CLINICAL STUDY PROTOCOL

Protocol 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:	APD334-205
Version:	Amendment 2.0, dated 25 May 2021
Compound name or number:	Etrasimod (APD334)
Study phase:	Phase 2
Indication:	Alopecia areata
Sponsor name:	Arena Pharmaceuticals, Inc.
Legal registered address:	6154 Nancy Ridge Drive San Diego, California 92121 USA
Sponsor's Responsible Medical Officer:	PPD , MD, MBA PPD Clinical Development, and Chief Medical Officer
Clinical lead:	PPD PPD Clinical Science Arena Pharmaceuticals, Inc. PPD
SAE reporting:	PPD
Sponsor approval:	This protocol was approved by the Sponsor's Responsible Medical Officer or delegate. The electronic signature manifest is appended.

PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 2.1	Regional	25 May 2021
Amendment 2.0	Global	25 May 2021
Amendment 1.1	Regional	09 December 2020
Amendment 1.0	Global	09 December 2020
Amendment 0.2	Regional	15 May 2020
Amendment 0.1	Global	15 May 2020
Original Protocol	Not applicable	14 January 2020

PROTOCOL SYNOPSIS

Sponsor: Arena Pharmaceuticals, Inc.

Name of Investigational Study Drug: APD334 (etrasimod)

Protocol 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: APD334-205

Phase: 2

Country(ies)/Region(s) (planned): United States and Canada

Objectives:

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 Treatment Period.

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.

Study Design:

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 Double-Blind Treatment Period, a 28-week Open-Label Extension Period, and a 4-week Safety Follow-Up Period for a maximum total study duration of 60 weeks.

This study will include approximately 78 subjects with moderate-to-severe AA with current episode of hair loss for ≥ 6 months but < 5 years (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:

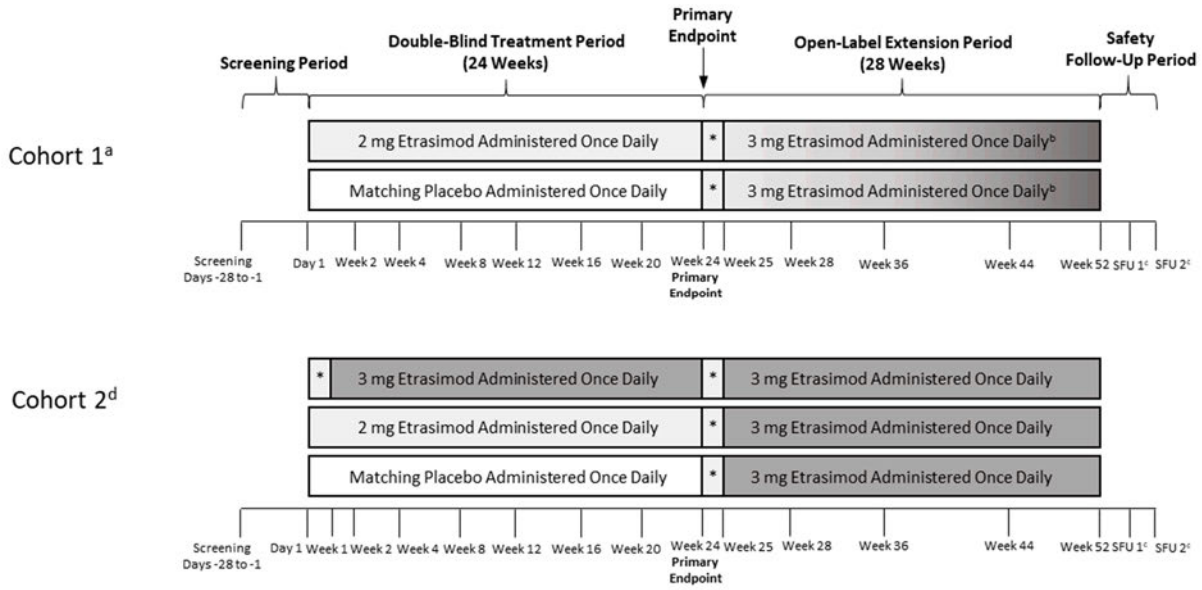
Cohort 1: All subjects (approximately 36 subjects) enrolled under the original protocol, and Amendments 0.1, 0.2, 1.0, and 1.1.

Subjects were randomized in a 2:1 ratio to receive etrasimod 2 mg or placebo orally, once daily. Randomization was stratified by Severity of Alopecia Tool I (SALT I) score (< 100, 100) at Day 1/Baseline. Subjects will complete the Double-Blind Treatment Period per their original randomization assignment. Subjects who have entered the Open-Label Extension 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 Open-Label Extension 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 Open-Label Extension Period.

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 Double-Blind Treatment Period. Randomization will be stratified by SALT I score (< 50, ≥ 50) at Day 1/Baseline. During the Double-Blind 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 Double-Blind Treatment Period. During the Open-Label Extension 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 Open-Label Extension Period.



[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 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 for information on re-initiation of treatment after dose interruptions
ET, early termination; N, number (of subjects); SFU, Safety Follow-Up.

Study visits will take place for Screening; Day 1/Baseline; Weeks 1, 2, 4, 8, 12, 16, 20, 24, 25, 28, 36, 44, and 52, as applicable (Week 1 visit is applicable to Cohort 2 only); and 2 weeks and 4 weeks after the last dose of study drug (for Safety Follow-Up).

Number of Subjects (Planned):

A total of approximately 78 subjects are planned to be enrolled in this study.

It is estimated that approximately 36 subjects will be enrolled in Cohort 1, including 24 subjects in the etrasimod 2 mg group and 12 subjects in the placebo group.

Approximately 42 subjects are planned to be enrolled in Cohort 2, including 24 subjects in the etrasimod 3 mg group, 6 subjects in the etrasimod 2 mg group, and 12 subjects in the placebo group.

Eligibility Criteria:

Inclusion Criteria:

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

Key inclusion criteria

1. Men or women between ≥ 18 and ≤ 70 years of age at the time of informed consent
2. Moderate-to-severe AA as assessed by a SALT I score ≥ 25 and < 95 at Screening and Day 1/Baseline. Severity will also be confirmed by central review of photographs taken during Screening
3. Current episode of hair loss for ≥ 6 months but < 5 years
4. Stable disease condition (no significant growth of hair) in the last 6 months as assessed by the Investigator
5. Willing to keep the same hair style and color (eg, hair products, process, and timing for hair appointments) for the duration of the study

General inclusion criteria

6. Willing and able to comply with all clinic visits and study-related procedures and understand and complete study-related questionnaires
7. Provide signed informed consent prior to conducting any procedures
8. Females must meet either a or b of the following criteria and males must meet criterion c to qualify for the study:
   a. Female who is not of childbearing potential by one of the following:
      - Postmenopausal, defined as no menses for 12 months without an alternative medical cause
      - Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
   b. Nonpregnant female of childbearing potential and agrees to using a highly effective contraception method during treatment and for 30 days following treatment that can achieve a failure rate of less than 1% per year when used consistently and correctly. The following are considered highly effective birth control methods:
      - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
      - Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
      - Intrauterine device (IUD)
      - Intrauterine hormone-releasing system
      - Bilateral tubal occlusion
      - Vasectomized partner, provided that partner is the sole sexual partner of the female of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success
      - Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study drug). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study

and the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods) is not acceptable.

c. Male with a pregnant or nonpregnant female of childbearing potential partner and agrees to using condoms during treatment and for 30 days following treatment

Exclusion Criteria:

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

Key exclusionary criteria

1. History of male or female pattern hair loss > Hamilton stage III or > Ludwig stage II
2. Other types of alopecia (eg, cicatricial/scarring alopecia [including central centrifugal cicatricial alopecia], traction alopecia, or telogen effluvium) or other diseases that could cause hair loss
3. Active scalp inflammation, scalp infection, scalp psoriasis, or any other scalp condition that may interfere with the SALT I assessment
4. Previous use of a Janus kinase (JAK) inhibitor (oral or topical), including participation in clinical studies of JAK inhibitors

Exclusionary criteria related to medications, therapies, or skin disease

5. Phototherapy on scalp within 4 weeks of Screening
6. Treatment with the following medications within 12 weeks of Screening:
    a. Intralesional or systemic corticosteroids
    b. Systemic glucocorticoids (inhaled or intranasal delivery are not exclusionary)
    c. Immunoglobulin or blood products
7. Use of any biological agents (eg, dupilumab, adalimumab, ustekinumab, secukinumab) regardless of indication or systemic immunosuppressive/immunomodulating drugs (eg, cyclosporine, azathioprine, methotrexate) within 5 half-lives (if known) or 12 weeks before Screening, whichever is longer
8. Treatment with the following medications within 4 weeks of Screening:
    a. Topical corticosteroids
    b. Topical immunotherapy (eg, diphenylcyclopropenone, squaric acid)
    c. Topical calcineurin inhibitors
    d. Topical or oral minoxidil
9. Use of sphingosine 1-phosphate receptor modulators (eg, fingolimod, siponimod, ozanimod, ponesimod), α4β1-integrin receptor antagonists (eg, natalizumab), and lymphocyte-depleting therapies (eg, rituximab, cyclophosphamide, bone marrow transplantation, total body irradiation) within 6 months before Screening or until lymphocyte count returns to normal, whichever is longer
10. History of or planned hair transplant procedure during the study
11. Planned microblading or micropigmentation of the scalp during the study
12. Received any investigational agent, including non-biologic agents and topical agents, within 5 half-lives (if known) or 4 weeks (whichever is longer) before Screening

13. Use of moderate/strong inducers or inhibitors that inhibit or induce at least two of the following: Cytochrome P450 (CYP) 2C8, CYP2C9, and CYP3A4 (eg, fluconazole, enzalutamide; Table 4) within 4 weeks before Screening.

Exclusionary criteria related to medical history

14. Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis [TB] or atypical mycobacterial disease) or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 4 weeks before Screening or during Screening, or oral antibiotics within 2 weeks before Screening or during Screening. Superficial fungal infection of the nail bed is allowed

15. Have any of the following conditions or risk factors:

    a. Primary or secondary immunodeficiency syndromes (eg, hereditary immunodeficiency syndrome, acquired immunodeficiency syndrome, drug-induced immune deficiency)
    b. History of organ transplant (except corneal transplant)
    c. History of an opportunistic infection (eg, *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis, progressive multifocal leukoencephalopathy [PML])
    d. History of disseminated herpes simplex or disseminated herpes zoster, or any episode of herpes zoster
    e. Test positive for human immunodeficiency virus, hepatitis B virus (positive for hepatitis B surface antigen [HBsAg]), or active hepatitis C virus (HCV) (positive HCV antibody with detectable viral load) at Screening
    f. History of active or latent TB (refer to Appendix 3 for details of TB screening and interpretation of test results). The following is the EXCEPTION to the exclusion criterion:

        - Subjects with treated latent TB or latent TB diagnosed at Screening who have received ≥ 2 weeks of TB prophylaxis treatment prior to randomization, ruled out for active TB, and have not had recent close contact with a person with active TB. It is the responsibility of the Investigator to verify the adequacy of TB prophylaxis treatment and provide appropriate documentation. Note: The exception to the exclusion criterion outlined above does NOT apply to subjects residing in countries identified by the WHO as a high multi-drug resistance (MDR) TB burden country due to the risk of latent infection with MDR TB.

16. Received any live or live-attenuated vaccines within 4 weeks before Screening (Section 6.9 offers additional details regarding vaccines)

17. History of malignancy of any organ system (other than localized squamous cell or basal cell carcinoma of the skin that have been excised or resolved), treated or untreated, within the past 5 years

18. Have any of the following conditions or receiving treatments that may affect cardiovascular function:

    a. Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure within 8 weeks before Screening
    b. History or presence of second-degree or third-degree atrioventricular block, sick sinus syndrome, or periods of asystole for > 3 seconds without a functional pacemaker
    c. Recurrent symptomatic bradycardia or recurrent cardiogenic syncope
    d. Screening **OR** Baseline (Day 1) pre-randomization vital signs (taken in the sitting position) with a heart rate (HR) < 50 beats per minute (bpm), systolic blood pressure (BP)

< 90 mm Hg, OR diastolic BP < 55 mm Hg. Vital signs may be repeated up to 3 times during a visit to confirm abnormal readings

e. Screening **OR** Baseline (Day 1) pre-randomization electrocardiogram (ECG) with PR interval ≥ 200 ms or QT interval corrected using Fridericia's formula (QTcF) ≥ 450 ms in males or ≥ 470 ms in females
f. Start, stop, or change dosage of Class I-IV anti-arrhythmic drugs within 1 week of Screening

19. A history of or active diabetic retinopathy, uveitis, retinitis pigmentosum, or macular edema. Any recent intraocular surgery within 1 year of Screening
20. Active severe pulmonary disease (eg, chronic obstructive pulmonary disease or pulmonary fibrosis) or chronic pulmonary disease requiring intravenous corticosteroid treatment or hospitalization within 12 months before Screening or during the Screening Period
21. Have forced expiratory volume at 1 second (FEV_1) or forced vital capacity (FVC) < 70% of predicted values at Screening
22. Have any uncontrolled systemic disease(s) (eg, thyroid disorder, hypertension, diabetes). If the condition is considered controlled and the subject is on any medications (eg, thyroid medication or hormonal therapy) for treatment of diseases, the subject may be allowed to participate but must have been on a stable dose for at least 6 months prior to Screening and remain on a stable dose throughout the study.

Exclusionary criteria related to test or laboratory results (performed by central laboratory)
Note: A confirmed result means there have been 2 consecutive assessments showing a consistent abnormal, clinically relevant result.

23. Confirmed total white blood cell (WBC) count ≤ 3.5×10^9 cells/L OR absolute neutrophil count (ANC) ≤ 1.5×10^9 cells/L OR absolute lymphocyte count (ALC) < 1.0×10^9 cells/L at Screening
24. Confirmed estimated glomerular filtration rate < 30 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening
25. Confirmed aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN) and total bilirubin > 1.5 × ULN (unless consistent with a history of Gilbert's Syndrome) at Screening

General exclusionary criteria

26. Lactating female who is breastfeeding
27. Any acute illness or medical condition including psychiatric disease, cognitive impairment, and alcohol/drug abuse/dependence, or signs/symptoms suspicious for a serious disease that, in the Investigator's opinion, could put the subject at increased risk for safety event(s), could interfere with participation in the study according to the study protocol, or with the ability of the subject to cooperate and comply with the study procedures

Note: If a subject fails ≥ 1 Screening laboratory (or other) assessment criteria, the assessment(s) may be repeated once at the discretion of the Investigator, and the subject may be randomized if criteria are then met, provided the assessments are completed within the Screening Period. Any rescreening laboratory assessments beyond 1 time will need to be discussed with the Medical Monitor before proceeding.

Exclusion Criteria (for the Open-Label Extension Period):

Subjects will be excluded from the Open-Label Extension Period if they meet the following exclusion criterion at the Week 24 visit:

1. Week 24 predose vital signs (taken in the sitting position) with an HR < 50 bpm, systolic BP < 90 mm Hg, OR diastolic BP < 55 mm Hg. Vital signs may be repeated up to 3 times during the visit to confirm abnormal readings.
2. Confirmed predose Week 24 ECG with PR interval ≥ 200 ms or QT interval corrected using Fridericia's formula (QTcF) ≥ 450 ms in males or ≥ 470 ms in females. Presence on Week 24 ECG of second-degree or third-degree atrioventricular block, sick sinus syndrome, or periods of asystole for > 3 seconds without a functional pacemaker.
3. The Investigator considers the subject to be unsuitable for any reason to participate in the Open-Label Extension study.

Note: If a subject fails to enter the Open-Label Extension Period due to Exclusion Criterion 1 or 2, the assessment may be repeated once at the discretion of the Investigator, and the subject may be dosed if the criterion is then met, provided the assessment is completed within the Week 24 visit window. Any repeated vital sign assessments beyond 1 time will need to be discussed with the Medical Monitor before proceeding.

Test Product, Dose, and Mode of Administration:

Etrasimod 2 mg in the Double-Blind Treatment Period of Cohort 1 will be administered daily as a 2 mg tablet. Etrasimod 2 mg in the Double-Blind Treatment Period of Cohort 2 will be administered daily as a 2 mg tablet and a placebo tablet. Etrasimod 2 mg may be administered in the Open-Label Extension Period of Cohort 1 daily as a 2 mg tablet.

Etrasimod 3 mg (in either the Double-Blind Treatment Period or the Open-Label Extension Period) will be administered daily as a 2 mg etrasimod tablet and a 1 mg etrasimod tablet.

Etrasimod tablets will be taken orally once daily during the Double-Blind Treatment Period and/or Open-Label Extension Period.

Duration of Study:

The overall duration of the study will be up to 60 weeks, including:

- Up to 4-week Screening Period
- 24-week Double-Blind Treatment Period
- 28-week Open-Label Extension Period
- 4-week Safety Follow-Up Period after the last dose of treatment

Reference Therapy, Dose, and Mode of Administration:

Subjects assigned to the placebo group in the Double-Blind Treatment Period of Cohort 1 will be administered 1 matching placebo tablet orally once daily. Subjects assigned to the placebo group in the Double-Blind Treatment Period of Cohort 2 will be administered 2 matching placebo tablets orally once daily. There is no reference therapy (no placebo) treatment arm during the Open-Label Extension Period.

Safety Assessments:

Safety will be assessed through the incidence of adverse events (AEs), clinical laboratory findings, physical examinations, ECGs (measured 4 hours following the first dose in the Double-Blind Treatment Period and the first dose in the Open-Label Extension Period), Holter monitoring (measured for 8 hours following dosing at Day 1 and Week 1 visits in the Double-Blind Treatment Period for Cohort 2, following dosing at Week 24 and Week 25 visits in the Open-Label Extension Period for Cohort 2, at the Week 24 visit and following transition from 2 mg to 3 mg in the Open-Label Extension Period for subjects in Cohort 1, and when a subject re-initiates study drug after a dosing interruption of a specified period [Section 6.3.2]), vital signs (measured hourly for at least 4 hours following the first dose in the Double-Blind Treatment Period and the first dose in the Open-Label Extension Period), pulmonary function tests (FEV_1, FVC, and forced expiratory flow at 25 to 75% measurements), diffusing capacity of the lungs for carbon monoxide (where locally available), ophthalmoscopy, and optical coherence tomography.

