least one dose of study drug in the OLE Period. All efficacy analysis in the OLE Period will be performed using OLE FAS. All subjects will be analyzed according to the actual treatment they received. In case a subject received more than one actual treatments, the first treatment received will be used.

5.2 Adjustments for Covariates

For the continuous efficacy endpoints (e.g., change and percent change from baseline), disease duration and baseline value will be included as covariates in the statistical models, where disease duration, in years, will be calculated as follows:

Disease duration (years) = (Randomization date - Initial onset date +1)/365.25

Should the day be missing for the initial onset date, it will be imputed to the 1st of the month. Should both the day and month be missing for the initial onset date, they will be imputed to January 1st. Completely missing initial onset date will not be imputed.

For binary efficacy endpoints, Cochran-Mantel-Haenszel (CMH) tests will be stratified by the stratification factor for SALT I based on the value used by the IWRS at the time of randomization. If there are more than 10% of subjects who were mis-stratified, a sensitivity analysis will be conducted using the value from the clinical database.

5.3 Handling of Dropouts or Missing Data

See Section 5.2 for handling of completely or partially missing dates for disease duration.

See Appendix **2** for handling of completely or partially missing dates for prior and concomitant medications and AEs.

In DB Treatment Period, missing continuous efficacy data will not be imputed before being summarized using descriptive statistics and analyzed using a Mixed Model Repeated Measures (MMRM) as primary analysis (See section 10.1). For binary efficacy endpoints, subjects with missing data for any reason will be imputed as per the Non-Responder Imputation (NRI) method i.e., considered as a 'non-responder'. As sensitivity analyses to the primary analysis of the primary efficacy endpoint and main analysis of the secondary efficacy endpoints, missing SALT I scores will be imputed as specified in sections 10.1 and 10.2.

In the OLE Period, missing efficacy data will not be imputed.

Unless otherwise specified, there will be no imputation for missing safety data for both study periods (DB Treatment Period and OLE Period).

5.4 Interim Analysis and Data Monitoring

No formal interim analysis of efficacy is planned.

5.5 Multicenter Studies

Study will be conducted at multiple (approximately 29) study sites in the United States and Canada. All sites will be combined for the statistical analyses owing to the small number of subjects expected per site.

5.6 Multiple Comparisons/Multiplicity

No formal testing strategy or adjustments of the Type I error will be employed for the primary and secondary efficacy endpoints. Estimates and two-sided 95% Confidence Intervals (CIs) for treatment groups and from treatment comparisons will be reported in an exploratory manner.

5.7 Examination of Subgroups

Subgroup analysis by below variables will be performed using descriptive statistics only based on the following analysis set for the primary and secondary efficacy endpoints of the DB Treatment Period (refer to Sections 10.1 and 10.2, respectively) to explore whether the treatment effects are

consistent across different subgroups. Median will be derived based on subjects specific to each analysis set.

- Sex (male, female) – FAS
- Race (white, non-white) – FAS
- Age (≤ or > median) – FAS
- Baseline SALT I score (≤ or > median) – FAS
- Duration of AA from initial onset (≤ or > median) – FAS
- Current disease duration (0 - < 2.5 years, 2.5 years - < 5 years, ≥ 5 years): from onset of current episode – FAS
- Baseline AASIS (≤ or > median) – FAS
- Baseline AA-QLI (≤ or > median) – FAS

Additionally, subgroup analysis by below variables will also be performed using descriptive statistics only based on the following analysis set for demographic and other baseline characteristics (refer to Section 6.1), disposition of subjects (refer to Section 7.1), primary and secondary efficacy endpoints of the DB Treatment Period (refer to Sections 10.1 and 10.2, respectively), and exploratory efficacy endpoint of percent change from baseline in peripheral lymphocyte counts of the DB Treatment Period (refer to Section 10.3).

- Cohort (1 or 2) – FAS
- Baseline SALT I score (< 50 or ≥ 50) – FAS
- Baseline SALT I score (< 50, ≥ 50 to < 95 or ≥ 95) – Randomized Set
- Current disease duration (< 5 years, ≥ 5 years): from onset of current episode – FAS

The overall summary of AEs during the DB Treatment Period (refer to Section 11.1) and summary of vital signs of the observed and change from pre-dose values at Day 1 and Week 24 (refer to Section 11.3) will also be summarized by these subgroups for SAF.

6 SUBJECTS CHARACTERISTICS

6.1 Demographic and other Baseline Characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics based on the Randomized Set, FAS, and Safety Set for the DB Treatment Period and on the Open-Label

Extension Safety Set, Open-label Extension FAS for the OLE Period. The list of demographics and baseline characteristics to be summarized includes:

- Age (years) – at time of informed consent
- Sex (male, female)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, unknown)
- Race (White, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black or African American, not reported)
- Baseline height (cm)
- Baseline weight (kg)
- Baseline BMI (kg/m^2)
- Baseline BMI (kg/m^2) by category (≤ 25 kg/m^2, > 25 kg/m^2)
- Cohort (Cohort 1, Cohort 2)
- AA disease duration (years) since initial onset (refer to Section 5.2)
- AA disease duration (years) for current episode, where AA disease duration for current episode, in years, will be calculated as follows: (Date of randomization – Start date of current episode) + 1
- AA disease duration (years) for current episode by category (0 - <2.5 years, 2.5 - < 5 years, ≥ 5 years)
- Baseline SALT I score
- Baseline SALT I score by category (< 50, ≥ 50), (< 50, 50 - < 95, ≥ 95) , (< 95, 95 - < 100, 100)
- Baseline AASIS
- Baseline AA-QLI

A listing of all demographics and baseline characteristics will be provided.

6.2 Surgical/Medical History and Alopecia Areata History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.1.

Surgical and medical history will be summarized by system organ class (SOC) and preferred term (PT) on the safety analysis set. A subject who experienced the same surgical and medical history event multiple times will be counted only once for the corresponding PT. Similarly, if a subject experienced multiple surgical and medical history events within the same SOC, the subject will be counted only once for that SOC. Surgical and medical history events will be sorted alphabetically

by SOC and within each SOC the PT will be presented by decreasing order of total frequency within each SOC.

Disease history of the subject's AA, including the AA subtype at initial diagnosis and current episode diagnosis, any prior AA treatment taken, and current involvement of fingernail, eyelash, eyebrow, and facial hair will be summarized descriptively.

A listing of all surgical and medical history events will be provided. In addition, a listing of AA disease history will also be provided.

7 SUBJECTS ACCOUNTABILITY

7.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study. The number of subjects screened, enrolled, screen failed and the reason for screen failure will be presented for all screened subjects for each cohort and overall in the DB Treatment Period. The percentage of subject enrolled and screen failures will be calculated using the number of subjects screened in each cohort as denominator. The percentage of reasons for screen failure will be calculated using the number of screen failures in each cohort as denominator.

For the DB Treatment Period, the numbers and percentages of randomized subjects included in each analysis set (Randomized, FAS, modified FAS, PPS, and Safety) will be presented for each DB Treatment Period group and overall.

Study DB Treatment Period completion status and the reason for DB Treatment Period treatment discontinuation will also be presented for each DB Treatment Period treatment group and overall. The percentage of reasons for DB Treatment Period study discontinuation will be calculated using the number of subjects randomized in the DB Treatment Period as denominator.

The numbers and percentages of subjects enrolled into OLE period and subjects not enrolled into OLE Period will be presented for each DB Treatment Period treatment group and overall.

Subject disposition in the OLE Period and the full study (DB Treatment Period and OLE Period) will be summarized using frequency counts and percentages, including: OLE Period completion status, reason for treatment discontinuation in the OLE Period, full study completion status and reason for study discontinuation in the full study (overall and by OLE Period treatment group). The percentage of reasons for OLE Period study discontinuation will be calculated using the number of subjects randomized in the OLE Period as denominator.

A listing of subject's disposition will be provided. Information on first screening for subjects who were rescreened, including the rescreened subject identifier, will be presented under the first

screening subject identifier. A listing of subject's randomization information and a listing of subjects included in each of the study populations will also be provided.