Efficacy Assessments:

Efficacy assessments include percent change, change, and categorical percent change in hair loss (SALT I score); the following patient-reported outcomes (PROs): AA Symptom Impact Scale (AASIS) and AA Quality of Life Index (AA-QLI); serum biomarkers; and photographs 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.

The definitions used to assess the primary, secondary, and exploratory efficacy outcomes are described below.

Primary Efficacy Endpoint

- Percent change from Baseline in SALT I at Week 24

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

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 AASIS at Week 24
- Change from Baseline in 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

Efficacy Assessments During the Open-Label Extension Period

These efficacy outcomes will be measured at scheduled visits up to 52 weeks: SALT I; peripheral lymphocyte counts; AASIS; AA-QLI; serum biomarkers; photographs 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.

Pharmacokinetic Assessments:

Blood samples (4 mL) for plasma analysis of etrasimod will be collected at the following timepoints from all subjects who received ≥ 1 dose of study drug (etrasimod or placebo):

- Predose (within 60 minutes prior to dosing) and at 4 hours (± 15 minutes) postdose (after ECG) on Day 1 and Week 24
- Predose (trough; within 60 minutes prior to dosing) at Weeks 1 (Cohort 2 only), 2, 4, 8, 12, 16, 20, 25, 28, 36, and 44
- Anytime at Week 52 or at the ET visit, and the follow-up visits, as applicable
- If possible, at the time of any serious AE (SAE), AE leading to study drug discontinuation, or AE of special interest (AESI). The time of the last study drug dose should be documented

Plasma pharmacokinetic (PK) samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of etrasimod with plasma constituents.

Not all collected PK samples from placebo-treated subjects during the Double-Blind Treatment Period will be assayed.

Statistical Methods

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%.

Safety Analysis:

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

Efficacy Analysis:

The primary and secondary endpoints will be analyzed using the Full Analysis Set (FAS). The exploratory endpoints will be analyzed using the FAS and the Randomized Set. Other important statistical considerations, such as missing data imputation strategies, sensitivity analyses, and subgroup analyses will be described in the Statistical Analysis Plan.

The primary endpoint of percent change from Baseline to Week 24 in SALT I will be analyzed with a mixed-effects model repeated measures (MMRM) model. The MMRM model will include treatment group, visit, and interaction of treatment-by-visit as factors, and disease duration and Baseline SALT I score as covariates. An unstructured covariance matrix will be specified for the MMRM model. Least squares (LS) means at each visit and LS mean differences between treatment groups (each of the active arms versus placebo only) with p-values and corresponding 95% confidence intervals (CIs) will be reported. This method will also be applied to other score-based or continuous measures.

Proportion-based secondary endpoints at Week 24 will be analyzed using the Cochran-Mantel-Haenszel test method adjusted for the randomization stratification factor SALT I ($< 50, \geq 50$) at Baseline. Subjects with missing data for any reason will be considered as 'non-responder' or 'failure' for the endpoint. The number and percentage of subjects achieving the goal and the difference in proportion between treatment groups achieving the goal, along with p-values and the 95% CIs, will be reported.

Pharmacokinetic Analysis:

A descriptive summary of observed plasma concentrations will be displayed by time.

Interim Analysis:

No formal interim analysis of efficacy is planned. Periodic blinded assessments of the assumption regarding the SD of the percent change in SALT I from Baseline to Week 24 will be conducted. The planned sample size will not be reduced as a result of the SD assessments.

Statistical Methods for the Open-Label Extension Period:

No formal statistical testing will be performed. Only descriptive statistics will be provided.

TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AA	alopecia areata
AAD	American Academy of Dermatology
AA-QLI	Alopecia Areata Quality of Life Index
AASIS	Alopecia Areata Symptom Impact Scale
AD	atopic dermatitis
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATS	American Thoracic Society
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
bpm	beats per minute
CD	Crohn's disease
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	confidence interval
CMP	Clinical Monitoring Plan
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLCO	diffusing capacity of the lungs for carbon monoxide
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FA	fluorescein angiography
FAS	Full Analysis Set

Abbreviation	Explanation
FDA	Food and Drug Administration
FEF 25-75	forced expiratory flow at 25% to 75%
FEV_1	forced expiratory volume at 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGRA	interferon-gamma release assay
CCI	[redacted]
[redacted]	[redacted]
IMM	Independent Medical Monitor
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IWRS	Interactive Web Response System
JAK	Janus kinase
LS	least squares
MDR	multi-drug resistance
mFAS	Modified Full Analysis Set
MMRM	mixed-effects model repeated measures
OCT	optical coherence tomography
PFT	pulmonary function test
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula

Abbreviation	Explanation
RSI	Reference Safety Information
S1P	sphingosine 1-phosphate
$S1P_{1,4,5}$	sphingosine 1-phosphate receptors 1, 4, and 5
SAE	serious adverse event
SALT I	Severity of Alopecia Tool I
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SFU	Safety Follow-Up
SOP	standard operating procedure
TB	tuberculosis
TEAE	treatment-emergent adverse event
TMF	trial master file
TST	tuberculin skin test
UC	ulcerative colitis
UDP	uridine diphosphate
UGT	UDP glucuronosyltransferase
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Alopecia Areata

Alopecia areata (AA) is a T-cell-mediated autoimmune skin disorder with unmet medical need that causes non-scarring patchy hair loss, most often on the scalp. The disease may be limited to 1 or more discrete, round or oval patches of hair loss the size of a coin on the scalp, or it may progress to full hair loss of the scalp (alopecia totalis) or the entire body (alopecia universalis) (Hanlon 2019). The course of disease is unpredictable, with spontaneous regrowth of hair occurring in 80% of patients within the first year, and sudden relapse at any given time (Islam 2015, MacLean 2013). Patients with extensive disease (at least 50% total scalp hair loss) rarely have spontaneous hair regrowth (Renert-Yuval 2017). Patients with persistent moderate-to-severe AA also often suffer tremendous emotional and psychosocial distress and reduced quality of life as a result of their hair loss (de Hollanda 2014). Thus, psychosocial support and therapy is an important part of disease management, as this often-disfiguring disease can be psychosocially burdensome (Villasante Fricke 2015).

The estimated lifetime risk of AA is 1.7% among the general population (Safavi 1995) and represents the second most common form of human hair loss, second only to androgenetic alopecia (Villasante Fricke 2015). AA affects both sexes across all ethnicities (Hordinsky 2014) with most patients experiencing their first patch of hair loss before reaching adulthood (Alkhalifah 2010a).

The pathogenesis of AA is still not fully known, but a combination of factors such as autoimmunity, atopic state, genetic background, non-specific immune reactions, and emotional stress are thought to play a role (Sardesai 2012). The hair cycle consists of 3 phases: the growth phase (anagen), the resting phase (catagen), and the shedding phase (telogen). Ninety percent of hairs are in the anagen phase (Al Aboud 2019), which can last years (Plowman 2018). In AA, $CD4^+$ and $CD8^+$ T cells damage the anagen hair follicle, leading to loss of the growing hair shaft (Villasante Fricke 2015, Xing 2014). $CD8^+$ T cells are present in significantly lower quantities than $CD4^+$ cells (Gilhar 2012), yet a subset ($CD8^+$ $NKG2D^+$ T cells) are both necessary and sufficient to induce AA in rodents (Xing 2014). A predominant Th1 cytokine profile has been discovered at the site of AA lesions (Islam 2015, Petukhova 2010). Additionally, a genome-wide association study demonstrated a genetic predisposition to AA (Petukhova 2010).

To date, no cure has been found, and no therapy has been able to prevent disease relapse (Villasante Fricke 2015). There are also currently no approved drugs for the treatment of AA and success rates of available treatment options for hair loss in this population vary depending on the extent and duration of disease (Alkhalifah 2010b). Such treatments and their limitations include (Mikhaylov 2019):

- Topical therapies such as corticosteroids and calcineurin inhibitors that have low efficacy due to limited penetration
- Intralesional steroid injections that cannot be used for large areas
- Systemic treatments (ie, cyclosporine and oral corticosteroids) that result in general immunosuppression

Thus, there is a large unmet medical need for safe and more targeted treatments for patients with AA. To encourage clinical investigations of potential treatments for AA, the National Alopecia Areata Foundation developed a uniform protocol to provide a framework of suggested inclusions/exclusions, safety, and outcome assessment measures (Solomon 2015); the uniform protocol served as a resource for the development of Study APD334-205.

1.1.1. Etrasimod

Etrasimod (APD334) is an orally administered, synthetic, selective modulator of sphingosine 1-phosphate (S1P) receptors 1, 4, and 5 ($S1P_{1,4,5}$) that is being developed to treat immune-mediated inflammatory disorders.

$S1P_1$ is a cell surface expressed G protein-coupled receptor that has been shown to regulate lymphocyte migration out of lymphoid tissues (Brinkmann 2010). Synthetic small molecule $S1P_1$ agonists have been observed to act as functional antagonists by inducing sustained receptor internalization, thus inhibiting lymphocyte migration out of lymphoid tissues and lowering the amount of peripheral blood lymphocytes available to be recruited to sites of inflammation. In theory, a reduction in the number of circulating lymphocytes translates to less pro-inflammatory cytokines release, which mediates tissue damage (Nielsen 2017).

Modulation of the S1P/S1P receptor axis is thought to be a potential therapeutic approach to the management of a variety of immune-mediated disorders; as such, etrasimod may provide therapeutic benefit to patients with AA. Consistent with this hypothesis, S1P receptor modulators have been shown to be clinically beneficial in other T cell-mediated diseases including, but not limited to, inflammatory bowel disease, multiple sclerosis, and plaque psoriasis (Brinkmann 2010, Kappos 2010, Sandborn 2016, Vaclavkova 2014). Etrasimod demonstrated positive results in a Phase 2, randomized, double-blind, placebo-controlled study in subjects with moderately to severely active ulcerative colitis (UC) (Study APD334-003 (Cabell 2018) and its open-label extension Study APD334-005 (Cabell 2019)). Etrasimod significantly reduced circulating lymphocyte counts and demonstrated consistent and clinically meaningful improvements in endpoint measures reflecting cardinal symptoms of UC, and objective findings of endoscopic colorectal mucosal healing (Peyrin-Biroulet 2019, Sandborn 2018, Sandborn 2020, Vermeire 2019).

A complete summary of the nonclinical and clinical data relevant to etrasimod and its study in human subjects is provided in the current edition of the Investigator's Brochure (IB).

1.2. Benefit-Risk Considerations

As described in Section 1.1.1, modulation of the S1P/S1P receptor axis is thought to be a potential therapeutic approach to the management of a variety of immune-mediated disorders; as such, etrasimod may provide therapeutic benefit to patients with AA.

Etrasimod has been found to be safe and well-tolerated in subjects who have been dosed with the investigational drug. The safety and tolerability of etrasimod has been evaluated in Phase 1 studies with healthy adult subjects at single doses up to 5 mg and repeated doses up to 2 mg once daily without dose escalation and 4 mg once daily with dose escalation. Etrasimod has already demonstrated beneficial effects in another autoimmune inflammatory disease, UC.

While there have not been notable safety concerns with vital signs, electrocardiograms (ECGs), pulmonary function tests (PFTs), ophthalmoscopy, or laboratory test results with etrasimod, based on the mechanism of action of etrasimod and prior experience with S1P modulators fingolimod and siponimod, monitoring for these specific safety parameters is planned for this study. This monitoring includes PFTs, cardiac monitoring at first dose, when initiating 3 mg etrasimod, and on treatment re-initiation after a defined period of treatment interruption, liver function tests, and ophthalmoscopy with optical coherence tomography (OCT). Based on its mechanism of action, etrasimod is expected to dose-dependently reduce lymphocyte counts. This reduction is reversible, with lymphocyte counts returning to within normal limits following study drug discontinuation. Lymphocyte reduction may increase the risk of infections in some subjects. Any subject with a confirmed lymphocyte measurement $< 0.2 \times 10^9$ cells/L will be discontinued from study drug. Thus, serial assessment of white blood cell count and differential will be performed to assess the risk for serious and atypical infections, and study subjects will be closely monitored by Investigators.

S1P receptor modulators are associated with an expected, on target dose-dependent effect of reducing heart rate (HR) upon first dosing with HR recovery towards predose Baseline thereafter (Camm 2014). There have been no reported cases of symptomatic bradycardia on first dose, and rare first- or second-degree atrioventricular (AV) block found on ECG has been asymptomatic and transient (ie, spontaneous resolution) with etrasimod. A modest $S1P_1$-mediated HR reduction is maximal on the first day of dosing with etrasimod, which typically peaks approximately 3 hours postdose on Day 1 with recovery thereafter. In Study APD334-003, the mean transient HR decrease did not exceed 10 beats per minute (bpm) from Baseline on Day 1 up to 8 hours after dosing in all treatment groups, with the mean nadir of HR lowering for 2 mg etrasimod occurring 3 hours after dosing. This study includes an etrasimod 3 mg treatment group (refer to Section 3.3 for dose selection rationale). To attenuate the magnitude of HR reduction with the first etrasimod 3 mg dose, subjects assigned to etrasimod 3 mg will receive 2 mg once daily for 1 week, then escalate to 3 mg once daily; Phase 1 thorough QT (TQT) Study APD334-008 used a similar dosing paradigm. In Study APD334-008, the mean placebo-corrected change from baseline in HR was larger on Day 1 following 2 mg than on Day 8 and Day 13 when doses were escalated to 3 and 4 mg, respectively.

Subjects with certain cardiac risks, those with certain cardiac risks (eg, recent myocardial infarction, cardiac conduction delay, recurrent symptomatic bradycardia or syncope) will be excluded from the study. HR will be monitored closely via ECG and vital sign readings during the study, and direct observation will be performed at first dose (Double-Blind Treatment Period and Open-Label Extension Period) and on treatment re-initiation after a defined period of treatment interruption (refer to Section 10.5.7.4 for additional information on Day 1 monitoring). In addition to first-dose cardiac monitoring, continuous Holter monitoring (refer to Section 10.5.7.5) will be measured for 8 hours following dosing at Day 1 and Week 1 visits in the Double-Blind Treatment Period for Cohort 2, following dosing at Week 24 and Week 25 visits in the Open-Label Extension Period for Cohort 2, at the Week 24 visit and following transition from 2 mg to 3 mg in the Open-Label Extension Period for subjects in Cohort 1, and when a subject re-initiates study drug after a dosing interruption of a specified period (Section 6.3.2).

As additional safety measures, subjects with elevated liver enzymes, low lymphocyte counts, active severe pulmonary disease or a chronic pulmonary disease requiring intravenous

corticosteroid treatment or hospitalization, and active retinopathy or macular edema will be excluded from the study.

Further description of identified risks, any potential risks, and the Reference Safety Information (RSI) for etrasimod are provided in the current edition of the IB.

2. OBJECTIVES

Primary Objective

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

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

3. STUDY DESIGN

3.1. Overall Design

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 Double-Blind Treatment Period, a 28-week Open-Label Extension Period, and a 4-week Safety Follow-Up Period for a maximum total study duration of 60 weeks.

This study will include approximately 78 subjects with moderate-to-severe AA with current episode of hair loss for ≥ 6 months but < 5 years (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.

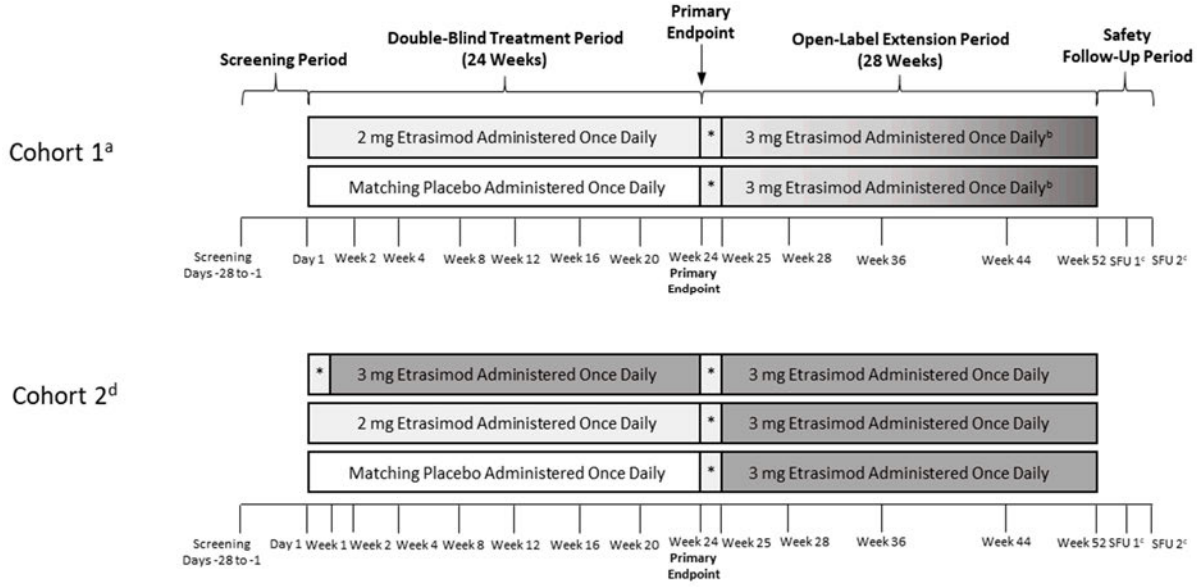
Subjects were randomized in a 2:1 ratio to receive etrasimod 2 mg or placebo orally, once daily. Randomization was stratified by SALT I score (< 100, 100) at Day 1/Baseline. Subjects will complete the Double-Blind Treatment Period per their original randomization assignment. Subjects who have entered the Open-Label Extension 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 Open-Label Extension 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 Open-Label Extension Period. 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.