In order to describe the impact of COVID-19, subjects discontinued from the study due to COVID-19 as the primary reason will be summarized in the above disposition table. The specific reasons for subjects discontinued due to COVID-19 such as subject decision, subject self-isolation, non-compliance with protocol, transportation issue, site restrictions, physician decision, site closed, lack of drug at site, sponsor decision, and severity of COVID-19 infection will be presented in the above disposition listing.

7.2 Protocol Deviations

PDs with a start date before the date of first dose in OLE will be considered a DB PD while PDs with a start date on or after the date of first dose in OLE will be considered an OLE PD.

A blinded data review will be conducted before the primary database lock by the Medical Monitor and Sponsor to classify each PD occurring during the DB Treatment Period as 1) important or non-important and 2) major or minor (refer to the PD Management Plan [PDMP]). Another data review will be conducted before the final database lock by the Medical Monitor and Sponsor to classify each PD occurring during the OLE period as 1) important or non-important and 2) major or minor (refer to the PDMP).

During the review conducted before the primary database lock for DB Treatment Period, major PDs potentially having an impact on the SALT I-related primary and secondary efficacy endpoints will be identified by the Medical Monitor and Sponsor and will lead to the exclusion from the PPS. These PDs might include, but are not limited to:

- Violation of eligibility criteria
- Receiving incorrect study treatment
- Compliance with study treatment < 80%
- Chronic use of prohibited medication while on study treatment

The number of events and the frequency count and percentage of subjects with at least one important PD, with a least one major PD, with at least one major PD potentially having an impact on the SALT I-related primary and secondary efficacy endpoints, and with at least one PD associated with COVID-19 will be summarized for the DB Treatment Period by treatment group, deviation category, and deviation sub-category using the randomized set. Important PDs, major PDs, and PDs related to COVID-19 will be summarized similarly overall using the randomized set and for the OLE period using the OLE SAF.

A listing of all protocol deviations will be provided. Important PDs, major PDs, major PDs potentially having an impact on the on the SALT I-related primary and secondary efficacy endpoints, and COVID-19 related PDs will be flagged in this listing.

8 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD), September 2021 B3.

Prior medications are defined as any medication started and discontinued prior to the first study treatment dose. Concomitant medications are defined as any medication taken from the first study treatment dose throughout the end of the study including those who started prior to the first study treatment date and continued past that date. See Appendix **2** for handling of completely or partially missing dates for prior and concomitant medications. Concomitant medications taken on or after the first dose of study treatment during the DB Treatment Period and before the first dose of study treatment during the OLE Period, including those started before the first dose of study treatment during the DB Treatment Period and continued past that date, will be assigned to the DB Treatment Period. Concomitant medication taken on or after the first dose of study treatment during the OLE Period, including those started before the first dose of study treatment during the OLE Period and continued past that date, will be assigned to the OLE Period.

Incidence of prior medications will be tabulated by anatomical therapeutic chemical (ATC) level 3 and Preferred Drug Name based on the SAF. Subject with the same medication taken multiple times within the same Preferred Drug Name will be counted only once for that Preferred Drug Name. Similarly, if a subject has taken more than one medication within the same ATC level, then the subject will be counted only once for that ATC. Concomitant medications will be summarized similarly by study period.

A listing of all prior and concomitant medications will be provided.

9 STUDY TREATMENT EXPOSURE AND TREATMENT COMPLIANCE

Duration of exposure to study drug, in days, will be computed overall and for each study period as follows:

Overall duration of exposure = (Date of last dose of study drug, regardless of the study period – Date of first dose of study drug during the DB Treatment Period) + 1

Duration of exposure for DB Treatment Period = (Date of last dose of study drug during the DB Treatment Period – Date of first dose of study drug during the DB Treatment Period) + 1

Duration of exposure for OLE Period = (Date of last dose of study drug during the OLE Period – Date of first dose of study drug during the OLE Period) + 1

Duration of exposure to etrasimod 2 mg and etrasimod 3 mg will also be computed overall and for the OLE Period as follows:

Overall duration of exposure to etrasimod 2 mg = (Date of last dose of etrasimod 2 mg, regardless of the study period – Date of first dose of etrasimod 2 mg, regardless of the study period) + 1

Overall duration of exposure to etrasimod 3mg = (Date of last dose of etrasimod 3 mg, regardless of the study period – Date of first dose of etrasimod 3mg, regardless of the study period) + 1

Duration of exposure to etrasimod 2 mg during the OLE Period = (Date of last dose of etrasimod 2 mg during the OLE Period – Date of first dose of etrasimod 2 mg during the OLE Period) + 1

Duration of exposure to etrasimod 3mg during the OLE Period = (Date of last dose of etrasimod 3 mg during the OLE Period – Date of first dose of etrasimod 3mg during the OLE Period) + 1

In addition, duration of dose interruptions (in days) will be calculated overall and by study period as follows:

$$\text{Overall duration of dose interruptions} =$$

$$\sum_{i=1}^{n}(\text{End date of dose interruption i} - \text{Start date of dose interruption i}) + 1$$

if subject has at least one dose interruption interval

0 if subject has no dose interruption intervals

where n = total number of dose interruption intervals during the whole study.

Duration of dose interruptions for the DB Treatment Period and OLE Period will be calculated similarly, but n will be the total number of dose interruptions during the DB Treatment Period and total number of dose interruptions during the OLE Period, respectively.

Compliance with study drug, in percentage, will be calculated overall and by study period as follows:

Compliance with study drug (%) for DB Treatment Period=

$$\frac{\text{Total number of tablets taken during the DB Treatment Period}}{} \times 100$$

Expected number of tablets to be taken during the DB Treatment Period

where the expected number of tablets to be taken during the BD Treatment Period is the duration of exposure to study drug during the DB Treatment Period, in days, multiplied by the number of tablets to be taken per day. For Cohort 1, the number of tablets to be taken per day is 1 while, for Cohort 2, the number of tablets to be taken per day is 2.

Compliance with study drug (%) for OLE Period=

$$\frac{\text{Total number of tablets taken during the OLE Period}}{\text{Expected number of tablets to be taken during the OLE Period}} \times 100$$

where the expected number of tablets to be taken during the OLE Period=

[Duration of exposure to etrasimod 3 mg during the OLE Period (days) * number of tablets to be taken /day (i.e., 2)]

+

[Duration of exposure to etrasimod 2 mg during the OLE Period (days) * number of tablets to be taken /day (i.e., 1)]

Overall compliance with study drug (%)=

$$\frac{\text{Total number of tablets taken overall}}{\text{Expected number of tablets to be taken overall}} \times 100$$

where expected number of tablets to be taken overall study will be the sum of expected number of tablets to be taken during the DB Treatment Period and expected number of tablets to be taken during the OLE Period.

Duration of exposure to study treatment (days), number of subjects with dose interruption, duration of dose interruption (days), and compliance with study treatment (%) will be summarized using descriptive statistics by treatment group, overall and by study period using the SAF. Compliance with study treatment will also be summarized using the frequency cout and percentage of subjects in each of the following categories based on the SAF: < 80%, [80% - 120%] and > 120%.

Exposure and compliance will be displayed in a listing of study treatment administration.

10 EFFICACY ANALYSIS

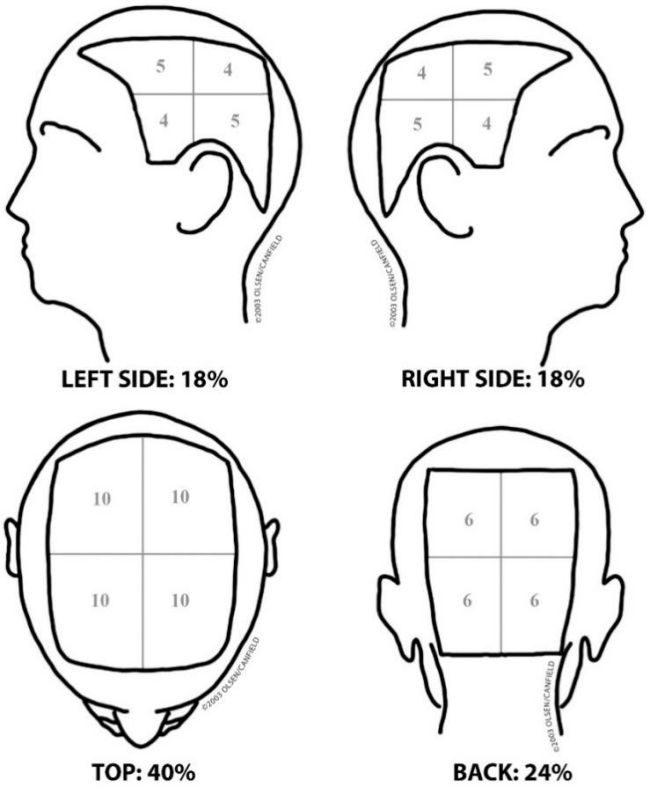
Unless otherwise indicated, efficacy endpoints will be summarized and analyzed using the FAS by visit and treatment group, as applicable.