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 Double-Blind Treatment Period. Randomization will be stratified by SALT I score (< 50, ≥ 50) at Day 1/Baseline. During the Double-Blind 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 Double-Blind Treatment Period. During the Open-Label Extension 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 Open-Label Extension 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 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 for information on re-initiation of treatment after dose interruptions
ET, early termination; N, number (of subjects); SFU, Safety Follow-Up.

Study visits will take place for Screening; Day 1/Baseline; Weeks 1, 2, 4, 8, 12, 16, 20, 24, 25, 28, 36, 44, and 52, as applicable (Week 1 is applicable to Cohort 2 only); and 2 weeks and 4 weeks after the last dose of study drug (for Safety Follow-Up).

3.2. Discussion and Scientific Rationale for Study Design

This Phase 2 study will be a randomized, double-blind, placebo-controlled, safety and efficacy study that is intended to support the development of etrasimod 2 mg and 3 mg for the treatment of moderate-to-severe AA. The subjects will be those with moderate-to-severe AA with current episode of hair loss for at least 6 months but less than 5 years (current episode must also be relatively stable during the last 6 months with no significant regrowth).

This study will assess etrasimod 2 mg and 3 mg monotherapy compared to placebo during the first 24 weeks of treatment. The choice of placebo as a control is appropriate for the objectives of this study since it will provide the most robust assessment of the safety and efficacy of etrasimod. The 24-week treatment duration was selected to ensure that etrasimod could reach its maximal efficacy with respect to hair regeneration while minimizing the time that a subject may be on placebo treatment. As this is a placebo-controlled study, the duration is limited. Subjects from Cohort 1 who are 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. All other subjects who continue to the Open-Label Extension Period, will receive etrasimod 3 mg once daily for a total etrasimod treatment duration of up to 52 weeks. The Open-Label Extension is designed to allow subjects to continue etrasimod therapy and to assess long-term safety and efficacy of 3 mg once daily dosing as a chronic therapy.

Efficacy will be assessed by percent change in hair loss using a well-validated metric and widely utilized tool (SALT I score) at each visit, with a primary endpoint of percent change in SALT I score from Baseline to end of the Double-Blind Treatment Period (Week 24).

Additionally, because patient-reported outcomes (PROs) can provide subject perspectives on aspects of their disease conditions and overall health status, several PROs will be explored in this study. The Alopecia Areata Symptom Impact Scale (AASIS) and Alopecia Areata Quality of Life Index (AA-QLI) will be administered every 12 to 16 weeks at study visits.

Exploratory measures will include cytokine and chemokine analysis of serum samples.

Photographs of the full scalp for all subjects and of the eyebrows and eyelashes for subjects who have hair loss in these areas at Baseline will also be required to assess changes in hair growth. Photographs of the fingernails for subjects with fingernail changes related to AA (eg, pitting, white spots, and roughness) at Baseline will also be taken. SALT I assessments of photographs will be performed by central review.

3.3. Rationale for Dose Selection

Taken together, the completed and ongoing Phase 1 studies conducted in healthy volunteers with doses up to 4 mg once daily and Phase 2 studies conducted in subjects with ulcerative colitis and atopic dermatitis (AD) patients with dosing up to 2 mg daily demonstrate acceptable tolerability with no significant safety signal.

In the concluded 12-Week Phase 2 Study (Study APD334-201) in subjects with AD, the etrasimod 2 mg dose demonstrated clear efficacy across various measures and demonstrated a greater effect than the etrasimod 1 mg dose. The overall data suggest potential for a higher etrasimod dose to provide a greater clinical benefit to the patient without compromising safety as the overall effect size was moderate for the 2 mg dose and had not plateaued at the Week 12 primary endpoint in the study. Both etrasimod 1 mg and 2 mg doses were well tolerated and there were no unanticipated safety signals.

S1P receptor modulators are associated with an expected, on target dose-dependent effect of reducing HR upon first dosing with HR recovery to predose baseline thereafter (Camm 2014). There have been no reported cases of symptomatic bradycardia on first dose and rare first- or second-degree AV block found on ECG has been asymptomatic and transient (ie, spontaneous resolution) with etrasimod. In Study APD334-003, the mean transient HR decrease did not exceed 10 beats per minute (bpm) on Day 1 up to 8 hours after dosing, with the mean nadir of HR lowering for 2 mg etrasimod occurring 3 hours after dosing. Therefore, a dose escalation regimen is not necessary for doses up to 2 mg. This study includes an etrasimod 3 mg treatment group. To attenuate the magnitude of first dose HR reduction with 3 mg etrasimod, subjects randomized to the 3 mg etrasimod group will receive 2 mg etrasimod daily for the first week and 3 mg etrasimod daily for the remainder of the study (refer to Section 1.2 for additional details).

While ulcerative colitis (UC), Crohn's disease (CD), AD, and AA have similar inflammatory mediated origins, there are differences in pathophysiology, disease location, and extent of disease that may result in a different optimal dose for the treatment of AA. Therefore, this study will evaluate the treatment effect of 2 mg and a higher dose of 3 mg. Based on Phase 1 data in healthy volunteers, Phase 2 data in UC patients, and Phase 2 data in AD patients, etrasimod 2 mg and 3 mg are expected to be safe and well-tolerated in AA patients.

3.4. End of Study

A subject is considered to have completed the study if he/she has completed all phases of the study, including the last study visit (ie, Safety Follow-Up [SFU] 2).

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

4. STUDY POPULATION

4.1. Inclusion Criteria

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

Key inclusion criteria

1. Men or women between ≥ 18 and ≤ 70 years of age at the time of informed consent
2. Moderate-to-severe AA as assessed by a SALT I score ≥ 25 and < 95 at Screening and Day 1/Baseline. Severity will also be confirmed by central review of photographs taken during Screening

3. Current episode of hair loss for ≥ 6 months but < 5 years
4. Stable disease condition (no significant growth of hair) in the last 6 months as assessed by the Investigator
5. Willing to keep the same hair style and color (eg, hair products, process, and timing for hair appointments) for the duration of the study

General inclusion criteria

6. Willing and able to comply with all clinic visits and study-related procedures and understand and complete study-related questionnaires
7. Provide signed informed consent prior to conducting any procedures
8. Females must meet either a or b of the following criteria and males must meet criterion c to qualify for the study:
    a. Female who is not of childbearing potential by one of the following:
        - Postmenopausal, defined as no menses for 12 months without an alternative medical cause
        - Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
    b. Nonpregnant female of childbearing potential and agrees to using a highly effective contraception method during treatment and for 30 days following treatment that can achieve a failure rate of less than 1% per year when used consistently and correctly. The following are considered highly effective birth control methods:
        - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
        - Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted
        - Intrauterine device (IUD)
        - Intrauterine hormone-releasing system
        - Bilateral tubal occlusion
        - Vasectomized partner, provided that partner is the sole sexual partner of the female of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success
        - Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study drug). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods) is not acceptable.

c. Male with a pregnant or nonpregnant female of childbearing potential partner and agrees to using condoms during treatment and for 30 days following treatment

4.2. Exclusion Criteria

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

Key exclusionary criteria

1. History of male or female pattern hair loss > Hamilton stage III or > Ludwig stage II
2. Other types of alopecia (eg, cicatricial/scarring alopecia [including central centrifugal cicatricial alopecia], traction alopecia, or telogen effluvium) or other diseases that could cause hair loss
3. Active scalp inflammation, scalp infection, scalp psoriasis, or any other scalp condition that may interfere with the SALT I assessment
4. Previous use of a Janus kinase (JAK) inhibitor (oral or topical), including participation in clinical studies of JAK inhibitors

Exclusionary criteria related to medications, therapies, or skin disease

5. Phototherapy on scalp within 4 weeks of Screening
6. Treatment with the following medications within 12 weeks of Screening:
    a. Intralesional or systemic corticosteroids
    b. Systemic glucocorticoids (inhaled or intranasal delivery are not exclusionary)
    c. Immunoglobulin or blood products
7. Use of any biological agents (eg, dupilumab, adalimumab, ustekinumab, secukinumab) regardless of indication or systemic immunosuppressive/immunomodulating drugs (eg, cyclosporine, azathioprine, methotrexate) within 5 half-lives (if known) or 12 weeks before Screening, whichever is longer
8. Treatment with the following medications within 4 weeks of Screening:
    a. Topical corticosteroids
    b. Topical immunotherapy (eg, diphenylcyclopropenone, squaric acid)
    c. Topical calcineurin inhibitors
    d. Topical or oral minoxidil
9. Use of S1P receptor modulators (eg, fingolimod, siponimod, ozanimod, ponesimod), α4β1-integrin receptor antagonists (eg, natalizumab), and lymphocyte-depleting therapies (eg, rituximab, cyclophosphamide, bone marrow transplantation, total body irradiation) within 6 months before Screening or until lymphocyte count returns to normal, whichever is longer
10. History of or planned hair transplant procedure during the study
11. Planned microblading or micropigmentation of the scalp during the study
12. Received any investigational agent, including non-biologic agents and topical agents, within 5 half-lives (if known) or 4 weeks (whichever is longer) before Screening

13. Use of moderate/strong inducers or inhibitors that inhibit or induce at least two of the following: Cytochrome P450 (CYP) 2C8, CYP2C9, and CYP3A4 (eg, fluconazole, enzalutamide; Table 4) within 4 weeks before Screening.

Exclusionary criteria related to medical history

14. Known active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis [TB] or atypical mycobacterial disease) or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 4 weeks before Screening or during Screening, or oral antibiotics within 2 weeks before Screening or during Screening. Superficial fungal infection of the nail bed is allowed
15. Have any of the following conditions or risk factors:
    a. Primary or secondary immunodeficiency syndromes (eg, hereditary immunodeficiency syndrome, acquired immunodeficiency syndrome, drug-induced immune deficiency)
    b. History of organ transplant (except corneal transplant)
    c. History of an opportunistic infection (eg, *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis, progressive multifocal leukoencephalopathy [PML])
    d. History of disseminated herpes simplex or disseminated herpes zoster, or any episode of herpes zoster
    e. Test positive for human immunodeficiency virus (HIV), hepatitis B virus (positive for hepatitis B surface antigen [HBsAg]), or active hepatitis C virus (HCV) (positive HCV antibody with detectable viral load) at Screening
    f. History of active or latent TB (refer to Appendix 3 for details of TB screening and interpretation of test results). The following is the EXCEPTION to the exclusion criterion:
        - Subjects with treated latent TB or latent TB diagnosed at Screening who have received ≥ 2 weeks of TB prophylaxis treatment prior to randomization, ruled out for active TB, and have not had recent close contact with a person with active TB. It is the responsibility of the Investigator to verify the adequacy of TB prophylaxis treatment and provide appropriate documentation. Note: The exception to the exclusion criterion outlined above does NOT apply to subjects residing in countries identified by the WHO as a high multi-drug resistance (MDR) TB burden country due to the risk of latent infection with MDR TB.
16. Received any live or live-attenuated vaccines within 4 weeks before Screening (Section 6.9 offers additional details regarding vaccines)
17. History of malignancy of any organ system (other than localized squamous cell or basal cell carcinoma of the skin that have been excised or resolved), treated or untreated, within the past 5 years
18. Have any of the following conditions or receiving treatments that may affect cardiovascular function:
    a. Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure within 8 weeks before Screening

b. History or presence of second-degree or third-degree AV block, sick sinus syndrome, or periods of asystole for > 3 seconds without a functional pacemaker
c. Recurrent symptomatic bradycardia or recurrent cardiogenic syncope
d. Screening **OR** Baseline (Day 1) pre-randomization vital signs (taken in the sitting position) with an HR < 50 bpm, systolic blood pressure (BP) < 90 mm Hg, OR diastolic BP < 55 mm Hg. Vital signs may be repeated up to 3 times during a visit to confirm abnormal readings
e. Screening **OR** Baseline (Day 1) pre-randomization ECG with PR interval ≥ 200 ms or QT interval corrected using Fridericia's formula (QTcF) ≥ 450 ms in males or ≥ 470 ms in females
f. Start, stop, or change dosage of Class I-IV anti-arrhythmic drugs within 1 week of Screening

19. A history of or active diabetic retinopathy, uveitis, retinitis pigmentosum, or macular edema. Any recent intraocular surgery within 1 year of Screening
20. Active severe pulmonary disease (eg, chronic obstructive pulmonary disease or pulmonary fibrosis) or chronic pulmonary disease requiring intravenous corticosteroid treatment or hospitalization within 12 months before Screening or during the Screening Period
21. Have forced expiratory volume at 1 second (FEV_1) or forced vital capacity (FVC) < 70% of predicted values at Screening
22. Have any uncontrolled systemic disease(s) (eg, thyroid disorder, hypertension, diabetes). If the condition is considered controlled and the subject is on any medications (eg, thyroid medication or hormonal therapy) for treatment of diseases, the subject may be allowed to participate but must have been on a stable dose for at least 6 months prior to Screening and remain on a stable dose throughout the study.

Exclusionary criteria related to test or laboratory results (performed by central laboratory)
Note: A confirmed result means there have been 2 consecutive assessments showing a consistent abnormal, clinically relevant result.

23. Confirmed total white blood cell (WBC) count ≤ 3.5×10^9 cells/L OR absolute neutrophil count (ANC) ≤ 1.5×10^9 cells/L OR ALC < 1.0×10^9 cells/L at Screening
24. Confirmed estimated glomerular filtration rate < 30 mL/min/1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening
25. Confirmed aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN) and total bilirubin > 1.5 × ULN (unless consistent with a history of Gilbert's Syndrome) at Screening

General exclusionary criteria

26. Lactating female who is breastfeeding
27. Any acute illness or medical condition including psychiatric disease, cognitive impairment, and alcohol/drug abuse/dependence, or signs/symptoms suspicious for a serious disease that, in the Investigator's opinion, could put the subject at increased risk for safety event(s), could interfere with participation in the study according to the study

protocol, or with the ability of the subject to cooperate and comply with the study procedures

Note: If a subject fails ≥ 1 Screening laboratory (or other) assessment criteria, the assessment(s) may be repeated once at the discretion of the Investigator, and the subject may be randomized if criteria are then met, provided the assessments are completed within the Screening Period. Any rescreening laboratory assessments beyond 1 time will need to be discussed with the Medical Monitor before proceeding.

4.3. Exclusion Criteria (for the Open-Label Extension Period)

Subjects will be excluded from the Open-Label Extension Period if they meet the following exclusion criteria at the Week 24 visit:

1. Week 24 predose vital signs (taken in the sitting position) with an HR < 50 bpm, systolic BP < 90 mm Hg, OR diastolic BP < 55 mm Hg. Vital signs may be repeated up to 3 times during the visit to confirm abnormal readings.
2. Confirmed predose Week 24 ECG with PR interval ≥ 200 ms or QT interval corrected using QTcF ≥ 450 ms in males or ≥ 470 ms in females. Presence on Week 24 ECG of second-degree or third-degree AV block, sick sinus syndrome, or periods of asystole for > 3 seconds without a functional pacemaker.
3. The Investigator considers the subject to be unsuitable for any reason to participate in the Open-Label Extension study.

Note: If a subject fails to enter the Open-Label Extension Period due to Exclusion Criterion 1 or 2, the assessment may be repeated once at the discretion of the Investigator, and the subject may be dosed if the criterion is then met, provided the assessment is completed within the Week 24 visit window. Any repeated vital sign assessments beyond 1 time will need to be discussed with the Medical Monitor before proceeding.

5. SUBJECT RESTRICTIONS

For dosing requirements, including holding the dose prior to the study visit on study visit days, refer to Dosage and Administration, Section 6.3. Prohibited medications/procedures are located in Section 6.8.2.

Subjects are expected to continue their usual scalp care routine without notable changes for the course of the treatment periods and follow-up period. Subjects are prohibited from using tanning booths and sunbathing, and from shaving their scalp 2 weeks prior to visits.

Subjects are to keep the same hair style and color for the duration of the study.

6. STUDY DRUG

6.1. Study Drug(s) Administered

Study drug(s) in this study include the investigational medicinal product(s), defined as a pharmaceutical form of the active substance being tested (test product) and the placebo being used as a reference (reference therapy). Study drug(s) are listed in Table 1.

Table 1: Study Drugs

Study Drug	Dose	Mode of Administration	Frequency	Formulation
Etrasimod	2 mg	Oral	Once daily	Tablet
Etrasimod	3 mg	Oral	Once daily	Tablet
Placebo	Not applicable	Oral	Once daily	Tablet

6.2. Identity of Study Drugs

6.2.1. Etrasimod

The active pharmaceutical ingredient in etrasimod tablets is APD334 L-arginine (the L-arginine salt of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]-indol-3-yl)acetic acid), which is an off-white to light-brown solid with an aqueous solubility of approximately 1.38 mg/mL at pH = 8.9 and 30°C. APD334 L-arginine is manufactured, packaged, tested, and released in compliance with cGMP.

Etrasimod tablet drug product is a blue, round, biconvex, plain, immediate-release, film-coated tablet. Etrasimod tablets are composed of APD334 L-arginine active pharmaceutical ingredient and excipients (microcrystalline cellulose, mannitol, sodium starch glycolate, magnesium stearate, and Opadry®II blue 85F90951) and is supplied in the dosage strength (based on etrasimod free-acid content) of 1 mg and 2 mg.

6.2.2. Placebo

The placebo tablet is a blue, round, biconvex, plain, film-coated tablet. The placebo tablet formulation is composed of excipients (microcrystalline cellulose, mannitol, sodium starch glycolate, magnesium stearate, and Opadry® II blue 85F90951). The placebo drug product is manufactured, packaged, tested, and released in compliance with cGMP.

6.3. Dosage and Administration

Subjects will self-administer study drug, except on study visit days, from Day 1 until the day prior to the Week 52 visit. Tablets (etrasimod 1 mg, etrasimod 2 mg, or placebo) are to be taken once daily with water (either with or without food) at approximately the same time each day, preferably in the morning according to the schedule described in Table 2 (Cohort 1) and Table 3 (Cohort 2).