10.1 Primary Efficacy Endpoint

The primary efficacy endpoint is percent change from Baseline in SALT I at Week 24.

SALT I is a well-validated metric and widely utilized tool for determining the degree of hair loss based on the percentage of scalp surface area involved on the top, back, and each side of the scalp for AA. Using the diagram in Figure 2, the Investigator will determine the percent scalp hair loss in a given quadrant, multiply this by the total scalp area delineated by that quadrant, and sum the resultant numbers for each quadrant to give the total percent scalp hair loss with a maximum score of 100. Change and percent change from Baseline in total percent of scalp hair loss will then be calculated as described in Section 4.1.

Figure 2: Visual Aid for Estimating Percentage Scalp Hair Loss Using the Severity of Alopecia Tool



Analysis of Primary Efficacy Endpoint

Primary Analysis

Missing data will be handled as described in Section 5.3.

Percent change from baseline in SALT I score will be summarized using descriptive statistics by visit and treatment group. Observed and change from Baseline in SALT I score will be summarized similarly.

The primary endpoint will be analyzed using a MMRM model. The MMRM model will include the treatment group (2 mg, 3 mg, and placebo), analysis visit (Weeks 1, 2, 4, 8, 12, 16, 20, and 24), and treatment-by-analysis visit interaction as fixed effects, and disease duration (years; refer to Section 5.2) and Baseline SALT I score as covariates.

An unstructured (UN) variance-covariance matrix will be specified for the MMRM model. If convergence issues arise, the autoregressive (order 1) [AR(1)] structure will be used. If the AR(1) structure also does not converge, other covariance structures deemed appropriate to fit the data will be used and the structure with the smallest finite-sample corrected Akaike

Information Criteria (AAIC) value will be retained. Least squares (LS) mean estimates, LS mean differences between treatment groups (each of the active arms versus placebo only), corresponding 95% CIs, and p-values will be reported for each visit. The primary comparisons of interest will be between each active arm and placebo at Week 24.

Sensitivity Analysis

In addition to the primary analysis, the following sensitivity analyses will be performed using imputed data or alternative analysis set:

1) ANCOVA at Week 24 with Multiple imputation (MI) using the FAS

All missing SALT I scores at scheduled visits up to Week 24 will be imputed using a multiple imputation (MI) technique with a fully conditional specification (FCS; Brand, 1999; van Buuren et al., 2007) predictive mean matching (PMM; Heitjan and Little, 1991; Schenker and Taylor, 1996) sequential regression multiple imputation model, where missing values for all variables (visits) are imputed sequentially one at the time, with preceding variables (visits) serving as covariates. For each variable (visit), the FCS PMM regression model will include the outcome at that visit as the dependent variable and as independent variables, the treatment group, disease duration, baseline SALT I score, and SALT I scores at the previous scheduled visits using a seed of 20210106. The number of observed values whose predicted values are closest to the predicted value of the missing value and among which an observed value will be randomly selected to impute the missing value will be the SAS default value (i.e., k = 5). This process will be repeated 100 times, resulting in a total of 100 complete analysis datasets.

The example SAS code for the multiple imputation process is as below:

```
PROC MI DATA=SALTI1 OUT=SALTI2 SEED=20210106 NIMPUTE=100;
CLASS TRTPN;
FCS REGPMM(SALT2=TRTPN DISDUR BASESALT);
FCS REGPMM(SALT3=TRTPN DISDUR BASESALT SALT2);
FCS REGPMM(SALT4=TRTPN DISDUR BASESALT SALT2 SALT3);
FCS REGPMM(SALT5=TRTPN DISDUR BASESALT SALT2 - SALT4);
FCS REGPMM(SALT6=TRTPN DISDUR BASESALT SALT2 - SALT5);
FCS REGPMM(SALT7=TRTPN DISDUR BASESALT SALT2 - SALT6);
FCS REGPMM(SALT8=TRTPN DISDUR BASESALT SALT2 - SALT7);
VAR TRTPN DISDUR BASESALT SALT2 - SALT8;
RUN;
```

For each multiply imputed dataset, percent change from Baseline in SALT I score will be derived using observed and imputed values and the percent change from Baseline at Week 24 will be analyzed using an ANCOVA model including the treatment group as fixed effect, and disease duration (years) and Baseline SALT I score as covariates. Results from each ANCOVA model (LS means [and associated standard errors], LS mean difference between each etrasimod treatment group and placebo [and associated standard errors], and parameter estimates) will be

combined and reported along with two-sided 95% CI and p-value using PROC MIANALYZE based on Rubin's rule.

2) Observed Cases (OC) in mFAS: The primary analysis of the primary endpoint will be repeated in mFAS based on observed data without imputation.

3) OC in PPS: The primary analysis of the primary endpoint will be repeated using the PPS to evaluate the influence of major protocol deviations on the primary results.

4) OC in Randomized Set: The primary analysis of the primary endpoint will be repeated in Randomized Set based on observed data without imputation.

5) OC in FAS Adjusting for the SALT I Stratification Variable and Cohort: The primary analysis of the primary endpoint will be repeated using the FAS based on observed data without imputation and will also include the stratification variable of SALT I (< 50 and ≥ 50) and cohort (1 and 2) as fixed effects to evaluate the influence of the change of randomization ratio between Cohort 1 and Cohort 2.

6) OC in FAS Including Cohort 2 Only: The primary analysis of the primary endpoint will be repeated using the FAS based on observed data without imputation but including only subjects randomized in Cohort 2. The stratification variable of SALT I (< 50 and ≥ 50) will also be included in the MMRM model as a fixed effect.

7) OC in FAS Excluding the Etrasimod 3 mg Treatment Group: The primary analysis of the primary endpoint will be repeated using the FAS based on observed data without imputation but excluding the Etrasmiod 3 mg treatment group. The stratification variable of SALT I (< 50 and ≥ 50) and Cohort (1 and 2) will also be included in the MMRM model as a fixed effect.

Subgroup Analyses

Subgroup analyses will be performed descriptively for the subgroups defined in Section 5.7.

10.2 Secondary Efficacy Endpoints

SALT I will also be analyzed as follows:

- Change from Baseline in SALT I at Week 24
- Proportion of subjects achieving a ≥ 30% improvement from Baseline in SALT I at Week 24
- Proportion of subjects achieving a ≥ 50% improvement from Baseline in SALT I at Week 24
- Proportion of subjects achieving a ≥ 75% improvement from Baseline in SALT I at Week 24

Analysis of Secondary Efficacy Endpoints

The secondary endpoints will be analyzed using the FAS.

Main Analysis

The change from Baseline in SALT I at Week 24 will be summarized and analyzed as for the primary analysis of the primary efficacy endpoint (refer to Section 10.1).

For proportion-based secondary endpoints at Week 24, subjects with missing data for any reason will be imputed as described in Section 5.3. Frequency count and percentage of subjects achieving the criteria (and associated two-sided 95% Clopper-Pearson exact CIs) will be reported for each treatment group. The differences in proportion between each etrasimod treatment group and placebo, along associated two-sided 95% unconditional exact CIs, and p-value will also be reported. The proportion of subjects achieving the criteria in each etrasimod treatment group vs. placebo will be analyzed using a CMH test, adjusted for the randomization stratification factor SALT I score (< 50, ≥ 50) at Baseline. Subjects in Cohort 1 will be considered in the ≥ 50 group as per inclusion criteria for Cohort 1.