Table 2: Study Drug Dosage and Administration for Cohort 1

Randomization Assignment[a]	Double-Blind Treatment Period	Open-Label Extension Period	
	Day 1 to Week 24 Visit[b]	Week 24 Visit to Week 25 Visit	Week 25 Visit to Week 52 Visit[c,d,e]
Placebo	1 × placebo	1 × 2 mg	1 × 2 mg + 1 × 1 mg or 1 × 2 mg[f]
2 mg etrasimod	1 × 2 mg	1 × 2 mg	1 ×2 mg + 1 × 1 mg or 1 × 2 mg[f]

[a] Randomization assignment refers to treatment assignment in the Double-Blind Treatment Period.
[b] No double-blind treatment is to be administered at the Week 24 visit. Treatment in the Open-Label Extension Period will start at Week 24 after all assessments of the Double-Blind Period are completed.
[c] 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. 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.
[d] No treatment is to be administered at the Week 52 visit.
[e] In case of study drug interruption of etrasimod 3 mg, treatment will be re-initiated by starting with etrasimod 2 mg for 1 week before transitioning to etrasimod 3 mg. Holter monitoring, as described in Section 10.5.7.5, must be performed any time a subject transitions from 2 mg to 3 mg etrasimod.
[f] 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.
SALT I, Severity of Alopecia Tool I

Table 3: Study Drug Dosage and Administration for Cohort 2

Randomization Assignment[a]	Double-Blind Treatment Period		Open-Label Extension Period	
	Day 1 to Week 1 Visit	Week 1 Visit to Week 24 Visit[b,c]	Week 24 Visit to Week 25 Visit	Week 25 Visit to Week 52 Visit[c,d]
Placebo	2 × placebo	2 × placebo	1 × 2 mg	1 × 2 mg + 1 × 1 mg
2 mg etrasimod	1 × 2 mg + 1 × placebo	1 × 2 mg + 1 × placebo	1 × 2 mg	1 × 2 mg + 1 × 1 mg
3 mg etrasimod	1 × 2 mg + 1 × placebo	1 × 2 mg + 1 × 1 mg	1 × 2 mg	1 × 2 mg + 1 × 1 mg

[a] Randomization assignment refers to treatment assignment in the Double-Blind Treatment Period.
[b] No double-blind treatment is to be administered at the Week 24 visit. Treatment in the Open-Label Extension Period will start at Week 24 after all assessments of the Double-Blind Period are completed.
[c] In case of study drug interruption of etrasimod 3 mg, treatment will be re-initiated by starting with etrasimod 2 mg for 1 week before transitioning to etrasimod 3 mg. Holter monitoring, as described in Section 10.5.7.5, must be performed any time a subject transitions from 2 mg to 3 mg etrasimod.
[d] No treatment is to be administered at the Week 52 visit.
SALT I, Severity of Alopecia Tool I

On study visit days when study drug is to be administered at the clinic (Schedules of Assessments, Appendix 1 and Appendix 2), subjects should be instructed not to take their dose until after their study visit assessments have been completed. On study visit days when plasma samples for pharmacokinetics (PK) are being collected, subjects should wait to take their assigned dose at the study site after predose blood samples for PK have been drawn and after all predose assessments and procedures have been completed. Subjects should be instructed to document the time of their last dose prior to the study visit and the time must be recorded in the electronic case report form (eCRF). The time of plasma sample collection and subsequent dosing should also be documented.

6.3.1. Instructions for Missed Dose(s)

Subjects should be instructed that if they forget to take a dose, they can take the dose within 8 hours of the normal dosing time; otherwise, they should take their next dose at the regular time on the following day. If the subject vomits the tablet(s), he/she should be instructed not to take additional tablet(s) on the same day but to take the next dose at the regular time on the following day.

Subjects should be instructed to contact the Investigator if they miss 2 or more consecutive doses. The Investigator is to refer to Section 6.3.2 for guidance regarding dose interruptions.

6.3.2. Dose Interruptions

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

The procedure for first-dose cardiac monitoring as outlined in Section 10.5.7.4 should be performed and discussed with the Medical Monitor any time a subject misses study drug dosing as follows:

- ≥ 2 consecutive days within the first week of study drug during the Double-Blind Treatment Period and within the first week of study drug during the Open-Label Extension Period
- ≥ 7 consecutive days after the first week of study drug during the Double-Blind Treatment Period and after the first week of study drug during the Open-Label Extension Period

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

Subjects assigned to 3 mg dosing will re-initiate treatment with 2 mg once daily for 1 week prior to transitioning to 3 mg. In order to maintain the study drug blind, after interruptions of study drug for the time periods defined above, all subjects must also return to an in-clinic visit the following week after re-initiating treatment and will receive a new kit dispensed. Holter monitoring is required any time a subject escalates from 2 mg to 3 mg etrasimod.

6.4. Method of Assigning Subjects to Treatment

For the Double-Blind Treatment Period, eligible subjects in Cohort 1 were centrally assigned to randomized study drug (2 mg etrasimod or placebo [2:1]) using an Interactive Web Response System (IWRS) and stratified by SALT I score (< 100, 100) at Day 1/Baseline. Eligible subjects in Cohort 2 will be centrally assigned to randomized study drug (etrasimod 3 mg, etrasimod 2 mg, or placebo [4:1:2]) using an IWRS and stratified by SALT I score (< 50, ≥ 50) at Day 1/Baseline.

During the Open-Label Extension Period, all eligible subjects in Cohort 1 will transition to etrasimod 3 mg as described in Section 3.1 and all eligible subjects in Cohort 2 will receive etrasimod 3 mg (no randomization).

6.5. Selection and Timing of Dose for Each Subject

Refer to Section 6.3 for information regarding the selection and timing of dose for each subject.

6.6. Blinding

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

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted based upon medical necessity.

Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason the blind was broken must be recorded in the source documentation and eCRF, as applicable.

S1P receptor modulators such as etrasimod are associated with an expected, on-target dose-dependent effect of reducing HR upon first dosing due to $S1P_1$ agonism and subsequent activation of G protein-coupled inwardly rectifying potassium channels that regulate HR (Camm 2014). Therefore, study staff, including investigators and study coordinators, should not disclose HR data to study subjects after treatment initiation during the cardiac monitoring period. If there are adverse events (AEs) associated with changes in HR during the treatment period, then investigators may discuss the relevant measurement with subjects, as needed, for appropriate AE inquiry and/or management. Trends in HR changes should not be discussed among study staff unless this is required to provide appropriate medical care to study subjects. Additionally, site staff including Investigators will be blinded to laboratory results as defined in Section 10.5.7.2, during the Double-Blind Treatment Period.

Additionally, site staff including Investigators will be blinded to the following laboratory results during the Double-Blind Treatment Period: WBC count and differential (percentage and absolute number), and lymphocyte subsets, except as described in Section 10.5.7.2. During the time when the Investigator is blinded to these results, they will be monitored by an Independent Medical Monitor (IMM; not providing direct medical oversight of study conduct), who will provide instructions to the site Investigator when actions are required as specified by the study protocol (Section 10.5.7.2).

During the Open-Label Extension Period, a subject's previous treatment from the Double-Blind Treatment Period will remain blinded until the unblinding of data from that treatment period.

For Suspected, Unexpected, Serious Adverse Reactions, the Sponsor's Pharmacovigilance designee responsible for managing serious adverse events (SAEs) will access the IWRS to obtain the subject's treatment assignment for the purpose of regulatory reporting.

6.7. Treatment Compliance

The Investigator is responsible for ensuring that subjects are correctly instructed on how to take the study drug and that each subject is fully compliant with the assigned regimen. The study drug should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained as described in Section 7.4.

Subject compliance will be based on tablet count per bottle. Lack of subject compliance should be evaluated by the Investigator regarding whether the subject should continue in the study or be discontinued from study drug.

6.8. Concomitant Therapy

6.8.1. Allowed Concomitant Therapy

There are no permitted medications for the treatment of AA for this study. Concomitant medications for medical conditions other than AA are permitted as clinically indicated, subject to specific protocol requirements outlined in Section 4.1 and Section 4.2. Any permitted medications also need to be approved in the country where it will be administered.

All medications (over the counter and prescribed) that are taken by subjects and all procedures that are performed during the Screening Period through the safety reporting period must be recorded in the eCRF along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

6.8.2. Prohibited Concomitant Therapy and Procedures

The following therapies are prohibited during the study:

- Topical, intralesional, or systemic corticosteroids
- Topical calcineurin inhibitors
- Topical or oral minoxidil
- Topical immunotherapy (eg, diphenylcyclopropenone, squaric acid)
- S1P receptor modulators (eg, fingolimod, siponimod, ozanimod, ponesimod), α4β1 integrin receptor antagonists (eg, natalizumab)
- Phototherapy on scalp

- Any biological agents (eg, dupilumab, adalimumab, ustekinumab, secukinumab) regardless of indication
- Any investigational agent other than the study drug, including non-biologic agents and topical agents
- Moderate/strong inducers or inhibitors that inhibit or inducer at least two of the following: Cytochrome P450 (CYP) 2C8, CYP2C9, and CYP3A4 (eg, fluconazole, enzalutamide; Table 4 for additional information refer to US FDA Drug development and drug interactions: Table of substrates, inhibitors and inducers (Flockhart 2019))

Table 4: Examples of Cytochrome P450 Inhibitors and Inducers

Cytochrome P450	Inhibitors (Strong/Moderate)	Inducers (Strong/Moderate)
CYP2C8	Clopidogrel, gemfibrozil, deferasirox, teriflunomide	Rifampin
CYP2C9	Fluconazole, amiodarone, felbamate, miconazole, piperine	Aprepitant, carbamazepine, enzalutamide, rifampin, ritonavir
CYP3A4	Boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole, aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil, clarithromycin, idelalisib, nefazodone, nelfinavir	Rifampin, apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, St. John's wort, bosentan, efavirenz, etravirine, phenobarbital, primidone

CYP, cytochrome P450

- Moderate/strong inhibitors or inducers of uridine diphosphate (UDP) glucuronosyltransferase (UGT) family 1 member A7 (UGT1A7)

In addition to being prohibited during the study, initiation of any of the following therapies will result in mandatory discontinuation from study drug:

- Topical JAK inhibitors
- Systemic glucocorticoids (excludes inhaled or intranasal delivery that are considered topical for any reason)
- Immunoglobulin or blood products
- Systemic immunosuppressive/immunomodulating drugs (eg, cyclosporine, azathioprine, methotrexate), including oral JAK inhibitors
- All live or live-attenuated vaccines
- Any cell-depleting agents, including but not limited to rituximab

- Hair transplant, microblading, or micropigmentation of the scalp

For concomitant procedures:

- Subjects should not undergo major elective surgery while on study drug
- Subjects may not donate blood during the study and for 30 days after the last dose of study drug
- Subjects may not donate sperm, or oocytes during the study and for 30 days after the last dose of study drug

6.9. Vaccinations

At this time, there are no data on the effect of etrasimod on vaccination, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus disease 2019 (COVID-19) vaccines. The American Academy of Dermatology (AAD) has published recommendations that advise patients on immunomodulating drugs to be vaccinated as *"The CDC does not consider COVID-19 vaccine to be contraindicated in persons taking biologic or traditional immunosuppressive medications, hedgehog pathway inhibitors, and PD1 inhibitors"* (AAD 2021).

If a subject receives a vaccination, the vaccination date and type (eg, SARS-CoV-2) should be captured as described in Section 6.8 in the Concomitant Medication log/eCRF. The vaccine brand, manufacturer, and lot number (if available) should be captured in the source documentation.

7. STUDY DRUG MATERIALS MANAGEMENT

7.1. Packaging and Labeling

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

Cohort 1: During the Double-Blind Treatment Period, subjects will be dispensed blinded etrasimod 2 mg or matching placebo bottles. During the Open-Label Extension Period, subjects will be dispensed open-label etrasimod 2 mg bottles for etrasimod 2 mg treatment and etrasimod 3 mg kits for etrasimod 3 mg treatment. Each etrasimod 3 mg kit will contain one etrasimod 2 mg bottle and one etrasimod 1 mg bottle, total of two bottles inside.

Cohort 2: During the Double-Blind Treatment Period, subjects will be dispensed blinded treatment kits, each kit will contain two blinded bottles. Placebo kit will contain two placebo bottles; etrasimod 2 mg kit will contain two bottles, consisting of one etrasimod 2 mg bottle and one placebo bottle; etrasimod 3 mg kit will contain two etrasimod bottles, consisting of one etrasimod 2 mg and one etrasimod 1 mg bottle. During the Open-Label Extension Period, subjects will be dispensed open-label etrasimod 2 mg bottles for etrasimod 2 mg treatment and etrasimod 3 mg kits for etrasimod 3 mg treatment. Each 3 mg kit will contain one etrasimod 2 mg bottle and one etrasimod 1 mg bottle, total of two bottles inside.

7.2. Storage and Handling

Bottles and kits should be stored between 15°C to 25°C (59°F to 77°F).

7.3. Preparation

No preparation by study site personnel is required.

7.4. Accountability

At specified study visits, previously dispensed study drug tablets (bottles or kits, as applicable) will be collected by the Investigator or qualified staff to assess subject compliance (Appendix 1 and Appendix 2).

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

7.5. Retention and Disposal

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

8. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

8.1. Discontinuation of Study Drug

Study drug *must* be discontinued in the following instances:

- Unacceptable AE or AE that, in the judgment of the Investigator, is considered to not be in the best interest of the subject to continue study drug
- Subject request to discontinue for any reason
- Pregnancy during the study (Section 10.5.9)
- Termination of the study by the Sponsor or at the request of a regulatory agency or an Institutional Review Board (IRB) or Independent Ethics Committee (IEC)
- Lost to follow-up
- Criteria met from cardiac HR monitoring to discontinue study drug (Section 10.5.7.4)
- Confirmed lymphocyte measurement $< 0.2 \times 10^9$ cells/L (Section 10.5.7.2)
- Received a prohibited concomitant medication that required discontinuation of study drug (Section 6.8.2)

- Other

Study drug *may* be discontinued in the following instances:

- Subject noncompliance
- Protocol deviation
- Drug-induced liver injury (Section 10.5.7.1)

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 for Safety Follow-Up Visits 2 weeks and 4 weeks after the last dose of study drug (ie, SFU 1 and SFU 2) (Appendix 1 and Appendix 2). If a subject fails to attend the follow-up visits, all reasonable efforts will be made to contact the subject to ensure that he/she is in satisfactory health. All contacts and contact attempts must be documented in the subject's medical record.

Whenever possible, subjects should continue on study and complete the remaining study visits and assessments even when study drug has been discontinued.

8.2. Discontinuation from the Study

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

- AE
- Death
- Pregnancy during the study (Section 10.5.9)
- Protocol deviation
- Physician decision
- Withdrawal by subject
- Lost to follow-up
- Termination of the study by the Sponsor or at the request of a regulatory agency or an IRB or IEC
- Other

A subject may elect to discontinue study participation at any time for any reason without prejudice to their future medical care by the physician or at the institution. If a subject withdraws consent, no further evaluation should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. The Investigator should make a reasonable attempt to document the specific reason why consent was withdrawn. Additional subjects may be randomized at the discretion of the Sponsor to replace subjects who discontinue from the study.

8.3. Lost to Follow-Up

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

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

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

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

8.4. Premature Termination of the Study or a Study Site

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

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

The Sponsor will notify the Investigator if the study is placed on hold or if the Sponsor decides to discontinue the study. Health authorities and IECs/IRBs will be informed about the termination of the study in accordance with applicable regulations.

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with ICH guidelines for GCP

9. STUDY PERIODS

9.1. Screening and Eligibility

Subjects must sign the informed consent before any study-specific procedure can be performed (Section 10.1). The Screening Period will last up to 4 weeks. A summary of Screening and enrollment events is provided in the Schedules of Assessments (Appendix 1 and Appendix 2).

Inclusion and exclusion criteria are listed in Section 4.1 and Section 4.2, respectively. Subjects who have met all inclusion/exclusion criteria requirements may be randomized into the study.

Screening procedures must be completed within 28 days prior to Day 1. The Medical Monitor should be consulted to see whether repeated testing is needed if the subject is planned to be randomized > 28 days from the signing of the informed consent form (ICF). Rescreening procedures are described in Section 10.2.1.

Subjects with a Screening Visit 12-lead ECG showing a second- or third-degree AV block, sick sinus syndrome without a functional pacemaker, periods of asystole > 3 seconds without an implanted cardiac pacemaker, PR interval ≥ 200 ms, or QTcF ≥ 450 ms (men) or QTcF ≥ 470 ms (women) are not eligible for rescreening.

Eligibility for the Open-Label Extension Period will be assessed at the Week 24 visit and is defined in Section 4.3.

9.2. Randomization and Double-Blind Treatment Period

Subjects enrolled with this version of the protocol (Amendments 2.0 and 2.1) 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. Subjects will self-administer study drug, except on study visit days, as described in Section 6.3. Study visits and assessments will be conducted according to the Schedule of Assessments (Appendix 2).

9.2.1. Day 1 Pre-Randomization

At the Day 1 visit, prior to randomization, inclusion and exclusion criteria must be evaluated again. To this end, vital signs including HR and BP must be measured first, followed by 12-lead ECG. Vital signs may be repeated up to 3 times to confirm abnormal readings.

Subjects with the following must not be randomized and should be considered screen failures:

- Sitting vital sign assessment: HR < 50 bpm, systolic BP < 90 mm Hg, OR diastolic BP < 55 mm Hg
- 12-lead ECG showing a second- or third-degree AV block, periods of asystole > 3 seconds, PR interval ≥ 200 ms, or QTcF ≥ 450 ms (males) or QTcF ≥ 470 ms (females)

All predose 12-lead ECGs should be obtained prior to blood sample collection.

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

Subjects who continue to meet all inclusion criteria and no exclusion criteria will be randomized as outlined in Section 6.4.

Once eligibility is confirmed, a Holter monitor will be placed on the subject and continuous Holter recording should begin approximately 15 minutes before first administration of study drug and continue for 8 hours post-treatment administration as described in Section 10.5.7.5.