Sensitivity Analysis

For the change from Baseline in SALT I at Week 24, the same sensitivity analyses as for the primary efficacy endpoint will be performed (refer to Section 10.1).

For the proportion-based secondary endpoints at Week 24, the following sensitivity analyses will be performed using imputed data or alternative analysis set:

1) MI in FAS: Missing response status will be derived based on the multiple imputed datasets for SALT I values using the same multiply imputed datasets than for sensitivity analysis #1 of primary efficacy endpoint (refer to Section 10.1). The same CMH test will then be performed and combined using Rubin's method. Combined proportion along with the 95% CI, and p-value will be reported.

2) NRI in mFAS: The main analysis of these secondary efficacy endpoints will be repeated based on the mFAS.

3) NRI in PPS: The main analysis of these secondary efficacy endpoints will be repeated based on the PPS.

4) OC in FAS: The proportion-based key secondary endpoints at Week 24 will be analyzed in FAS based on observed data without imputation.

5) NRI in Randomized Set: Missing proportion-based response status at Week 24 will be imputed as 'non-responders'. The same CMH test will then be performed in the

Randomized Set. The randomization stratification factor SALT I score (< 50, 50-< 95, ≥ 95) at Baseline will be used.

Subgroup Analyses

The same subgroup analyses as for the primary efficacy endpoint will be performed on all secondary endpoints descriptively using the FAS.

10.3 Exploratory Efficacy Endpoints

SALT I

SALT I (refer to Section 10.1) will also be analyzed as follows:

- Percent change from Baseline in SALT I over time
- Change from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 30% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 50% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 75% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 90% improvement from Baseline in SALT I at Week 24
- Percent change from Baseline in SALT I at Week 24 as assessed by blinded central review
- Change from Baseline in SALT I at Week 24 as assessed by blinded central review
- Proportion of subjects achieving a ≥ 30% improvement from Baseline in SALT I at Week 24 as assessed by blinded central review
- Proportion of subjects achieving a ≥ 50% improvement from Baseline in SALT I at Week 24 as assessed by blinded central review
- Proportion of subjects achieving a ≥ 75% improvement from Baseline in SALT I at Week 24 as assessed by blinded central review
- Proportion of subjects achieving a ≥ 90% improvement from Baseline in SALT I at Week 24 as assessed by blinded central review

AASIS

The AASIS is a 13-item, disease-specific measure that asks participants about symptoms related to AA and how these symptoms interfere with daily functioning. Subjects will be asked to rate

how severe each of the following 7 symptoms pertaining to AA symptoms have been in the past week using an 11-point scale ranging from 0 "not present" to 10 "as bad as you can imagine":

- Scalp hair loss
- Body or eye lashes hair loss
- Tingling/numbness of the scalp
- Itchy or painful skin
- Irritated skin
- Feeling anxious or worry
- Feeling sad

Subjects will also be asked to rate how severe each of the following 6 areas of daily functioning are interfered with by AA in the past week using an 11-point scale ranging from 0 = "did not interfere" to 10 "interfered completely": work, enjoyment of life, interaction with others, daily activities, sexual relationships, and quality of life. The overall scoring system ranges from of 0 to 10 (overall score is the arithmetic mean) with high scores indicative of greater AA symptom impact.

AASIS Symptoms Sub-score (1-7): If at least 4 out of 7 symptom items i.e., AASIS (1-7) questions have been answered, then AASIS symptoms sub-score will be the arithmetic mean of all answered symptom items; otherwise, the sub-score will be set to missing.

AASIS Interference Sub-score (8-13): If at least 3 out of 6 interference items i.e., AASIS (8-13) questions have been answered, then AASIS interference sub-score will be the arithmetic mean of all answered interference items; otherwise, the sub-score will be set to missing.

AASIS Total Score: If both AASIS Symptoms Sub-score (1-7) and AASIS Interference Sub-score (8-13) are not missing, then AASIS total score will be the arithmetic mean of all answered symptoms and interference items, otherwise the total score will be set to missing.

AASIS exploratory efficacy endpoint is:

- Change from Baseline in AASIS at Week 24

AA-QLI

The AA-QLI is a disease-specific questionnaire developed to evaluate the impact of AA on quality of life. The AA-QLI has been validated with the Dermatology Life Quality Index and shown to provide more comprehensive insights about psychological distress among AA patients specifically. The AA-QLI consists of 21 questions covering 3 areas of daily life: subjective symptoms, relationships, and objective signs. AA-QLI Total Score is derived as the sum of the scores for the 21 questions. The results are presented on a scale varying between 21 and 84; a score

of 21 represents the best quality of life, while a score of 84 represents the poorest quality of life outcomes. AA-QLI Total Score will be set to missing if at least one question is not answered.

AA-QLI exploratory efficacy endpoint is:

- Change from Baseline in AA-QLI at Week 24

Lymphocyte Counts and Infections

Clinical safety laboratory tests will be completed predose at each study visit.

Lymphocyte counts exploratory efficacy endpoint is:

- Percent change from Baseline in peripheral lymphocyte counts at Week 24

Exploratory Endpoint Analyses

Main Analysis

With the following exception, exploratory efficacy endpoints will be summarized and analyzed as for the main analysis of the secondary efficacy endpoints (refer to Section 10.2).

The exception is that the change and percent change from Baseline in SALT I at Week 24 as assessed by blinded central review will be summarized as the primary efficacy endpoint (refer to Section 10.1), but analyzed using an ANCOVA model based on observed-cases (missing data will not be imputed) and including treatment group as fixed effect, and disease duration (years) and Baseline SALT I score as covariates. LS means and LS mean difference between each etrasimod treatment group and placebo will be reported along with two-sided 95% CI and p-value.

Sensitivity Analyses

No sensitivity analyses will be performed for the exploratory efficacy endpoints.

Subgroup Analyses

The same subgroup analyses as for the primary efficacy endpoint will be performed for the exploratory efficacy endpoint of percent change from Baseline in peripheral lymphocyte counts at Week 24.

No subgroup analyses will be performed for other exploratory efficacy endpoints.

10.4 Other Efficacy Endpoints

The following other efficacy endpoints will also be summarized and analyzed:

- Proportion of subjects achieving a SALT I score ≤ 10 over time
- Proportion of subjects achieving a SALT I score ≤ 20 over time

- Proportion of subjects achieving a ≥ 90% improvement from Baseline in SALT I over time
- Change from Baseline in AASIS at Week 12
- Change from Baseline in AA-QLI at Week 12
- Percent change from Baseline in peripheral lymphocyte counts at Weeks 1 (Cohort 2 only), 2, 4, 8, 12, 16, and 20

Other efficacy endpoints will be summarized and analyzed as for the proportion-based exploratory efficacy endpoints or continuous exploratory efficacy endpoints, as applicable, for visits occurring during the DB Treatment Period (refer to Section 10.3).

No sensitivity analyses and no subgroup analyses will be performed for the other efficacy endpoints.

10.5 Exploratory Efficacy Endpoints during the Open-Label Extension Period

The following efficacy endpoints will be assessed at scheduled visits during the OLE Period up to 52 weeks:

- Change and percent change from Baseline in SALT I over time
- Change from Baseline in AASIS over time
- Change from Baseline in AA-QLI over time
- Change from Baseline in peripheral lymphocyte counts over time
- Proportion of subjects achieving a ≥ 30% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 50% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 75% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a ≥ 90% improvement from Baseline in SALT I over time
- Proportion of subjects achieving a SALT I score ≤ 10 over time
- Proportion of subjects achieving a SALT I score ≤ 20 over time

These endpoints will be summarized by visit using descriptive statistics based on the OLE FAS, with following considerations:

- Missing data will not be imputed

- Summaries will be provided for the three treatment groups in the OLE Period (OLE 2mg, OLE 2mg/3mg, OLE 3mg) and three randomized treatment groups in the DB Treatment Period (DB 2mg, DB 3mg, DB placebo)
- Change and percent change from baseline in continuous variables will be summarized using change from OLE Baseline and DB Baseline (refer to Section 4.1).

The photographic assessments of the full scalp for all subjects, of the eyebrows and eyelashes for subjects who have hair loss in these areas at Day 1/Baseline, and of the fingernails for subjects with fingernail changes related to AA (eg, pitting, white spots, and roughness) at Day 1/Baseline, will be reported in listing.