9.2.2. Day 1 Post-Randomization

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

- Questionnaire administration
- AE review
- Vital signs (performed with subject in the seated position)
- 12-lead ECG (performed with subject in the supine position)
- Physical examination including disease severity assessments
- Blood sample collection for laboratory tests and predose PK sampling
- Urine sample for urinalysis, drug screen, and pregnancy test if applicable

Day 1 pre-randomization vital signs (resting HR, BP, body temperature, and respiratory rate) will be used as Baseline measurements. The lowest predose HR measurement will be used for comparison to the postdose HR measurement. Refer to Section 10.5.7.5 for detailed guidance on Holter monitoring and Section 10.5.7.4 for detailed guidance on cardiac monitoring following administration of the first dose and subject discharge criteria postdose.

After dosing on Day 1:

- At Hours 1, 2, and 3 (± 15 minutes) postdose, HR and BP will be assessed with the subject in the seated position, with the time recorded. If the subject has an HR < 50 bpm, or if cardiovascular symptoms develop (eg, chest pain, dizziness, palpitations, and/or syncope associated with reduction of HR), the subject should remain closely monitored, including 12-lead ECGs as clinically indicated, until the discharge assessment at 4 hours.
- At the Hour 4 (± 15 minutes) discharge assessment, HR and BP will be assessed with the subject in the seated position; a 12-lead ECG will also be performed in the supine position. Subjects may be discharged from the clinic after the 4-hour assessment if they meet the criteria described in Table 7. Subjects not meeting the discharge criteria will require extended monitoring (Section 10.5.7.4).
- Subjects experiencing a clinically relevant treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, and/or syncope) associated with reduction of HR together with clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period should be discontinued from study drug (Table 8).

To minimize the risk of unintentional unblinding of treatment assignment, refer to guidance regarding disclosure of HR data discussed in Section 6.6.

A blood sample for PK assessment is to be taken 4 hours (± 15 minutes) postdose after the ECG on Day 1.

9.2.3. Double-Blind Treatment Period Study Visits After Day 1

There is no in-clinic cardiac monitoring at Week 1. However, all subjects will undergo Holter monitoring as described in Section 10.5.7.5 at the Week 1 visit.

After the Day 1/Baseline study visit, a visit window of ± 1 day is permitted for the Week 1 (Cohort 2 only) and a visit window of ± 3 days is permitted for the other study visits during the 24-Week Double-Blind Treatment Period.

Negative pregnancy test results must be documented for all women of childbearing potential prior to dosing at each study visit where study drug is administered. At each study visit, blood sample collections should be performed prior to dosing unless specified otherwise (eg, postdose PK assessments).

Subjects who discontinue treatment prematurely should have an ET visit within 1 week of when the last dose of study drug was taken (Section 9.5).

9.3. Open-Label Extension Period

After completing the 24-week Double-Blind Treatment Period, eligibility for participation in the Open-Label Extension Period will be determined (Section 4.3). All eligible subjects in Cohort 1 will receive etrasimod 2 mg orally, for at least 1 week during the Open-Label Extension Period. Subjects in Cohort 1 will transition to 3 mg at the Week 25 visit or at their next Open-Label Extension 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 Open-Label Extension Period and then transition to etrasimod 3 mg orally, once daily for the remainder of the Open-Label Extension Period. Subjects from Cohort 1 who are 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. A visit window of ± 3 days is permitted for all study visits during the 28-week Open-Label Extension Period, except for Week 25, for which a visit window of ± 1 day is permitted.

For subjects that continue into the Open-Label Extension Period cardiac monitoring will be performed for at least 4 hours after dosing, as outlined in Section 10.5.7.4.

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

Subjects will undergo Holter monitoring as described in Section 10.5.7.5 after dosing at the Week 24 visit, and at the Week 25 visit or following transition from 2 mg to 3 mg in the Open-Label Extension Period.

If a subject ends study drug prior to Week 52, the ET visit assessments (ie, Week 52 assessments; Section 9.5) should be performed within 1 week of the last dose of study drug.

9.4. Follow-Up/End of Study

Subjects who complete the Open-Label Extension Period will return for Safety Follow-Up Visits 2 weeks (± 3 days) and 4 weeks (± 3 days) after the last dose of study drug (which corresponds

to Week 54 and Week 56, respectively). Visit assessments are detailed in the Schedules of Assessments (Appendix 1 and Appendix 2).

Subjects who terminate the study drug early in the Double-Blind Treatment Period or Open-Label Extension Period should have Safety Follow-Up Visits 2 weeks (± 3 days) and 4 weeks (± 3 days) after the last dose of study drug.

The final Safety Follow-Up Visit (ie, SFU 2) will also be the End of Study Visit.

All AEs should be recorded for up to 30 days after last dose of study drug (Section 10.5.8.2.2).

9.5. Early Study Drug Termination

Subjects who stop taking study drug before Week 52 will return to the clinic for an ET visit. ET visit assessments are detailed in the Schedules of Assessments (Appendix 1 and Appendix 2). The ET visit should occur within 1 week of the last dose of study drug. Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible. Lymphocyte counts should be monitored until returned to approximately Baseline or stable. Whenever possible, subjects should continue in the study even if study drug has been discontinued. Subjects who discontinue study drug, but who consent to remain in the study will continue to comply with study visits and assessments.

Subjects who terminate the study drug early in the Double-Blind Treatment Period or Open-Label Extension Period should have Safety Follow-Up Visits 2 weeks and 4 weeks (± 3 days) after the last dose of study drug as described in Section 9.4.

9.6. End of Study Visit

The End of Study Visit for an individual subject is defined as the date of the final study contact (eg, the final Safety Follow-Up Visit [ie, SFU 2]) when assessments or procedures are done.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1. Subject Informed Consent

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject before any study-specific activities are performed (Section 12.3).

10.2. Screening and Eligibility

Subject eligibility will be assessed based on protocol inclusion and exclusion criteria as outlined in Section 4.1 and Section 4.2. All Screening evaluations must be completed and reviewed to confirm potential subjects meet all eligibility criteria.

Screening procedures must be completed within 28 days prior to receiving the first dose of study drug (Appendix 1 and Appendix 2).

An additional eligibility assessment will be performed at Week 24 to determine eligibility to continue into the Open-Label Extension Period, as outlined in Section 4.3.

10.2.1. Rescreening

If a subject fails ≥ 1 Screening laboratory (or other) assessment criteria, the assessment(s) may be repeated once at the discretion of the Investigator, and the subject may be randomized if criteria are then met, provided the assessments are completed within the Screening Period. Any rescreening laboratory assessments beyond 1 time will need to be discussed with the Medical Monitor before proceeding.

If a subject fails Screening, then 1 re-screening attempt during a new Screening Period may be made, if appropriate. Each subject must be reconsented prior to each Screening attempt.

10.2.2. Demography and Other Subject Characteristics

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

10.2.3. Social History

The amount and duration of tobacco and alcohol use will be collected at Screening.

A standard urine drug screen (Table 5) will be performed at Screening and Day 1. Subjects who test positive will be assessed for eligibility to participate by the Investigator.

10.2.4. Prior and Ongoing Therapies

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

10.2.5. Medical History/Alopecia Areata History

A complete medical history of each subject will be collected and documented during Screening and Day 1 to determine subject eligibility. The history should include recent blood donations (within 30 days), illnesses, hospitalizations, and participation in other investigational drug studies.

A detailed history of the subject's AA, including date of diagnosis and disease severity over time will be collected during Screening.

10.2.6. Pregnancy Testing

A serum pregnancy test for beta-human chorionic gonadotropin (β-hCG) will be performed at Screening on women of childbearing potential to determine eligibility. Post-Screening urine pregnancy tests (β-hCG) should be performed as indicated in the Schedules of Assessments (Appendix 1 and Appendix 2). A monthly home pregnancy test in non-visit months (Weeks 32, 40, and 48) should be performed and any positive result immediately reported to the Investigator. If at any point there is a case of a positive urine β-hCG test, the subject will have study drug interrupted and a serum sample will be submitted to the central laboratory for β-hCG testing. If the serum test confirms positive, the subject will be discontinued from the study drug and all the necessary follow-up will be conducted as per Section 10.5.9. If the serum test is negative, the subject may resume study drug.

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

10.2.7. Active Infections or Live Vaccines

Given the mechanism of action of etrasimod and the known pharmacodynamic effect of lymphocyte lowering, subjects with known active infections will be excluded from the study. Live vaccinations and live-attenuated vaccines cannot be administered within 4 weeks of Screening, during Screening, during the Treatment Periods with study drug, or prior to study completion. Refer to Section 6.9 for additional information on vaccines.

10.2.7.1. Known Active Infections

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

10.2.7.2. Known or Suspected Immunodeficiencies

Subjects who have known or suspected immunodeficiencies will be excluded from the study; for example, subjects who have any of the following conditions or risk factors:

a. Primary or secondary immunodeficiency syndromes (eg, hereditary immunodeficiency syndrome, acquired immunodeficiency syndrome, drug-induced immune deficiency)
b. History of organ transplant (except corneal transplant)
c. History of an opportunistic infection (eg, *Pneumocystis jirovecii* pneumonia, cryptococcal meningitis, PML)
d. History of disseminated herpes simplex or disseminated herpes zoster, or any episode of herpes zoster
e. Test positive for HIV, hepatitis B (positive for HBsAg), or active hepatitis C (positive hepatitis C antibody with detectable viral load) at Screening

10.2.8. Tuberculosis

TB screening should be done via an interferon-gamma release assay (IGRA) (eg, QuantiFERON-TB PLUS) in all subjects except those with a history of active or latent TB. In countries where IGRA testing is not approved/registered, a tuberculin skin test will be performed to screen for TB. Refer to Appendix 3 for details of TB screening and interpretation of test results.

10.3. Efficacy Assessments

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

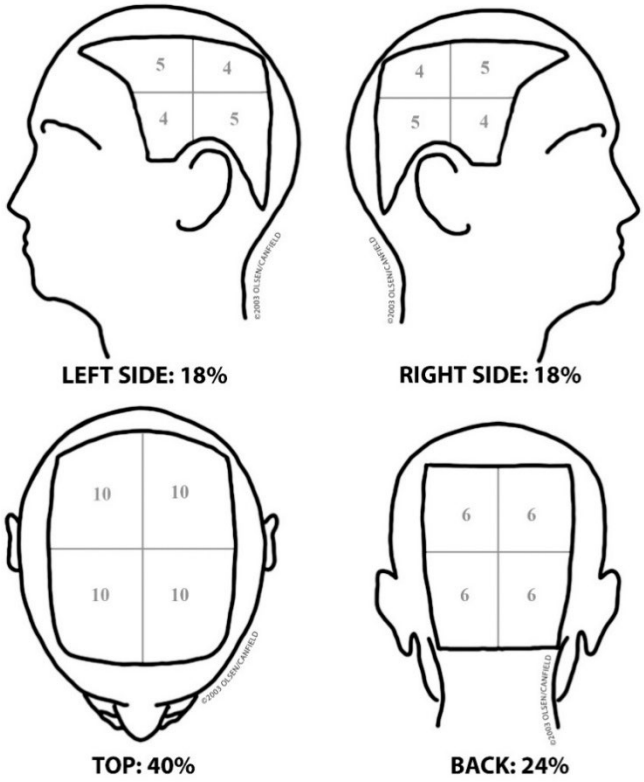
Wherever possible, to maintain consistency, the same individual at the site should administer the investigator assessments for a given subject for the duration of the study.

10.3.1. Severity of Alopecia Tool

To participate in this study, a subject must have moderate-to-severe AA as assessed by a SALT I score of ≥ 50 (Cohort 1) and ≥ 25 and < 95 (Cohort 2) at Screening and Day 1/Baseline as described in Section 4.1.

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 (Olsen 2004). SALT I scores at Screening, Baseline, and Week 24 will also be assessed by central review.

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



Source: (Olsen 2004).

The SALT I will be assessed at timepoints according to the Schedules of Assessments (Appendix 1 and Appendix 2).

10.3.2. Scalp, Eyebrows, Eyelashes, and Fingernails Photography

Standardized photographs of the full scalp should be taken of the 4 views of the head (top, back, and each side of the scalp; Figure 2) at the visits specified in Appendix 1 and Appendix 2. A stereotactic positioning device on which the patient's chin and forehead are fixed, and on which a given camera and flash device are mounted, may be used to assure that the view, magnification, and lighting are the same for all study visits. Photographs will be reviewed by central review to confirm AA severity (moderate to severe) at Screening.

Photographs of the eyebrows and eyelashes for subjects who have hair loss in these areas at Baseline will also be taken as will photographs of the fingernails for subjects with fingernail changes related to AA (eg, pitting, white spots, and roughness) at Baseline.

Any photographs taken of any identifiable features (such as the face, tattoos, or birthmarks) will be de-identified (eg, a masking bar over the eyes). In addition, codes will be used to identify photographs to the appropriate subject.

Subjects are to keep the same hair style and color; Baseline hair parting and combing should be duplicated for post-Baseline photos. Paired comparison of global photographs (before and after treatment) will be performed using central review.

Photographs will be taken at timepoints according to the Schedules of Assessments (Appendix 1 and Appendix 2).

10.3.3. Biomarkers

Blood samples for exploratory serum biomarker analysis will be collected in this study, as specified in the Schedules of Assessments (Appendix 1 and Appendix 2).

Serum from blood samples may be analyzed by specialty laboratory(ies) following completion of the study. Exploratory proteomic analysis may assess the efficacy and mechanism of action of etrasimod. Cytokines and chemokines CCI [redacted] may be measured by enzyme-linked immunosorbent assay, mass spectrometry, or comparable technology. Details for collection, processing, and storage will be provided in the Laboratory Manual.

Residual samples will be stored at a facility selected by the Sponsor for up to 10 years (or in accordance with local regulations) after the last subject's last visit for the study and may be used for future additional analyses to further understand AA, the response to treatment, and the mechanism of action of etrasimod. This may include analyses of biomarker variants thought to play a role in AA. These additional analyses (as appropriate) will only be conducted where allowed by the regulatory authorities and local ethics committees.

10.3.4. Patient-Reported Outcomes

Planned timepoints for all PROs are provided in the Schedules of Assessments (Appendix 1 and Appendix 2).

10.3.4.1. Alopecia Areata Symptom Impact Scale

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 (Mendoza 2018). 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.

10.3.4.2. Alopecia Areata-Related Quality of Life Index

The AA-QLI is a disease-specific questionnaire developed to evaluate the impact of AA on quality of life (Fabbrocini 2013). The AA-QLI has been validated with the Dermatology Life Quality Index (Basra 2015) and shown to provide more comprehensive insights about psychological distress among AA patients specifically. 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. The AA-QLI consists of questions covering 3 areas of daily life: Subjective symptoms, relationships, and objective signs.

10.4. Pharmacokinetic Assessments

Blood samples (4 mL) for plasma analysis of etrasimod will be collected at the following timepoints from all subjects who received ≥ 1 dose of study drug (etrasimod or placebo):

- Predose (within 60 minutes prior to dosing) and at 4 hours (± 15 minutes) postdose (after ECG) on Day 1 and Week 24
- Predose (trough; within 60 minutes prior to dosing) at Weeks 1 (Cohort 2 only), 2, 4, 8, 12, 16, 20, 25, 28, 36, and 44
- Anytime at Week 52 or at the ET visit, and at the follow-up visits, as applicable
- If possible, at the time of any SAE, AE leading to study drug discontinuation, or AE of special interest (AESI). The time of the last study drug dose should be documented

Detailed procedures for blood sample collection and processing will be provided in a separate laboratory manual.

Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of etrasimod with plasma constituents.

PK samples from placebo-treated subjects during the Double-Blind Treatment Period may be selectively assayed.

On study visit days when plasma samples for PK are being collected, subjects should wait to take their assigned dose at the study site after predose blood samples for PK have been drawn and after all predose assessments and procedures have been completed. Subjects should be instructed to document the time of their last dose prior to the study visit and the time must be recorded in the eCRF (Section 6.3). The time of administration of study drug during the study visits where plasma samples for PK are obtained must also be recorded in the source along with the time of each sample.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Planned timepoints for all PK assessments are provided in the Schedules of Assessments (Appendix 1 and Appendix 2).

10.5. Safety Assessments

Planned timepoints for all safety assessments are provided in the Schedules of Assessments (Appendix 1 and Appendix 2).

10.5.1. Vital Signs

Resting vital signs measurements will be made with the subject in the seated position and include HR, BP, body temperature, and respiratory rate. Vital signs will be measured prior to any blood draws that occur at the same study visit or overlapping timepoint. Planned timepoints for vital signs assessments are provided in the Schedules of Assessments (Appendix 1 and Appendix 2).

To minimize the risk of unintentional unblinding of treatment assignment, please refer to guidance regarding disclosure of HR data discussed in Section 6.6.

10.5.2. Physical Examinations

Full physical examination includes the following assessments:

- General inspection
- Cardiac examination
- Auscultation of lungs
- Skin and nails
- Head/eyes/ears/nose/throat
- Neck and thyroid
- Lymph nodes
- Abdomen (liver, spleen, and lower abdomen)
- Musculoskeletal
- Body weight
- Neurological
- Height (Screening only)

Planned timepoints for physical examinations are provided in the Schedules of Assessments (Appendix 1 and Appendix 2). For visits where a full physical examination is not required, symptom-directed physical examinations should assess any new signs or symptoms. Symptom-directed physical examination may be performed at the Investigator's discretion at any time during the study. In addition to a symptom-directed physical examination, assessment at each study visit should include, at a minimum, measurement of weight. Findings will be documented in the eCRF.

10.5.3. Electrocardiography

ECGs will be recorded from a 12-lead ECG machine. Every attempt should be made to ensure the subject ECG readings are obtained using the same machine throughout the study. All 12-lead ECGs will be recorded with subjects in supine position. Planned timepoints for ECG are

provided in the Schedules of Assessments (Appendix 1 and Appendix 2). Parameters to be provided on the confirmed read for each safety ECG are HR and the following intervals: RR, PR, QRS, QT, QT interval corrected (QTc), and QTcF.

The Investigator or designee will be responsible for the initial review and interpretation of 12-lead ECGs on site and assessing if the ECG is normal, abnormal clinically insignificant, or abnormal clinically significant. Findings will be documented in the eCRF. The ECG tracings will also be sent to a central reader for final interpretation.