10.6 Summary of Efficacy Analyses

Table 3. Summary of Efficacy Analyses

Efficacy Endpoint	Primary/Main Analysis	Sensitivity Analysis
DB Treatment Period		
Primary		
Percent change from baseline in SALT I	FAS, OC (MMRM)	#1 FAS, MI (ANCOVA) #2 mFAS, OC (MMRM) #3 PPS, OC (MMRM) #4 Randomized Set, OC (MMRM) #5 FAS, OC (MMRM), adjusting for the SALT I stratification variable and cohort #6 FAS, OC (MMRM), including Cohort 2 only and adjusting for the SALT I stratification variable #7 FAS, OC (MMRM), excluding Etrasimod 3 mg and adjusting for the SALT I stratification variable and cohort
Secondary		
Change from baseline in SALT I	FAS, OC (MMRM)	#1 FAS, MI (ANCOVA) #2 mFAS, OC (MMRM) #3 PPS, OC (MMRM) #4 Randomized Set, OC (MMRM) #5 FAS, OC (MMRM), adjusting for the

Efficacy Endpoint	Primary/Main Analysis	Sensitivity Analysis
		SALT I stratification variable and cohort #6 FAS, OC (MMRM), including Cohort 2 only and adjusting for the SALT I stratification variable #7 FAS, OC (MMRM), excluding Etrasimod 3 mg and adjusting for the SALT I stratification variable and cohort
Binary secondary endpoints in SALT I	FAS, NRI (CMH)	#1 FAS, MI (CMH), #2 mFAS, NRI (CMH) #3 PPS, NRI (CMH) #4 FAS, OC (CMH) #5 Randomized Set, NRI (CMH)
Exploratory		
Change and percent change from Baseline in SALT I over time Change from Baseline in AASIS at Week 24 Change from Baseline in AA-QLI at Week 24 Percent change from baseline in peripheral lymphocyte counts at Week 24	FAS, OC (MMRM)	
Binary exploratory endpoints in SALT I over time	FAS, NRI (CMH)	
Change and percent change from Baseline in SALT I by blinded	FAS, OC (ANCOVA)	

Efficacy Endpoint	Primary/Main Analysis	Sensitivity Analysis
central review at Week 24		
Binary exploratory endpoints in SALT I by blinded central review at Week 24	FAS, NRI (CMH)	
Other		
Binary other endpoints in SALT I over time	FAS, NRI (CMH)	
Change from Baseline in AASIS at Week 12 Change from Baseline in AA-QLI at Week 12 Percent change from baseline in peripheral lymphocyte counts over time	FAS, OC (MMRM)	
OLE Period		
Change and percent change from DB and OLE Baseline in SALT I over time Change from DB and OLE Baseline in AASIS over time Change from DB and OLE Baseline in AA-QLI over time	OLE FAS, OC (Descriptive)	

Efficacy Endpoint	Primary/Main Analysis	Sensitivity Analysis
Change from DB and OLE Baseline in peripheral lymphocyte counts over time		
Proportion-based exploratory endpoints in SALT I over time	#1: OLE FAS, OC (Descriptive) #2: OLE FAS, NRI (Descriptive)	

11 SAFETY ANALYSIS

Unless otherwise indicated, safety data will be summarized overall and by treatment group and visit, when applicable, for each study period separately, based on the SAF for the DB Treatment Period and OLE SAF for the OLE Period.

11.1 Adverse Events

AEs will be coded according to the MedDRA, Version 24.1, and will be summarized overall and by treatment group for across both study periods and for each study period separately.

Treatment emergent adverse events (TEAEs) are defined as any AEs with onset date during or after the first study treatment dose. See Appendix **2** for handling of completely or partially missing dates for AEs. AEs starting on the first study treatment dosing date and related to a pre-dose study assessment will not be considered as TEAE. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent.

Furthermore, TEAEs will be assigned to the DB Treatment Period or OLE Period depending on their onset date – if the AE onset date is before the date of first dose in OLE, the AE will be assigned to the DB Treatment Period AE. If the AE had an onset on or after the date of first dose in OLE, the AE will be assigned to an OLE Period. AEs starting on the Week 24 and related to a pre-dose study assessment will be assigned to DB Treatment Period.

An overall summary table of adverse events will be provided. The number of events and the frequency count and percentage of subjects who experienced an AE, TEAE, TEAE by maximum reported relationship, TEAE by maximum reported Common Terminology Criteria for Adverse Events (CTCAE) severity, serious AE (SAE), serious TEAE, TEAE leading to study drug

discontinuation, TEAE leading to study discontinuation, treatment emergent AE of Special Interest (AESI) and AE leading to death will be presented.

Of note, prior to each database lock (primary and final), AESIs will be flagged as such by the Sponsor Clinical Development/Medical teams from the subset of AEs that will have been classified programmatically as Targeted Medical Events (TMEs) based on an exhaustive list of SOCs and PTs provided by the Sponsor. The list of AEs deemed as AESIs will be finalized prior to each database lock.

Unless otherwise specified, a subject experiencing a TEAE multiple times within the same PT will be counted only once for the corresponding PT. Similarly, if a subject experiencing multiple TEAEs within the same SOC, the subject will be counted only once for that SOC. TEAEs will be sorted by decreasing order of total frequency of SOC and PT within each SOC.

Frequency and percentage of subjects who experience TEAE will be summarized by PT and also by SOC and PT.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC, PT, and maximum reported relationship (treatment-related or not treatment-related). A treatment-related AE is defined as any TEAE that is assessed by the Investigator as Related or Probably Related to study treatment. TEAE that is assessed as Unlikely Related or Not Related will be defined as not treatment-related. TEAE with an unknown relationship will be considered as treatment-related.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC, PT, and maximum reported severity. The severity will be graded according to the CTCAE (Grade 1 - mild, Grade 2 - moderate, Grade 3 - severe, Grade 4 – life-threatening or Grade 5 - death). If a subject experience more than one TEAE within different severity categories within the same SOC/PT, only the worst case (maximum reported severity) will be reported. TEAE with an unknown severity will be considered as severe.

Frequency and percentage of subjects who experience serious TEAE will be summarized by SOC and PT within SOC.

Frequency and percentage of subjects who experience treatment emergent AESI will be summarized by AESI category and PT.

Frequency and percentage of subjects who experience non-serious TEAE will be summarized by SOC and PT for DB and OLE period separately.

Listings of all AEs, all AEs leading to death, all serious AEs, all TEAEs leading to study drug discontinuation, and all TEAEs leading to study discontinuation will be provided.

11.2 Clinical Laboratory

For quantitative laboratory test, descriptive statistics will be presented for data related to chemistry, hematology (including coagulation) and quantitative urinalysis. Observed values and change from baseline values will be presented for each post-baseline visit. Frequencies and percentages of subjects in each result category will be provided for qualitative urinalysis data.

Shift tables from baseline to each post-baseline visits describing shifts to abnormality (low or high) will be provided as well. Only subjects with a baseline result and a result at the specified visit for the parameter will be considered.

Separate listings of all data for chemistry, hematology (including coagulation), urinalysis and pregnancy test will be provided.

In addition, separate listings of data for chemistry, hematology (including coagulation), and urinalysis will be provided for each parameter where a subject had at least one abnormal result.

Incidence of hepatic enzyme elevations will be summarized by visit. The following hepatic enzyme elevations will be reported:

- ALT > 1, >2, > 3, > 5, > 8, > 10, and > 20 x upper limit of normal (ULN)
- AST > 1, > 2, > 3, > 5, > 8, > 10, and > 20 x ULN
- ALT or AST > 3, > 5, > 10, and > 20 x ULN
- ALP > 1, > 1.5, > 2, > 3, > 5, > 8, > 10, and > 20 x ULN
- GGT > 1, > 2, > 3, > 5, > 8, > 10, and > 20 x ULN
- Total bilirubin >1, > 1.5, >2, and >3 x ULN
- ALT or AST > 3 x ULN *AND* total bilirubin > 1.5 x ULN
- ALT or AST > 3 x ULN *AND* total bilirubin > 2 x ULN
- ALT or AST > 3 x ULN *AND* ALP > 1.5 x ULN
- Symptomatic elevation in ALT or AST, defined as an ALT or AST elevation > 3 x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue, where temporal association is defined as onset of symptoms within +/- 14 days of the elevation.

Incidence of absolute lymphocyte count decrease at any time during a study period (post-dose on Day 1 to pre-dose on Week 24 for the DB Treatment Period and post-dose on Week 24 to the 2nd SFU visit for the OLE Period) will be summarized. The following categories will be presented:

- Grade 1, defined as an absolute lymphocyte count ≥ 0.8 to < 1.02 x 10^9/L
- Grade 2, defined as an absolute lymphocyte count ≥ 0.5 to < 0.8 x 10^9/L
- Grade 3, defined as an absolute lymphocyte count ≥ 0.2 to < 0.5 x 10^9/L

- Grade 4, defined as an absolute lymphocyte count ≥ 0.0 to < 0.2 x 10^9/L
- Any Grade 3 or 4
- Any Grade 1 to 4

11.3 Vital Signs

Descriptive statistics will be presented for data related to vital signs (systolic blood pressure diastolic blood pressure, pulse rate, respiratory rate, temperature, and weight). Observed values, and change from baseline values will be presented for each post-baseline assessment.

At nominal Day 1 and Week 24 visits, descriptive statistics for the observed and change from pre-dose measurement in vital signs will be presented at pre-dose (observed values only), 1 hour, 2 hours, 3 hours, and 4 hours after treatment initiation. Frequency count and percentage will also be reported for the following cardiac monitoring categories:

- Heart rate (HR) < 40 bpm at any time during the first 4 hours post-dose
- HR < 50 bpm at any time during the first 4 hours post-dose
- HR < 40 bpm at the 4-hour post-dose timepoint
- HR < 50 bpm at the 4-hour post-dose timepoint

A listing of all vital sign assessments will be provided.

11.4 Physical Examination

Clinically significant physical examination abnormalities will be recorded and summarized as medical history or AEs, as applicable.

11.5 Electrocardiogram

Descriptive statistics will be presented for data related to ECGs ([HR, RR, PR, QRS, QT, QTcB, and QTcF intervals). Observed values and change from baseline values will be presented for each post-baseline visit.

At nominal Day 1 and Week 24 visits, descriptive statistics for the observed values and change from pre-dose measurement in ECG parameters will be presented at pre-dose (observed values only) and 4 hours after treatment initiation. Frequency count and percentage will also be reported by treatment group for the following cardiac monitoring categories:

- HR < 40 bpm at the 4-hour post-dose timepoint
- HR < 50 bpm at the 4-hour post-dose timepoint

Additionally, an outlier analysis will be performed on all subjects with QTcF values > 500 msec or change from pre-dose measurement > 60 msec in the absence of pre-dose ECG abnormalities

that preclude accurate surface ECG assessment of ventricular repolarization (eg, bundle branch block); frequency and percentage of those subjects with QTcF values > 500 msec or change from pre-dose to 4-hour post-dose > 60 msec will be summarized for nominal Day 1 and Week 24 visit.

A listing of all ECG assessments will be provided. Overall interpretation with abnormal findings will be presented in the listing as well.

11.6 Pulmonary Function Test

Pulmonary function tests (PFTs) will be performed according to the Schedules of Assessments (refer to Appendix 1 and Appendix 2 in the protocol) and include forced expiratory volume at 1 second (FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25 to 75% (FEF 25-75) measurements. Where locally available, diffusing capacity of the lungs for carbon monoxide (DLCO) measurements will also be performed.

The observed values and change from baseline values in each of the following PFT measurements will be summarized using descriptive statistics by visit:

- FEV_1 (L)
- % Predicted FEV_1
- FVC (L)
- % Predicted FVC
- FEV_1/FVC ratio
- % Predicted FEV_1/FVC ratio
- FEF 25-75 (L/sec)
- % Predicted FEF 25-75
- Total Lung Capacity (TLC; L)
- % Predicted TLC
- DLCO (mL/min/mmHg)
- % Predicted DLCO

Frequency count and percentage of subjects with markedly abnormal values will be reported by visit as well as at any time after baseline for each of the following predefined markedly abnormal criteria separately:

- % Predicted $FEV_1 < 50\%$
- % Predicted FVC < 50%
- % Predicted FEV_1/FVC ratio < 50%

Incidence of subjects with potentially important PFT abnormal measurements will also be identified using the criteria below and summarized similarly:

- Decrease from DB baseline > 20% in FEV_1, i.e., percent change from DB baseline < -20%
- Decrease from DB baseline > 20% in FVC, i.e., percent change from DB baseline < -20%
- Decrease from DB baseline > 20% in DLCO, i.e., percent change from DB baseline < -20%

Shift tables from baseline to each scheduled post-baseline in Investigators' overall interpretation of the PFT (normal, abnormal NCS or abnormal CS) will be provided as well. Only subjects with a baseline result and a result at the specified post-baseline visit will be considered.

All PFT results and overall interpretation of PFTs will be listed and markedly, potentially important abnormal values will be flagged.

11.7 Ophthalmoscopy and Optical Coherence Tomography

A complete ophthalmoscopy and optical coherence tomography (OCT) assessment will be performed according to the Schedule of Assessments (refer to Appendix 1 and Appendix 2 in the protocol).

Frequency count and percentage of subjects in each result category of each ophthalmic exam test/part of the eye will be reported by visit. Observed values and change from baseline values in central foveal thickness (µm) and intraocular pressure (mmHg) will also be summarized using descriptive statistics by visit for each eye separately.

Frequency count and percentage of subjects with markedly increased central foveal thickness (as defined below) will also be reported by visit as well as at any time post-baseline:

- Increase from DB baseline in either eye > 40 µm in central foveal thickness

A listing of ophthalmoscopy (best corrected visual acuity- right eye, left eye, and combined) and all OCT assessments will be provided and markedly increased in central foveal thickness will be flagged. Additionally, separate listings for ophthalmic examination (eye pressure, slit lamp and dilated fundus) will also be provided.

11.8 Safety Analyses during the Open-Label Extension Period

Safety analyses will follow general considerations in previous sections 11.1 to section 11.7 with the following exceptions:

- Summaries will be provided by visit based on the OLE FAS overall, for the three treatment groups in the OLE period (OLE 2mg, OLE 2mg/3mg, OLE 3mg), and the three

randomized treatment groups in the DB Treatment Period (DB 2mg, DB 3mg, DB placebo).

- Change from Baseline will be summarized using change from OLE Baseline and DB Baseline (refer to Section 4.1).

12 CHANGES TO THE ANALYSIS FROM THE PROTOCOL

Table 4: Summary of Changes to the Analysis from the Protocol

Description of the change	Rationale for change
Original text: Baseline for the Open-Label Extension Period is defined as the last measurement prior to the first etrasimod dose started at Week 24. Changed to: The OLE Period Baseline (OLE Baseline) will be defined as the last nonmissing assessment prior to the first etrasimod dose started at Week 24 for the subject who received placebo during the DB Treatment Period. For subjects who were on etrasimod in the DB Treatment Period, the OLE Baseline will be taken from the DB Baseline.	To clarify baseline for the Open-Label Extension Period for safety and efficacy analyses for the OLE Period.
Full Analysis Set (FAS): The FAS includes all randomized subjects in the Randomized Set with a SALT I < 95 at Baseline, irrespective of whether they received any study drug. Changed to The FAS includes all randomized subjects with a SALT I < 95 at Baseline who received at least 1 dose of study drug.	To prevent bias in the main analysis of the proportion-based secondary endpoints using non-responder imputation, the randomized subjects who failure to take at least one dose of trial medication will be excluded from the full analysis sets.
The Per Protocol Set consists of all subjects in the FAS who adhere to the protocol. Changed to: The Per Protocol Set consists of all subjects in the FAS with no major protocol deviations potentially having an impact on the SALT I-related primary and secondary efficacy endpoints.	To clarify that only subjects with major PDs potentially having an impact on the efficacy endpoints will be excluded from the PPS, not all subjects with at least one PD.
Add OLE Full Analysis Set (OLE FAS): The OLE FAS includes all subjects with a SALT I < 95 at Baseline who received at least one dose of study drug in the Open-Label Extension Period. All efficacy analysis in the OLE Period will be performed over OLE FAS.	To be consistent with analysis set with SALT I < 95 for the efficacy analysis in the Double-Blind period. All safety analysis will still be based on OLE Safety Set.