Specific guidance on ECG following the first dose of study drug during the Double-Blind Treatment and Open-Label Extension Periods is provided in Section 9.2.2 and Section 10.5.7.4.

10.5.4. Clinical Laboratory Assessments

Details regarding clinical laboratory sample collection, preparation, and shipment are provided in the laboratory manual by the central laboratory. All laboratory assessments required by the protocol will be performed by a central laboratory unless otherwise stated. Refer to Table 5 for the list of clinical laboratory tests to be performed and the Schedules of Assessments (Appendix 1 and Appendix 2) for timing and frequency for each test.

Clinical safety laboratory tests should be completed predose. The Investigator must review the laboratory report, document the review, and record any clinically relevant changes on the AE section of the eCRF (results of the white blood cell differential and ALC will be reviewed and monitored as described in Section 10.5.7.2). The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator. If such values do not return to normal or Baseline, or otherwise resolve to a nonclinically significant value within a reasonable period of time, as judged by the Investigator, the etiology should be identified, and the Medical Monitor should be notified. In cases when laboratory values from non-protocol-specified assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the Investigator (eg, AE or dose modification), then the results must be recorded in the eCRF.

Information on the grading and management of laboratory abnormalities according to assessed severity is provided in Appendix 4 and Appendix 5.

Table 5: Clinical Laboratory Tests

Infectious Disease HBsAg, HCV antibody (with reflex PCR), HIV, TB[a]	**Drugs of Abuse** Urine drug screen: amphetamine, barbiturates, benzodiazepines, cocaine metabolites, opiates
Pregnancy and Postmenopausal Status Testing Serum pregnancy test for β-HCG (Screening, only for females of childbearing potential) Urine β-HCG (only for females of childbearing potential) FSH (Screening, only if needed to determine postmenopausal status)	**Coagulation** Activated partial thromboplastin time International Normalized Ratio Prothrombin time
Urinalysis Appearance Bilirubin Color Glucose Ketones Microscopic examination of sediment Nitrite Occult blood pH Protein Specific gravity Urobilinogen	**Hematology** Hematocrit Hemoglobin Lymphocyte subsets (eg, $CD4^+$, $CD8^+$ and NK cells)[b] Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count Red blood cell count White blood cell count with differential[b]
Serum Chemistry Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine with eGFR by CKD-EPI Creatine kinase Gamma-glutamyl transferase Glucose Lactate dehydrogenase	Lipase Magnesium Phosphorus Potassium Sodium Thyroid-stimulating hormone Thyroxine (T4) free Total bilirubin Triiodothyronine (T3) free Direct bilirubin Total cholesterol Total protein Triglycerides Uric acid
Exploratory Biomarkers May be analyzed for changes in cytokines and chemokines from serum samples CCI [redacted]	

[a] TB screening will be done via an IGRA (eg, QuantiFERON-TB PLUS or equivalent assay) in all subjects except those with a history of active or latent TB. In countries where the QuantiFERON-TB PLUS test is not approved/registered, a tuberculin skin test will be performed to screen for TB.

[b] In the Double-Blind Treatment Period, these results will be monitored by an IMM. The IMM not be involved in any other aspects of study conduct or data analysis (Section 10.5.7.2). Investigators will remain blinded to the results.

β-hCG, beta-human chorionic gonadotropin; CD, cluster of differentiation; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; FSH, follicle-stimulating hormone; eGFR, estimated glomerular filtration rate; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IGRA, interferon-gamma release assay; CCI [redacted] IMM, Independent Medical Monitor; NK, natural killer; PCR, polymerase chain reaction; TB, tuberculosis

10.5.5. Pulmonary Function Test

Subjects with known active severe pulmonary disease (eg, chronic obstructive pulmonary disease or pulmonary fibrosis) or chronic pulmonary disease requiring intravenous corticosteroid treatment or hospitalization ≤ 12 months before Screening or during the Screening Period will be excluded from the study.

PFTs will be performed according to the Schedules of Assessments (Appendix 1 and Appendix 2) and include FEV_1, 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. Because carbon monoxide binds readily to hemoglobin, the diffusion capacity needs to be corrected for hemoglobin in order to reflect an altered lung gas transport rather than altered hemoglobin.

Due to the COVID-19 pandemic, access to pulmonary function laboratories and respiratory departments may be restricted or limited. As an option for conducting these assessments, sites may use adequately trained internal or external staff and appropriate equipment. These tests will be conducted in compliance with the standards set forth by the American Thoracic Society (ATS) and the protocol. Reviews of the pulmonary function test measurements will be conducted by a respiratory specialist to ensure that the pulmonary measurements meet these standards. These tests will be conducted in all subjects in a manner consistent with the American Thoracic Society/European Respiratory Society guidelines for standardization of spirometry and single breath determination of carbon monoxide uptake in the lung (MacIntyre 2005, Miller 2005a, Miller 2005b).

Patient respiratory history will be collected at the Screening Visit, and any condition that might affect the outcome of PFT testing, including infection, respiratory symptoms, occupational exposures (including asbestos), and cigarette smoking, will be collected before every PFT and recorded in the eCRF. Furthermore, any issues with subject effort or compliance with the test procedure should be explicitly recorded in the eCRF. This information is important to determine whether PFT abnormalities may be the result of poor effort or compliance with test procedure.

The window to perform PFTs and DLCO is between Day –28 and Day –1 for the Screening Visit, –14 days for the Week 24 visit, and ± 10 days for all other post-screening visits. PFT assessment may be required at the 4-week Follow-Up visit if PFT results at the Week 52 or ET visit demonstrate a clinically significant decrease relative to Baseline. In addition, subjects reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing) should be seen at an unscheduled visit for clinical assessment and full PFT assessment, preferably on the same day. Additional guidance on clinical monitoring of pulmonary functions is provided in Section 10.5.7.5.

10.5.6. Ophthalmoscopy and Optical Coherence

Subjects with a history of or active diabetic retinopathy, uveitis, retinitis pigmentosum or macular edema will be excluded from the study, as well as those with recent intraocular surgery.

A complete ophthalmoscopy and OCT assessment will be performed according to the Schedules of Assessments (Appendix 1 and Appendix 2). The window to perform this testing is between Day –28 and Day –1 for the Screening Visit, –14 days for the Week 24 Visit, and ± 10 days for all other post-screening visits.

A standard visual acuity chart should be used for the visual acuity assessment. The OCT machine used should preferably not be changed during the study to allow for comparison of central foveal thickness measurements within each subject across timepoints.

Screening Visit:

At the Screening Ophthalmology Visit, the eye examination will include:

- Ophthalmologic history
- Best corrected visual acuity measurement (autorefraction, using Snellen chart internationally)
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- Measurement of central foveal thickness by OCT (recorded in micrometers; required for all subjects regardless of the results of visual acuity or ophthalmoscopy)
- Retinal photographs should be taken
- Ophthalmic findings should be recorded
- If there is a suspicion of macular edema by ophthalmoscopy and increased central foveal thickness by OCT, then a fluorescein angiography (FA) may be performed (at the discretion of the ophthalmologist). Subjects with diagnosed macular edema at Screening should be deemed a screening failure and should not be randomized

Scheduled Post-Screening Visits:

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

- Ophthalmic history
- Best corrected visual acuity measurement
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- Measurement of central foveal thickness by OCT
- Retinal photographs should be taken
- Ophthalmic findings should be recorded

Subjects experiencing unexpected ophthalmic symptoms without a known suspected etiology or experiencing a relevant ophthalmic AE may need to have repeated ophthalmoscopy and OCT testing performed. Guidance on clinical monitoring of ophthalmic symptoms is provided in Section 10.5.7.7.

10.5.7. Safety Monitoring Guidance

10.5.7.1. Drug-Induced Liver Injury

Based on US FDA guidance for drug-induced liver injury (FDA 2009), discontinuation of study drug should be considered if any of the following occur:

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

Information on the grading and management of laboratory abnormalities according to assessed severity is provided in Appendix 4 and Appendix 5.

10.5.7.2. Total WBC, WBC Differential, Lymphocyte Counts, and Infections

Etrasimod prevents lymphocyte egress from lymphoid tissues, resulting in a reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. To minimize the risk of unintentional unblinding of treatment assignment, site staff including Investigators will be blinded to total white blood cell (WBC) count, WBC differential (percentage and absolute number), and lymphocyte subset results during the Double-Blind Treatment Period. Investigators should minimize review of WBC count and differential, and lymphocyte subset results obtained by other health care providers caring for study subjects when review of those data is not required to ensure the safety of study subjects.

In the Double-Blind Treatment Period, total WBC count, WBC differential, and lymphocyte subset results will be monitored by an IMM. The IMM will not be involved in any other aspects of study conduct or data analysis. If these laboratory values require follow-up during the Double-Blind Treatment Period, the IMM will notify the Investigator and provide instruction. Blinded values may be released to treating physicians and Investigators as deemed medically necessary.

The Investigator will not be blinded to laboratory results during the Open-Label Extension. Investigators should refer to Appendix 5 for laboratory adverse events aside from ALC decreases.

ALC reduction is an on-target effect of etrasimod treatment. However, if ALC is confirmed below the 0.2×10^9 cells/L limit, study drug should be interrupted and should not be re-initiated if the ALC remains below this threshold. Investigators will repeat complete blood count with differentials weekly until ALC > 0.5×10^9 cells/L. Re-initiation of the study drug should only be considered when ALC > 0.5×10^9 cells/L. If a subject in the Open-Label Extension has a treatment interruption due to ALC < 0.2×10^9 cells/L, then that subject may be re-initiated at 2 mg etrasimod and maintained for the rest of the Open-Label Extension without escalation to 3 mg etrasimod (Section 6.3.2).

Refer to Section 10.5.7.3 for information on monitoring for signs and symptoms of infections and diagnostic work-up and treatment of infections.

10.5.7.3. Guidance on Monitoring Subjects for Infections

Reduction in peripheral lymphocyte count may have immunosuppressive effects. Low lymphocyte counts with the use of other S1P receptor modulators in patients with multiple sclerosis have been associated with serious and atypical infections (GILENYA 2010, MAYZENT 2019).

To date, there have been no reports of PML with the use of etrasimod in clinical studies. Nevertheless, Investigators should remain vigilant in monitoring for signs and symptoms of serious and atypical infections during the study and after discontinuation of study drug (ie, the 4-week Follow-Up Period).

If a subject exhibits signs and symptoms suspicious for PML, study drug must be interrupted and cannot be restarted until diagnostic evaluation is completed and PML has been excluded. The Medical Monitor should be informed of any suspected cases of PML. Refer to Appendix 6 for PML signs and symptoms and case evaluation algorithm. In the evaluation and management of treatment-emergent infections, Investigator may consult with infectious disease or relevant experts, as needed.

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

10.5.7.4. Guidance for Cardiac Monitoring Following Treatment Initiation or Re-Initiation

Cardiac monitoring following treatment initiation applies to both the Double-Blind Treatment (Day 1) and Open-Label Extension (Week 24) Periods. Cardiac monitoring may also be necessary to re-initiate study drug after dosing interruption (refer to Section 6.3.2).

Pre-randomization (ie, Baseline) and Week 24 predose vital signs (resting HR, BP, body temperature, and respiratory rate) will be used as the Baseline measurements for each respective visit. The lowest predose HR measurement will be used for comparison to the postdose measurement.

To minimize the risk of unintentional unblinding of treatment assignment, please refer to guidance regarding disclosure of HR data discussed in Section 6.6.

First Dose Heart Rate Monitoring

In-clinic cardiac monitoring, of at least 4 hours following the first dose, will occur on Day 1, Week 24 and at treatment re-initiation and will include the following (Table 6):

- Full Baseline vital signs (HR, BP, body temperature, and respiratory rate) and 12-lead ECG will be assessed pre-randomization (ie, Baseline) for Day 1 and predose for Week 24.
- Holter monitoring will be performed as described in Section 10.5.7.5.
- After the dose of study drug on Day 1 and, Week 24, and for the first dose when a subject re-initiates study drug, subjects must remain under direct observation in the clinic for at least 4 hours.
- At Hours 1, 2, and 3 (± 15 minutes) postdose, HR and BP will be assessed via vital signs with the subject in the seated position, with the time recorded. If the subject has an HR < 50 bpm, or if cardiovascular symptoms develop (eg, chest pain, dizziness, palpitations, and/or syncope associated with reduction of HR), the subject should

remain closely monitored, including 12-lead ECGs as clinically indicated, until the Hour 4 discharge assessment.

- At the Hour 4 (± 15 minutes) discharge assessment, HR and BP will be assessed via vital signs with the subject in the seated position; a 12-lead ECG in the supine position will also be performed. Subjects may be discharged from the clinic after the 4-hour assessment if they meet the criteria described in Table 7. Subjects not meeting the discharge criteria will require extended monitoring as described below.
- Subjects experiencing a clinically relevant treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, and/or syncope) associated with reduction of HR together with clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period should be discontinued from study drug (Table 8).

Table 6: Procedures to be Performed During the Cardiac Monitoring Period

Procedure	Predose	Hours 1, 2, and 3 Postdose[a]	Hour 4 Postdose[a]
Blood pressure and heart rate[b]	X	X	X
12-lead electrocardiogram	X		X
Holter monitor[c]	X		
Assess discharge criteria			X

[a] Measurements may be taken ± 15 minutes of the scheduled time.
[b] Heart rate is based on vital signs.
[c] Monitoring from 15 minutes before dosing until Hour 8 (± 15 minutes) postdose (Section 10.5.7.5).

Table 7: Discharge Criteria After Cardiac Monitoring

Subjects will be released from the clinical site after dosing on Day 1 and Week 24 (but no sooner than 4 hours postdose) when they fulfill the following discharge criteria:
• Vital sign heart rate ≥ 50 bpm
• If vital sign heart rate < 50 bpm, then the decrease from Baseline must be < 10 bpm
• No evidence from ECG of second-degree AV block or higher
• No patient-reported cardiac symptoms (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope)

Note: Subjects should have written instructions on when to return to the clinic and a 24-hour contact phone number to call in the event of any new or worsened cardiovascular symptoms.
AV, atrioventricular; bpm, beats per minute; ECG, electrocardiogram

Extended Cardiac Monitoring

Subjects who do not meet discharge criteria at 4 hours postdose will require extended cardiac monitoring:

- Vital signs will be assessed hourly and a 12-lead ECG may be performed, as clinically indicated, until the subject meets the discharge criteria (Table 7).
- The Medical Monitor should be contacted if the subject does not meet the discharge criteria after ≥ 4 hours of extended cardiac monitoring.

- Any subject who requires extended monitoring must return the following day for the subsequent dose and will be re-monitored as on the previous day. These subjects will be discontinued from study drug if they do not meet the discharge criteria at 4 hours after the subsequent dose during re-monitoring. Extended cardiac monitoring should be continued until the subject meets the discharge criteria (Table 7).
- Subjects experiencing a symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, and/or syncope) at any time during the 4-hour monitoring period that is not associated with either a reduction in HR or clinically relevant change in 12-lead ECG, may be discharged provided they meet the discharge criteria (Table 7), as deemed appropriate by the Investigator; however, these subjects must return the following day for the subsequent dose and will be re-monitored as on the previous day. These subjects should be discontinued from treatment if they do not meet the discharge criteria at 4 hours after the subsequent dose during re-monitoring and extended cardiac monitoring should be continued until the subject meets the discharge criteria (Table 7).

Study Drug Discontinuation Related to Postdose Cardiac Monitoring

A complete list of reasons for study drug discontinuation is provided in Section 8.1. Reasons for study drug discontinuation specific to postdose cardiac monitoring are provided in Table 8. The Medical Monitor should be contacted before discontinuing a subject from study drug.

Table 8: Discontinuation of Study Drug Related to Postdose Cardiac Monitoring

Reasons for Study Drug Discontinuation Related to Postdose Cardiac Monitoring[a]
• Subjects who have a cardiovascular treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, and/or syncope) associated with reduction of the HR or associated with clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period on Day 1 or Week 24 (or the following day during re-monitoring as applicable).
• Subjects who have not met the discharge criteria on Day 1 or Week 24 after ≥ 4 hours of extended monitoring, or the subsequent day during re-monitoring by 4 hours postdose.

[a] All treatment discontinuations should be discussed with the Medical Monitor.
ECG, electrocardiogram; HR, heart rate

Cardiac Monitoring Upon Treatment Re-Initiation Following Dose Interruption

The procedure for first-dose cardiac monitoring as outlined should be performed and discussed with the Medical Monitor any time a subject misses study drug dosing as follows:

- ≥ 2 consecutive days within the first week of study drug during the Double-Blind Treatment Period and within the first week of study drug during the Open-Label Extension Period
- ≥ 7 consecutive days after the first week of study drug during the Double-Blind Treatment Period and after the first week of study drug during the Open-Label Extension Period

If these doses of study drug are missed, subjects must contact the Investigator to discuss treatment re-initiation and are required to return to the study site before taking their next dose of study drug at the study site.

10.5.7.5. Holter Monitoring

Continuous Holter recording will be performed for subjects from 15 minutes pre-treatment through 8 hours post-treatment any time a subject transitions from 2 mg to 3 mg etrasimod and at all timepoints specified in Appendix 1 and Appendix 2. A subject will be discharged from the study site with the Holter monitor in place and continue to wear the Holter monitor until Hour 8 (± 15 minutes) post-treatment administration. Subjects will be instructed how to remove and store the Holter monitor, record the time the device is removed, and to return the device for analysis at the next in-person study visit. If the subject requires extended in-clinic cardiac monitoring ≥ 8 hours, the Holter will be removed on-site at Hour 8 prior to discharge. Holter data will be captured on the device and sent to the Holter laboratory. The Holter laboratory will be responsible for central reading, analysis, and interpretation. Holter recording results may be made available to study sites.

Holter recording will principally be used for determination of HR and potential arrhythmias (eg, pauses, AV block). Point estimates will be obtained at specified times. The central Holter laboratory may determine additional parameters or perform additional analyses from digitized Holter monitor recordings including but not limited to those indicated by the initial analyses or safety events. Additional information is provided in the Holter manual.