13 REFERENCES

Brand, J. P. L. (1999). Development, Implementation, and Evaluation of Multiple Imputation Strategies for the Statistical Analysis of Incomplete Data Sets. Ph. D. thesis, Erasmus University.

Heitjan, F., and Little, R. J. A. (1991). Multiple Imputation for the Fatal Accident Reporting System. Journal of the Royal Statistical Society, Series C 40:13-29.

Schenker, N., and Taylor, J. M. G. (1996). Partially Parametric Techniques for Multiple Imputation. Computational Statistics and Data Analysis 22:425-446.

Van Buuren, S. (2007). Multiple Imputation of Discrete and Continuous Data by Fully Conditional Specification. Statistical Methods in Medical Research 16:219-242.

14 APPENDICES

Appendix 1 Output Conventions

TLF will be generated using SAS® and will be displayed on letter size paper with landscape orientation, 1-inch margins and 9 pt Courier New font.

The header section will comprise the Sponsor's name, the protocol number, the TLF number, the TLF title, the analysis set, and the page number (Page X of Y). The footer section will include the TLF footnotes, the CRO's name, the reference listing, the delivery description, the data cut-off date (if applicable), the date and time of the execution of the program, and the name of the program.

P-values ≥ 0.0001 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as "<0.0001"; p-values greater than 0.9999 will be reported as ">0.9999".

Mean, median and quantiles will be displayed to one more decimal place than the original value; minimum and maximum will keep the same number of decimal places as the original value; standard deviation, standard error and CI will be displayed to two more decimal places than the original value. If derived parameters are to be summarized, the number of decimals of the derived values is to be chosen on a case-by-case basis, but the rule above applies. The percent change from baseline for each subject will be derived with 1 decimal and treated as original value.

For categorical summary tables, percentages will be reported to one decimal place. Percentages between 0 and 0.1 (both exclusive) will be displayed as "<0.1". The denominator for each percentage will be the number of subjects within the population per treatment group unless otherwise specified.

Listings will be ordered by treatment group in DB Treatment Period/OLE Period, subject number, date and visit (where applicable) and timepoint (where applicable). Imputed dates and imputed missing data will not be presented in the listings.

Dates & Times Format

Date and time (if available) will be presented in the format yyyy-mm-dd/hh:mm.

Presentation of Treatment Groups

When applicable, study treatments will be represented as follows in the different outputs:

Data presentation for DB Treatment Period and Full Study

Study Treatment Full Names	Study Treatment Output Names
Etrasimod 2 mg	Etrasimod 2 mg
Etrasimod 3 mg	Etrasimod 3 mg
Placebo	Placebo

Data presentation for OLE Period

DB Treatment Group			OLE Treatment Group			
Etrasimod 2 mg	Etrasimod 3 mg	Placebo	Etrasimod 2 mg^	Etrasimod 2 mg-3 mg*	Etrasimod 3 mg#	Total

^ Cohort 1 subjects who completed or discontinued from OLE before protocol amendment 2.0/2.1 implementation as well as Cohort 1 and 2 subjects who discontinued from OLE before transitioning to 3 mg .

* Cohort 1 subjects who took 2 mg and transitioned to 3 mg in OLE after treatment initiation.

Cohort 1 subjects who took 2 mg for a week and transitioned to 3 mg in OLE after treatment initiation and Cohort 2 subjects.

Appendix 2 Algorithm for Imputation of Start/End Date of Adverse Events and Prior/Concomitant Medications

Event Start Date Imputation

- Imputation of event end date should be done before imputation of event start date.
- Completely missing: Impute to the first study treatment date.
- Missing day and month: Impute to January 1st, unless year is the same as year of first study treatment dose then impute to the first study treatment date.
- Missing day: Impute to the 1st of the month, unless month and year are the same as month and year of first study treatment dose then impute to the first study treatment date.
- If imputed event start date is after event end date (imputed or not), set the event start date to the imputed event end date.

Event End Date Imputation

- Completely Missing (not flag "ongoing"): Impute to the last contact date.
- Missing day and month: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date.
- Missing day: Impute to the last day of the month, unless year and month are the same as year and month of last contact date then impute to the last contact date.

Appendix 3 List of Tables, Listings, and Figures for the Primary and Final Analyses

Primary Analysis – Batch 1

Table Number	Table Title
Table 14.1.1.1.2	Subject Disposition - Double-Blind Treatment Period (Randomized Set)
Table 14.1.1.1.3.1	Subject Disposition - Double-Blind Treatment Period (Full Analysis Set)
Table 14.1.1.1.3.2.1	Subgroup Analysis: Subject Disposition - Double-Blind Treatment Period - Cohort (Full Analysis Set)
Table 14.1.1.1.3.2.2	Subgroup Analysis: Subject Disposition - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >= 50) (Full Analysis Set)
Table 14.1.1.1.3.2.3	Subgroup Analysis: Subject Disposition - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >=50 to < 95, or >=95) (Randomized Set)
Table 14.1.1.1.3.2.4	Subgroup Analysis: Subject Disposition - Double-Blind Treatment Period - Current Disease Duration (Full Analysis Set)
Table 14.1.2.2.1	Demographic and Baseline Characteristics - Double-Blind Treatment Period (Full Analysis Set)
Table 14.1.2.2.2.1	Subgroup Analysis: Demographic and Baseline Characteristics - Double-Blind Treatment Period - Cohort (Full Analysis Set)
Table 14.1.2.2.2.2	Subgroup Analysis: Demographic and Baseline Characteristics - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >= 50) (Full Analysis Set)
Table 14.1.2.2.2.3	Subgroup Analysis: Demographic and Baseline Characteristics - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >=50 to < 95, or >=95) (Randomized Set)
Table 14.1.2.2.2.4	Subgroup Analysis: Demographic and Baseline Characteristics - Double-Blind Treatment Period - Current Disease Duration (Full Analysis Set)
Table 14.2.1.1	Primary Analysis: Summary and Statistical Analysis of SALT I Score - Observed Cases - Double-Blind Treatment Period (Full Analysis Set)
Table 14.2.1.2.1	Sensitivity Analysis #1: Summary and Statistical Analysis of SALT I Score – Multiple Imputation - Double-Blind Treatment Period (Full Analysis Set)
Table 14.2.1.2.2	Sensitivity Analysis #2: Summary and Statistical Analysis of SALT I Score – Observed Cases - Double-Blind Treatment Period (modified Full Analysis Set)
Table 14.2.1.2.3	Sensitivity Analysis #3: Summary and Statistical Analysis of SALT I Score – Observed Cases - Double-Blind Treatment Period (Per Protocol Set)

Table Number	Table Title
Table 14.2.1.2.4	Sensitivity Analysis #4: Summary and Statistical Analysis of SALT I Score – Observed Cases - Double-Blind Treatment Period (Randomized Set)
Table 14.2.1.2.5	Sensitivity Analysis #5: Summary and Statistical Analysis of SALT I Score – Observed Cases, Adjusting for SALT I Stratification Variable and Cohort - Double-Blind Treatment Period (Full Analysis Set)
Table 14.2.1.2.6	Sensitivity Analysis #6: Summary and Statistical Analysis of SALT I Score – Observed Cases, Including Cohort 2 Only and Adjusting for SALT I Stratification Variable - Double-Blind Treatment Period (Full Analysis Set)
Table 14.2.1.2.7	Sensitivity Analysis #7: Summary and Statistical Analysis of SALT I Score – Observed Cases, Excluding Etrasimod 3 mg Treatment Group and Adjusting for Cohort - Double-Blind Treatment Period (Full Analysis Set)
Table 14.2.1.3.1	Subgroup Analysis: Summary of Change and Percent Change from Baseline in SALT I Score - Observed Cases - Double-Blind Treatment Period - Cohort (Full Analysis Set)
Table 14.2.1.3.6	Subgroup Analysis: Summary of Change and Percent Change from Baseline in SALT I Score - Observed Cases - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >= 50) (Full Analysis Set)
Table 14.2.1.3.7	Subgroup Analysis: Summary of Change and Percent Change from Baseline in SALT I Score - Observed Cases - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >=50 to < 95, or >=95) (Randomized Set)
Table 14.2.1.3.9	Subgroup Analysis: Summary of Change and Percent Change from Baseline in SALT I Score - Observed Cases - Double-Blind Treatment Period - Current Disease Duration (Full Analysis Set)
Table 14.2.2.1	Summary and Statistical Analysis of Proportion of Subjects Achieving Improvement in SALT I - Non-responder Imputation - Double-Blind Treatment Period (Full Analysis Set)
Table 14.2.2.3.1	Subgroup Analysis: Summary of Proportion of Subjects Achieving Improvement in SALT I - Non-Responder Imputation - Double-Blind Treatment Period - Cohort (Full Analysis Set)
Table 14.2.2.3.6	Subgroup Analysis: Summary of Proportion of Subjects Achieving Improvement in SALT I - Non-Responder Imputation - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >= 50) (Full Analysis Set)
Table 14.2.2.3.7	Subgroup Analysis: Summary of Proportion of Subjects Achieving Improvement in SALT I - Non-Responder Imputation - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >=50 to < 95, or >=95) (Randomized Set)
Table 14.2.2.3.9	Subgroup Analysis: Summary of Proportion of Subjects Achieving Improvement in SALT I - Non-Responder Imputation - Double-Blind Treatment Period - Current Disease Duration (Full Analysis Set)
Table 14.2.5.1.1	Summary and Statistical Analysis of Percent Change from Baseline in Peripheral Lymphocyte Counts - Observed Cases - Double-Blind Treatment Period (Full Analysis Set)

Table Number	Table Title
Table 14.2.5.1.2.1	Subgroup Analysis: Summary of Percent Change from Baseline in Peripheral Lymphocyte Counts - Observed Cases - Double-Blind Treatment Period - Cohort (Full Analysis Set)
Table 14.2.5.1.2.2	Subgroup Analysis: Summary of Percent Change from Baseline in Peripheral Lymphocyte Counts - Observed Cases - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >= 50) (Full Analysis Set)
Table 14.2.5.1.2.3	Subgroup Analysis: Summary of Percent Change from Baseline in Peripheral Lymphocyte Counts - Observed Cases - Double-Blind Treatment Period - Baseline SALT I Score (< 50, >=50 to < 95, or >=95) (Randomized Set)
Table 14.2.5.1.2.4	Subgroup Analysis: Summary Analysis of Percent Change from Baseline in Peripheral Lymphocyte Counts - Observed Cases - Double-Blind Treatment Period - Current Disease Duration (Full Analysis Set)
Table 14.2.7	Summary and Statistical Analysis of Proportion of Subjects Achieving a SALT I Score ≤ 10 and ≤ 20 – Observed Cases - Double-Blind Treatment Period (Full Analysis Set)
Table 14.2.8	Summary of Change and Percent Change from Baseline in SALT I Score at Week 36 - Observed Cases - Open-Label Extension Period (Open-Label Extension Full Analysis Set)
Table 14.2.9	Summary of Proportion of Subjects Achieving Improvement in SALT I at Week 36 - Observed Cases - Open-Label Extension Period (Open-Label Extension Full Analysis Set)
Table 14.2.13	Summary of Proportion of Subjects Achieving a SALT I Score ≤ 10 and ≤ 20 at Week 36 – Observed Cases - Open-Label Extension Period (Open-Label Extension Full Analysis Set)
Table 14.3.1.1.1	Overall Summary of Adverse Events - Double-Blind Treatment Period (Safety Set)
Table 14.3.1.2.1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Double-Blind Treatment Period (Safety Set)
Table 14.3.1.5.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Reported CTCAE Severity - Double-Blind Treatment Period (Safety Set)
Table 14.3.1.6.1	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Double-Blind Treatment Period (Safety Set)
Table 14.3.1.7.1	Summary of Treatment Emergent Adverse Events of Special Interest by Category and Preferred Term - Double-Blind Treatment Period (Safety Set)
Table 14.3.2.4	Listing of Treatment Emergent Adverse Events Leading to Study Discontinuation (Safety Set)
Table 14.3.4.12.1	Incidence of Hepatic Enzyme Elevations by Visit - Double-Blind Treatment Period (Safety Set)
Table 14.3.4.13.1	Incidence of Absolute Lymphocyte Count Decrease - Double-Blind Treatment Period (Safety Set)
Table 14.3.5.2	Summary of Vital Signs Cardiac Monitoring I - Full Study (Safety Set)

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Primary Analysis – Batch 2

Table Number	Table Title
Table 14.1.1.0	Study Information
Table 14.1.1.1.1	Subject Disposition - Screening (All Subjects)
Table 14.1.1.2.1	Analysis Sets – Double-Blind Treatment Period (Randomized Set)
Table 14.1.2.1	Demographic and Baseline Characteristics - Double-Blind Treatment Period (Randomized Set)
Table 14.1.2.3	Demographic and Baseline Characteristics - Double-Blind Treatment Period (Safety Set)
Table 14.1.3.1.1	Important Protocol Deviations - Double-Blind Treatment Period (Randomized Set)
Table 14.1.3.2.1.1	Major Protocol Deviations - Double-Blind Treatment Period (Randomized Set)
Table 14.1.3.2.1.2	Major Protocol Deviations Leading to the Exclusion from the Per Protocol Set - Double-Blind Treatment Period (Randomized Set)
Table 14.1.3.3.1	Protocol Deviations Associated to COVID-19 - Double-Blind Treatment Period (Randomized Set)
Table 14.1.4.1	Surgical and Medical History (Safety Set)
Table 14.1.4.2.1	Alopecia Areata Disease History (Safety Set)
Table 14.1.4.2.2	Alopecia Areata Disease History (Full Analysis Set)
Table 14.1.5	Prior Medications - Double-Blind Treatment Period (Safety Set)
Table 14.1.6.1	Concomitant Medications - Double-Blind Treatment Period (Safety Set)
Table 14.1.7.1	Study Treatment Exposure and Compliance - Double-Blind Treatment Period (Safety Set)
Table 14.2.1.3.2	Subgroup Analysis: Summary of SALT I Score - Observed Cases - Double-Blind Treatment Period - Sex (Full Analysis Set)
Table 14.2.1.3.3	Subgroup Analysis: Summary of SALT I Score - Observed Cases - Double-Blind Treatment Period - Race (Full Analysis Set)
Table 14.2.1.3.4	Subgroup Analysis: Summary of SALT I Score - Observed Cases - Double-Blind Treatment Period - Age (Full Analysis Set)
Table 14.2.1.3.5	Subgroup Analysis: Summary of SALT I Score - Observed Cases - Double-Blind Treatment Period - Baseline SALT I Score (Median) (Full Analysis Set)
Table 14.2.1.3.8	Subgroup Analysis: Summary of SALT I Score - Observed Cases - Double-Blind Treatment Period - Duration of AA Disease from Initial Onset (Full Analysis Set)
Table 14.2.1.3.10	Subgroup Analysis: Summary of SALT I Score - Observed Cases - Double-Blind Treatment Period - Baseline AASIS (Full Analysis Set)

Table Number	Table Title
Table 14.2.1.3.11	Subgroup Analysis: Summary of SALT I Score - Observed Cases - Double-Blind Treatment Period - Baseline AA-QLI (Full Analysis Set)
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Table Number	Table Title
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Table Number	Table Title
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Table 14.3.1.4.2	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Reported Relationship - Open-Label Extension Period (Open-Label Extension Safety Set)
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Table Number	Table Title
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Listing Number	Listing Title
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Listing 16.2.12.3.1	Ophthalmic Exam – Eye Pressure Exam (mmHg) (Safety Set)
Listing 16.2.12.3.2	Ophthalmic Exam – Slit Lamp Exam (Safety Set)
Listing 16.2.12.3.3	Ophthalmic Exam – Dilated Fundus Exam (Safety Set)

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