10.5.7.6. Pulmonary Function Monitoring

Based on changes in pulmonary function observed with the use of S1P receptor modulators fingolimod and siponimod, approved for relapsing multiple sclerosis (GILENYA 2010, MAYZENT 2019), pulmonary function will be assessed in this study at Screening, Week 12, Week 24, Week 52, and ET if applicable (Appendix 1 and Appendix 2).

Subjects experiencing clinically significant dyspnea or other respiratory AEs may need to have additional PFT testing as clinically indicated. Severity of respiratory AEs should be categorized using the CTCAE scale described in Appendix 4. Investigators should consider interruption of study drug when there is a clinically significant respiratory AE considered related to study drug that leads to limitations in instrumental or self-care activities of daily living. The decision to interrupt study drug should be discussed with the Medical Monitor. Subjects should be promptly referred to a pulmonologist for further evaluation and treatment. The pulmonologist should be provided with a standard referral letter explaining the reason for the referral along with information about the investigational drug. Clinically significant respiratory AEs should be followed until there is stability, improvement, or resolution.

Re-initiation of study drug can only be considered if the respiratory AE has improved, stabilized, and/or resolved, the individual risk-benefit is favorable (as determined by the Investigator, in agreement with the pulmonologist) and after discussion with the Medical Monitor.

10.5.7.7. Ophthalmic Symptom Monitoring

Based on reports of macular edema observed with the use of S1P receptor modulators fingolimod and siponimod, approved for relapsing multiple sclerosis (GILENYA 2010, MAYZENT 2019), ophthalmic testing, including OCT, will be assessed in this study at Screening, Week 12, Week 24, Week 52, and ET if applicable (Appendix 1 and Appendix 2).

Subjects experiencing unexpected ophthalmic symptoms, including blurred vision, decreased visual acuity, or other clinically significant ocular AEs, without a known/suspected etiology may need to have repeated ophthalmoscopy and OCT testing performed. If there is evidence of new onset macular edema considered related to study drug, then study drug should be interrupted as appropriate and the subject should be monitored closely with the appropriate diagnostic and clinical work-up.

Unscheduled ophthalmology visits in case of any visual complaint:

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

At an unscheduled ophthalmology visit, the eye examination will include

- Best corrected visual acuity measurement
- Ophthalmoscopy (may include contact lens biomicroscopy to examine the macula and optic disc)
- OCT for all subjects to investigate a suspected diagnosis of macular edema

Note: For both scheduled and unscheduled visits, in case of suspected macular edema based on the ophthalmoscopy or a relevant increase of central foveal thickness, then FA may be performed.

Subjects with a diagnosis of macular edema considered related to study drug during the study must interrupt the study drug. These subjects must be followed up monthly with ophthalmologic evaluations until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of not less than 3 months). These evaluations will include repeated best-corrected visual acuity, fundus examination, and OCT. FA may also be performed at the discretion of the ophthalmologist. If the subject does not show definite signs of improvement on examination by specialist testing (eg, OCT, FA) after interruption of study drug, then therapy for macular edema in conjunction with an ophthalmologist experienced in the management of this condition should be initiated at the Investigator's discretion.

For subjects diagnosed with macular edema, copies of the colored OCT and FA images (if conducted) should be kept by the investigative site as source documents. These documents may need to be submitted for review by an independent panel.

10.5.8. Adverse Events

10.5.8.1. Definitions

10.5.8.1.1. Adverse Event

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

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

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

Information on the grading and management of laboratory abnormalities according to assessment severity is provided in Appendix 4 and Appendix 5, respectively.

10.5.8.1.2. Serious Adverse Event

An AE should be classified as an SAE if it meets 1 of the following criteria:

Fatal:	The AE resulted in death.
Life-threatening:	The AE placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this definition.
Disabling/ incapacitating:	The AE resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the study drug before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent 1 of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

Additionally, in this study, any diagnosis of PML will be considered an SAE.

10.5.8.1.3. Adverse Drug Reaction

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

10.5.8.1.4. Adverse Events of Special Interest

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

10.5.8.1.5. Severity

The severity of each AE will be assessed at the onset by the Investigator. When recording the outcome of the AE, the maximum severity of the AE experienced will also be recorded. The severity of each AE will be graded according to the CTCAE:

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

Additional information on CTCAE grading of AEs is provided in Appendix 4.

10.5.8.1.6. Relationship

The Investigator is obligated to assess the relationship (causal relationship) between the study drug and each occurrence of each AE. The AE relationship (causal relationship) to study drug must be characterized as 1 of the following categories:

Not Related:	The AE does not follow a reasonable temporal sequence from administration of the drug, does not abate upon discontinuation of the drug, does not follow a known or hypothesized cause-effect relationship, and (if applicable) does not reappear when the drug is reintroduced, furthermore, there may exist a clear alternative medical explanation (eg, underlying disease state) or association with study procedure or study conduct.
Unlikely Related:	The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
Probably Related:	The AE follows a reasonable temporal sequence from administration of the drug and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject.

Related:	The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

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

10.5.8.2. Eliciting, Recording, and Reporting Adverse Events

10.5.8.2.1. Eliciting Adverse Events

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

10.5.8.2.2. Recording Adverse Events

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

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

Investigator and study personnel will record all AEs and SAEs whether received through an unsolicited report by a subject, elicited during subject questioning, discovered during physical examination, laboratory testing, and/or other means by recording them on the eCRF and SAE Report Form, as appropriate. The following information should be recorded on the AE eCRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study drug or other causality
- Action taken with study drug

- Outcome

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

The following should be considered when recording SAEs:

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

10.5.8.2.3. Diagnosis Versus Signs or Symptoms

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

10.5.8.3. Reporting Serious Adverse Events

All SAEs are subject to reporting requirements.

10.5.8.3.1. Serious Adverse Events

All SAEs, whether or not considered related to study drug, must be reported to the Sponsor Contact **within 24 hours of becoming aware of the event**. In addition, a completed report using the Sponsor's SAE Report Form must be submitted within 24 hours of awareness to the designated Sponsor Contact.

If additional follow-up information is required or becomes available for a previously reported SAE, the new information should be reported to the designated Sponsor Contact **within 24 hours of awareness.**

Elective hospitalization and/or surgery for clearly pre-existing conditions (eg, a surgery that has been scheduled prior to the subject's entry into the study) will not be reported as an SAE.

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

10.5.8.3.2. Serious, Unexpected Adverse Drug Reactions

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

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

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

10.5.9. Pregnancy

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

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

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

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

10.6. Procedures for Overdose

The current version of the IB should be referenced for overdose procedures.

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

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

1. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow AE reporting process, including contacting the Medical Monitor.
2. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of study drug, if possible, and if requested by the Medical Monitor.
3. Document the total quantity of the excess dose, taking into consideration the duration of the overdose in the eCRF and the time frame.

Subjects who overdose will be counseled on correct dosing and administration of study drug. Decisions regarding study discontinuation, dose interruptions, or dose modifications will be

made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

11. PLANNED STATISTICAL METHODS

11.1. General Considerations

Statistical considerations will be discussed in Section 11.2 to Section 11.9 for the Double-Blind Treatment Period, and in Section 11.10 for the Open-Label Extension Period. An analysis of efficacy and safety data will be performed after all subjects have completed or early terminated from the 24-week Double-Blind Treatment Period. A final analysis of efficacy and safety data will be performed once all subjects completed or early terminated from the study. Details regarding the statistical analyses will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock of the double-blind portion of the study.

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

All summaries, statistical analyses, and individual subject data listings described in this section will be produced using SAS® (Version 9.4 or later; SAS Institute, Inc. Cary, NC).

11.2. Determination of 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%.

11.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined (Table 9).

Table 9: Analysis Sets

Analysis Set	Description
Randomized Set	The Randomized Set includes all randomized subjects, irrespective of whether they received any study drug.
Full Analysis Set (FAS)	The FAS includes all randomized subjects with a SALT I < 95 at Baseline, irrespective of whether they received any study drug.
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.
Per Protocol Set	The Per Protocol Set consists of all subjects in the FAS who adhere to the protocol. The Per Protocol Set will be used in sensitivity analyses of the primary and key secondary endpoints to evaluate the influence of major protocol violators and protocol deviators on the primary results. Subjects may be excluded from this set if they violate the eligibility criteria or significantly deviate from the study plan. Specific reasons for warranting exclusion from this set will be documented prior to database lock and may include, but are not limited to, study drug noncompliance, receiving incorrect study drug, missing more than a defined number of visits while still on study, and chronic prohibited medication use while on study drug. The list of major protocol violations and protocol deviations that exclude subjects from the Per Protocol Set will be finalized prior to database lock.
Safety Set	The Safety Set consists of all randomized subjects who received at least 1 dose of study drug.
Pharmacokinetic Set	The Pharmacokinetic Set consists of all randomized subjects who received at least 1 dose of etrasimod and with at least 1 postdose PK measurement.

11.4. Handling of Dropouts and Missing Data

All available data will be presented in descriptive summaries and included in statistical models as appropriate. All subjects who are included in the full analysis set (FAS), modified FAS (mFAS), Safety Set, or Pharmacokinetic Set will be included in analyses, and their missing data will not be imputed. For dichotomous efficacy endpoints, subjects with missing data for any reason will be considered as a ‘non-responder’ or ‘failure’.

11.5. Demographics and Baseline Characteristics

Demographics and Baseline characteristics will be summarized for the FAS and Safety Set. The summaries of data will include frequencies and percentages for categorical variables and mean, SD, median, minimum, and maximum for continuous variables.

11.6. Efficacy Analyses

The primary and secondary endpoints will be analyzed using the FAS. The exploratory endpoints will be analyzed using the FAS and the Randomized Set. Other important statistical

considerations, such as missing data imputation strategies, sensitivity analyses, and subgroup analyses will be described in the SAP.

The primary endpoint of percent change from Baseline to Week 24 in SALT I will be analyzed with a mixed-effects model repeated measures (MMRM) model. The MMRM model will include treatment group, visit, and interaction of treatment-by-visit as factors, and disease duration and Baseline SALT I score as covariates. An unstructured covariance matrix will be specified for the MMRM model. Least squares (LS) means at each visit and LS mean differences between treatment groups (each of the active arms versus placebo only) with p-values and corresponding 95% confidence intervals (CIs) will be reported. This method will also be applied to other score-based or continuous measures.

Proportion-based secondary endpoints at Week 24 will be analyzed using the Cochran-Mantel-Haenszel test method adjusted for the randomization stratification factor SALT I (< 50, ≥ 50) at Baseline. Subjects with missing data for any reason will be considered as 'non-responder' or 'failure' for the endpoint. The number and percentage of subjects achieving the goal and the difference in proportion between treatment groups achieving the goal, along with p-values and the 95% CIs, will be reported.

11.6.1. Endpoint Definitions

Efficacy will be assessed by changes in AA as measured by SALT I score. PROs will be assessed using the AASIS and AA-QLI. The definitions used to assess efficacy outcomes are described in Section 11.6.1.1 to Section 11.6.1.4.

11.6.1.1. Primary Efficacy Endpoint

- Percent change from Baseline in SALT I at Week 24

11.6.1.2. 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

11.6.1.3. 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 AASIS at Week 24
- Change from Baseline in 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

11.6.1.4. Efficacy Assessments During the Open-Label Extension Period

These efficacy outcomes will be measured at scheduled visits up to 52 weeks: SALT I; peripheral lymphocyte counts; AASIS; AA-QLI; serum biomarkers; and photographs 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.

11.6.2. Pharmacokinetics

- Plasma concentrations of etrasimod will be assessed from samples collected prior to dosing and 4 hours (± 15 minutes) postdose (after ECG) on Day 1 and Week 24.
- Plasma concentrations of etrasimod will be assessed 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, 25, 28, 36, and 44.
- Plasma concentrations of etrasimod will be assessed from samples collected anytime at Week 52 or at the ET visit, and the follow-up visits, as applicable.

The Pharmacokinetic Set will be used to analyze plasma levels. A descriptive summary of observed plasma concentration will be displayed by time and by treatment group.

Full details of PK analysis will be provided in the SAP.

11.6.3. Subgroup Analyses

The following major subgroup analyses for the primary and secondary efficacy endpoints will be performed to explore whether the treatment effects are consistent across different subgroups:

- Sex (male, female)
- Race (white, non-white)
- Age (≤ or > median)
- Baseline SALT I score (≤ or > median)
- Baseline SALT I score (< 50 or ≤ 50)

The SAP will provide a complete list and definition of the subgroups and analysis methods.

11.7. Testing Strategy

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

11.8. Interim Analysis

No formal interim analysis of efficacy is planned. Periodic blinded assessments of the assumption regarding the SD of the percent change in SALT I from Baseline to Week 24 will be conducted. The planned sample size will not be reduced as a result of the SD assessments.

11.9. Safety Analyses

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

11.9.1. Safety Endpoints

- Incidence and severity of AEs
- Incidence and severity of laboratory abnormalities and change from Baseline in laboratory values (to include hematology, serum chemistry, coagulation, and urinalysis)
- Incidence of clinically significant vital sign abnormalities and changes from Baseline (may include 4 hours postdose on Day 1 and Week 24)
- ECGs
- Holter Monitoring
- Physical examination findings

11.9.2. Adverse Events

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

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

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

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

11.9.3. Extent of Exposure

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

11.9.4. Clinical Laboratory Parameters

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

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

11.9.5. Holter Recording

Holter recording will principally be used for determination of HR and potential arrhythmias (eg, pauses, AV block). Point estimates will be obtained at specified times. The central Holter laboratory may determine additional parameters or perform additional analyses from digitized Holter monitor recordings including but not limited to those indicated by the initial analyses or safety events. Additional information is provided in the Holter manual.

11.9.6. Electrocardiograms and Vital Signs

Individual ECG values will be listed by visit and summarized using descriptive statistics. Parameters to be provided for each ECG are HR and the following intervals: RR, PR, QRS, QT, QTc, and QTcF. Post-Baseline ECGs for each subject will be compared with the Baseline ECG. Any clinically significant change from Baseline may be recorded as an AE if deemed appropriate by the Investigator, or the Investigator in consultation with the Sponsor or delegate. Outlier analysis will be performed on all subjects with QTcF values > 500 ms or change from Baseline > 60 ms in the absence of Baseline ECG abnormalities that preclude accurate surface ECG assessment of ventricular repolarization (eg, bundle branch block).

Descriptive statistics for vital signs (BP, HR, respirations, and body temperature) will be presented by treatment group.

The change from Baseline for each of the vital signs and ECG parameters will be summarized. Incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

11.9.7. Physical Examination

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

11.10. Statistical Considerations for the Open-Label Extension Period

The objectives of the Open-Label Extension Period are to evaluate long-term safety and efficacy up to 52 weeks.

All safety outcomes will be analyzed using the Safety Set in the Open-Label Extension, which includes all subjects who received at least 1 dose of etrasimod in the Open-Label Extension Period.

Baseline for the Open-Label Extension Period is defined as the last measurement prior to the first etrasimod dose started at Week 24.

Safety analyses will follow general considerations in Section 11.9.2 to Section 11.9.7 with the following exceptions:

- One treatment group in the Open-Label Extension Period and 3 treatment subgroups in the Double-Blind Treatment Period will be analyzed
- Change from Baseline will be analyzed using change from Double-Blind Treatment Period Baseline and change from Open-Label Extension Period Baseline

Only descriptive statistics will be presented for all efficacy assessments during the Open-Label Extension Period. Dichotomous response outcomes derived from specific scores will be assessed. Continuous variables will be summarized by visit using the number of observations, mean, SD, median, minimum, and maximum; and categorical variables will be summarized by visit using frequency counts and percentages.

12. ETHICAL CONSIDERATIONS

12.1. Ethical Conduct of the Study

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

12.2. Institutional Review Board or Independent Ethics Committee Approval

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

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

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

12.3. Informed Consent

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

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

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

12.4. Confidentiality

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

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

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

12.5. Protocol Compliance

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

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

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

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

13. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

13.1. Training of Study Site Personnel

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

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

13.2. Monitoring

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

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

13.3. Audit

Audits of vendors contracted by Arena for this study may be performed. An audit of 1 or more participating study site may be performed independently of, and separately from, routine monitoring to evaluate clinical study conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Management

14.1.1. Case Report Forms

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

The documentation related to the validation of the eCRFs will be maintained in the trial master file (TMF). The TMF will be maintained by the CRO and the Sponsor.

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

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

14.1.2. Source Documents

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

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

14.2. Study Documentation and Records Retention

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

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

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

Records will be available for 2 years after the last marketing application approval, or if the application is not approved or never submitted, 2 years after the appropriate regulatory authorities have been notified of the discontinuation of clinical development of the investigational product. The Sponsor will provide written notification when it is appropriate for the Investigator to discard the study-specific documents referenced above.

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

- If the custody of documentation will be transferred or moved to another location
- If the Investigator is unable to retain documentation for the specified period

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

14.3. Clinical Study Report

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

14.4. Disclosure of Study Results

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

15. RESPONSIBILITIES

15.1. Investigator Responsibilities

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

The Investigator is responsible for ensuring an investigation is conducted according to the signed Investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of drugs

under investigation. An Investigator shall, in accordance with the provisions of 21 CFR Part 50, obtain the informed consent of each human subject to whom the drug is administered.

15.2. Sponsor Responsibilities

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

16. REFERENCES

AAD. COVID-19 vaccine administration guidance. American Academy of Dermatology Association. https://assets.ctfassets.net/1ny4yoiyrqia/2gTpp7G9GNSTtAHwPHNtbc/b23a62ab746ad4672158a0c9633ca7aa/COVID_vaccine_administration_guidance_2-15-21.pdf. Published 2021. Accessed May 12, 2021.

Al Aboud AM, Zito PM. Alopecia. In: Treasure Island (FL): StatPearls Publishing LLC; 2019. On file at Arena.

Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update: Part I. Clinical picture, histopathology, and pathogenesis. *J Am Acad Dermatol.* 2010a;62(2):177-188.

Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update: Part II. Treatment. *J Am Acad Dermatol.* 2010b;62(2):191-202.

Basra MKA, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): Further data. *Dermatology.* 2015;230(1):27-33.

Brinkmann V, Billich A, Baumruker T, et al. Fingolimod (FTY720): Discovery and development of an oral drug to treat multiple sclerosis. *Nat Rev Drug Discov.* 2010;9(11):883-897.

Cabell C. An extension study of APD334-003 in patients with moderately to severely active ulcerative colitis. San Diego, CA: Arena Pharmaceuticals, Inc.; July 30, 2019. Clinical Study Report APD334-005. On file at Arena.

Cabell CH. A Phase 2, randomized, double-blind, placebo-controlled, parallel group, multi-center study to investigate the safety and efficacy of APD334 in patients with moderately to severely active ulcerative colitis. San Diego, CA: Arena Pharmaceuticals, Inc.; July 30, 2018. Clinical Study Report APD334-003. On file at Arena.

Camm J, Hla T, Bakshi R, Brinkmann V. Cardiac and vascular effects of fingolimod: Mechanistic basis and clinical implications. *Am Heart J.* 2014;168(5):632-644.

de Hollanda TR, Sodre CT, Brasil MA, Ramos-e-Silva M. Quality of life in alopecia areata: A case-control study. *Int J Trichology.* 2014;6(1):8-12.

Fabbrocini G, Panariello L, De Vita V, et al. Quality of life in alopecia areata: A disease-specific questionnaire. *J Eur Acad Dermatol Venereol.* 2013;27(3):e276-281.

FDA. Drug-induced liver injury: Premarketing clinical evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry Web site. https://www.fda.gov/downloads/guidances/UCM174090.pdf. Published 2009. Accessed April 25, 2019.

Flockhart DA. Drug Interactions Flockhart Table™. Indiana University, Department of Medicine, Clinical Pharmacology. https://drug-interactions.medicine.iu.edu/MainTable.aspx. Published 2019. Accessed November 15, 2019.

GILENYA. Fingolimod capsules, for oral use [Package Insert]. Novartis Pharmaceuticals Corporation. https://www.novartis.us/sites/www.novartis.us/files/gilenya.pdf. Published 2010. Accessed June 7, 2020.

Gilhar A, Etzioni A, Paus R. Alopecia areata. *N Engl J Med.* 2012;366(16):1515-1525.

Hanlon J. The fundamentals of alopecia areata. HealthPrep. https://healthprep.com/conditions/fundamentals-of-alopecia-areata/?utm_source=bing&utm_medium=search&utm_campaign=328752041&utm_content=1139094607077362&utm_term=alopecia%20areata&msclkid=b8a3ab0ecb5c1d240a42f6aa273b93d5. Published 2019. Accessed October 24, 2019.

Hordinsky M, Donati A. Alopecia areata: An evidence-based treatment update. *Am J Clin Dermatol.* 2014;15(3):231-246.

Islam N, Leung PSC, Huntley AC, Gershwin ME. The autoimmune basis of alopecia areata: A comprehensive review. *Autoimmun Rev.* 2015;14(2):81-89.

Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med.* 2010;362(5):387-401.

MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J.* 2005;26(4):720-735.

MacLean KJ, Tidman MJ. Alopecia areata: More than skin deep. *Practitioner.* 2013;257(1764):29-32.

MAYZENT. Siponimod tablets, for oral use [Package Insert]. Novartis Pharmaceuticals Corporation. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/mayzent.pdf. Published 2019. Accessed April, 2019.

Mendoza TR, Osei J, Duvic M. The utility and validity of the Alopecia Areata Symptom Impact Scale in measuring disease-related symptoms and their effect on functioning. *J Investig Dermatol Symp Proc.* 2018;19(1):S41-S46.

Mikhaylov D, Pavel A, Yao C, et al. A randomized placebo-controlled single-center pilot study of the safety and efficacy of apremilast in subjects with moderate-to-severe alopecia areata. *Arch Dermatol Res.* 2019;311(1):29-36.

Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J.* 2005a;26(1):153-161.

Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005b;26(2):319-338.

Nielsen OH, Li Y, Johansson-Lindbom B, Coskun M. Sphingosine-1-phosphate signaling in inflammatory bowel disease. *Trends Mol Med.* 2017;23(4):362-374.

Olsen EA, Hordinsky MK, Price VH, et al. Alopecia areata investigational assessment guidelines--Part II. *J Am Acad Dermatol.* 2004;51(3):440-447.

Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature.* 2010;466(7302):113-117.

Peyrin-Biroulet L, Panes J, Chiorean MV, et al. Histologic remission and mucosal healing in a randomized, placebo-controlled, Phase 2 study of etrasimod in patients with moderately to severely active ulcerative colitis. *Gastroenterology.* 2019;156(6):S-217.

Plowman JE, Harland DP. The follicle cycle in brief. In: Plowman JE, ed. *The Hair Fibre: Proteins, Structure and Development, Advances in Experimental Medicine and Biology.* Vol 1054. Springer Nature Singapore Pte Ltd.; 2018:15-17.

Renert-Yuval Y, Guttman-Yassky E. The changing landscape of alopecia areata: The therapeutic paradigm. *Adv Ther.* 2017;34(7):1594-1609.

Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ, 3rd. Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. *Mayo Clin Proc.* 1995;70(7):628-633.

Sandborn WJ, Feagan BG, Wolf DC, et al. Ozanimod induction and maintenance treatment for ulcerative colitis. *N Engl J Med.* 2016;374(18):1754-1762.

Sandborn WJ, Peyrin-Biroulet L, Trokan L, et al. A randomized, double-blind, placebo-controlled trial of a selective, oral sphingosine 1-phosphate (S1P) receptor modulator, etrasimod (APD334), in moderate to severe ulcerative colitis (UC): Results from the OASIS study. *Am J Gastroenterol.* 2018;113(Suppl):S327-S328.

Sandborn WJ, Peyrin-Biroulet L, Zhang J, et al. Efficacy and safety of etrasimod in a Phase 2 randomized trial of patients with ulcerative colitis. *Gastroenterology.* 2020;158:550-561.

Sardesai VR, Prasad S, Agarwal TD. A study to evaluate the efficacy of various topical treatment modalities for alopecia areata. *Int J Trichology.* 2012;4(4):265-270.

Solomon JA. Development of uniform protocol for alopecia areata clinical trials. *J Investig Dermatol Symp Proc.* 2015;17(2):63-66.

Vaclavkova A, Chimenti S, Arenberger P, et al. Oral ponesimod in patients with chronic plaque psoriasis: A randomised, double-blind, placebo-controlled phase 2 trial. *Lancet.* 2014;384(9959):2036-2045.

Vermeire S, Panes J, Chiorean M, et al. Long-term efficacy and safety of etrasimod for ulcerative colitis: Results from the open-label extension of the OASIS study. United European Gastroenterology Week (UEGW); October 19-23, 2019; Barcelona, Spain. On file at Arena.

Villasante Fricke AC, Miteva M. Epidemiology and burden of alopecia areata: A systematic review. *Clin Cosmet Investig Dermatol.* 2015;8:397-403.

Xing L, Dai Z, Jabbari A, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. *Nat Med.* 2014;20(9):1043-1049.

APPENDIX 1: SCHEDULE OF ASSESSMENTS – COHORT 1

Evaluation	Screening Period	Double-Blind Treatment Period								Open-Label Extension Period[a]					Safety Follow-Up Period[b]	
		Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 25	Week 28	Week 36	Week 44	Week 52/ET[c]	SFU 1	SFU 2
Window (days)	**Days –28 to –1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Informed consent	X															
I/E criteria	X	X							X							
Demographics	X															
Medical history[d]	X	X														
Social history, AA history	X															
Physical examination	X[e,f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[e]	X[e]	X[g]	X[g]	X[g]	X[e]		X[e]
Urine drug screen[h]	X	X														
Pregnancy test[i]	X	X		X	X	X	X	X	X		X	X	X	X		X
Infectious disease serology	X															
TB screening	X															
Laboratory tests[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]	X
Randomization		X														
Vital signs[l]	X	X[m]	X	X	X	X	X	X	X[m]	X	X	X	X	X	X	X
12-lead ECG	X	X[n]				X			X[n]			X	X	X		X
Holter monitor[o]									X	X						
Administer study drug in clinic[p]		X	X	X	X	X	X	X	X	X	X	X	X			

Evaluation	Screening Period	Double-Blind Treatment Period								Open-Label Extension Period[a]					Safety Follow-Up Period[b]	
		Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 25	Week 28	Week 36	Week 44	Week 52/ET[c]	SFU 1	SFU 2
Window (days)	**Days −28 to −1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Dispense study drug		X		X	X	X	X	X	X	X	X	X	X			
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X		
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PFT, DLCO[q]	X					X			X					X		
Ophthalmoscopy and OCT[q]	X					X			X					X		
SALT I	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Photography[r]		X				X			X			X	X	X		X
Pharmacokinetics[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarkers (from serum sample)		X				X			X					X		
PRO questionnaires[t]		X				X			X			X		X		X

[a] Subjects who entered 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. 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.

[b] Subjects who complete the Open-Label Extension Period will return for SFU Visits 2 weeks and 4 weeks (± 3 days) after the last dose of study drug (which corresponds to Week 54 and Week 56, respectively). Subjects who terminate the study drug early in the Double-Blind Treatment Period or Open-Label Extension Period should have SFU Visits 2 weeks and 4 weeks (± 3 days) after the last dose of study drug.

[c] If a subject ends study drug prior to Week 52, the ET visit assessments (ie, Week 52 assessments) should be performed within 1 week of the last dose of study drug. Whenever possible, subjects should continue in the study even if study drug has been discontinued.
[d] Includes a review of prior/ongoing medications.
[e] Complete examination, including a general inspection; cardiac examination; auscultation of the lungs; assessments of the skin, nails, head, eyes, ears, nose, throat, neck, thyroid, lymph nodes, abdomen (liver, spleen, and lower abdomen), musculoskeletal, and body weight; and a neurological assessment.
[f] Height will be measured at Screening only.
[g] Symptom-directed examination.
[h] Includes amphetamines, barbiturates, cocaine metabolites, opiates, and benzodiazepines (Table 5).
[i] Only for females of childbearing potential. A monthly home pregnancy test in non-visit months (Weeks 32, 40, and 48) should be performed and any positive result immediately reported to the Investigator (Section 10.2.6). Serum pregnancy test at Screening and urine pregnancy test at all other visits where pregnancy testing is indicated.
[j] Includes serum chemistry, hematology (including coagulation), and urinalysis (Section 10.5.4). FSH at screening, only if needed to determine postmenopausal status. Investigators will be blinded to certain results during the Double-Blind Treatment Period. Refer to Section 10.5.7.2 and Table 5 for additional details.
[k] Hematology only.
[l] Vital signs (resting HR, BP, body temperature, and respiratory rate) will be assessed at all indicated study visits with the subject in the seated position (Section 10.5.1).
[m] Performed prior to randomization for Day 1, predose for Week 24, and at Hours 1, 2, 3, and 4 (± 15 minutes) postdose as part of the first dose cardiac monitoring procedure for Day 1 and Week 24 (Section 10.5.7.4).
[n] Performed prior to randomization for Day 1, predose for Week 24, and at Hour 4 (± 15 minutes) postdose as part of the first dose cardiac monitoring procedure for Day 1 and Week 24 (Section 10.5.7.4).
[o] A Holter monitor will be placed on the subject at the study site and continuous Holter recording should begin approximately 15 minutes before in-clinic dosing. Subjects will be instructed how to remove and store the Holter monitor at Hour 8, record the time the device is removed, and to return the device for analysis at the next in-person study visit. Holter monitoring is required any time a subject escalates from 2 mg to 3 mg etrasimod (eg, subjects who enter the Open-Label Extension Period before implementation of Amendments 2.0 and 2.1 will transition to 3 mg once daily at their next study visit and will require Holter monitoring). Additional details are provided in Section 10.5.7.5.
[p] On study visit days, subjects should be instructed not to take their dose until after their study visit assessments have been completed. On study visit days when plasma samples for PK are being collected, subjects should wait to take their assigned dose at the study site after predose blood samples for PK have been drawn and after all predose assessments and procedures have been completed (Section 6.3). Of note, in case of dose interruption, an unscheduled visit may be planned to re-initiate study drug (Section 6.3.2).
[q] PFTs/DLCO and ophthalmoscopy/OCT may be conducted between Day –28 and Day –1 for the Screening Visit, within 14 days for the Week 24 Visit, and ± 10 days for all other post-screening visits (Section 10.5.5 and Section 10.5.6). Unscheduled PFT assessments should be performed for subjects reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the same day (Section 10.5.5). PFT assessment may be required at the 4-Week Follow-Up Visit if PFT results at the last on-treatment study visit or ET Visit demonstrate a clinically significant decrease relative to Baseline. Unscheduled ophthalmoscopy/OCT assessments may also be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (Section 10.5.7.7).
[r] Photographs of the full scalp will be taken for all subjects, of the eyebrows and eyelashes for subjects who have hair loss in these areas at Baseline, and of the fingernails for subjects with fingernail changes related to AA (eg, pitting, white spots, and roughness) at Baseline (Section 10.3.2).
[s] Collected predose (within 60 minutes prior to dosing) and at 4 hours (± 15 minutes) postdose (after ECG) on Day 1 and Week 24; predose (trough; within 60 minutes prior to dosing) at Weeks 2, 4, 8, 12, 16, 20, 25, 28, 36, and 44; anytime at Week 52 or at the ET visit, and the follow-up visits, as applicable; and if possible, at the time of any SAE, AE leading to study drug discontinuation, or AESI.
[t] PRO measures include AASIS and AA-QLI (Section 10.3.4).

AA, alopecia areata; AASIS, Alopecia Areata Symptom Impact Scale; AA-QLI, Alopecia Areata Quality of Life Index; AE, adverse event; AESI, adverse event of special interest; BP, blood pressure; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; HR, heart rate; I/E, inclusion and exclusion criteria; OCT, optical coherence tomography; PFT, pulmonary function test; PK, pharmacokinetic; PRO, patient-reported outcome; SAE, serious adverse event; SALT I, Severity of Alopecia Tool I; SFU, Safety Follow-Up; TB, tuberculosis

APPENDIX 2: SCHEDULE OF ASSESSMENTS – COHORT 2

Evaluation	Screening Period	Double-Blind Treatment Period									Open-Label Extension Period					Safety Follow-Up Period[a]	
		Day 1	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 25	Week 28	Week 36	Week 44	Week 52/ET[b]	SFU 1	SFU 2
Window (days)	**Days –28 to –1**		**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Informed consent	X																
I/E criteria	X	X								X							
Demographics	X																
Medical history[c]	X	X															
Social history, AA history	X																
Physical examination	X[d,e]	X[f]	X[d]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[d]	X[d]	X[f]	X[f]	X[f]	X[d]		X[d]
Urine drug screen[g]	X	X															
Pregnancy test[h]	X	X			X	X	X	X	X	X		X	X	X	X		X
Infectious disease serology	X																
TB screening	X																
Laboratory tests[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X
Randomization		X															
Vital signs[k]	X	X[l]	X	X	X	X	X	X	X	X[l]	X	X	X	X	X	X	X
12-lead ECG	X	X[m]					X			X[m]			X	X	X		X
Holter monitor[n]		X	X							X	X						

Evaluation	Screening Period	Double-Blind Treatment Period									Open-Label Extension Period					Safety Follow-Up Period[a]	
		Day 1	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 25	Week 28	Week 36	Week 44	Week 52/ET[b]	SFU 1	SFU 2
Window (days)	**Days −28 to −1**		**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**
Administer study drug in clinic[o]		X	X	X	X	X	X	X	X	X	X	X	X	X			
Dispense study drug		X	X		X	X	X	X	X	X	X	X	X	X			
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X		
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PFT, DLCO[p]	X						X			X					X		
Ophthalmoscopy and OCT[p]	X						X			X					X		
SALT I	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Photography[q]	X	X					X			X			X	X	X		X
Pharmacokinetics[r]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarkers (from serum sample)		X					X			X					X		
PRO questionnaires[s]		X					X			X			X		X		X

[a] Subjects who complete the Open-Label Extension Period will return for SFU Visits 2 weeks and 4 weeks (± 3 days) after the last dose of study drug (which corresponds to Week 54 and Week 56, respectively). Subjects who terminate the study drug early in the Double-Blind Treatment Period or Open-Label Extension Period should have SFU Visits 2 weeks and 4 weeks (± 3 days) after the last dose of study drug.

[b] If a subject ends study drug prior to Week 52, the ET visit assessments (ie, Week 52 assessments) should be performed within 1 week of the last dose of study drug. Whenever possible, subjects should continue in the study even if study drug has been discontinued.

[c] Includes a review of prior/ongoing medications.
[d] Complete examination, including a general inspection; cardiac examination; auscultation of the lungs; assessments of the skin, nails, head, eyes, ears, nose, throat, neck, thyroid, lymph nodes, abdomen (liver, spleen, and lower abdomen), musculoskeletal, and body weight; and a neurological assessment.
[e] Height will be measured at Screening only.
[f] Symptom-directed examination.
[g] Includes amphetamines, barbiturates, cocaine metabolites, opiates, and benzodiazepines (Table 5).
[h] Only for females of childbearing potential. A monthly home pregnancy test in non-visit months (Weeks 32, 40, and 48) should be performed and any positive result immediately reported to the Investigator (Section 10.2.6). Serum pregnancy test at Screening and urine pregnancy test at all other visits where pregnancy testing is indicated.
[i] Includes serum chemistry, hematology (including coagulation), and urinalysis (Section 10.5.4). FSH at screening, only if needed to determine postmenopausal status. Investigators will be blinded to certain results during the Double-Blind Treatment Period. Refer to Section 10.5.7.2 and Table 5 for additional details.
[j] Hematology only.
[k] Vital signs (resting HR, BP, body temperature, and respiratory rate) will be assessed at all indicated study visits with the subject in the seated position (Section 10.5.1).
[l] Performed prior to randomization for Day 1, predose for Week 24, and at Hours 1, 2, 3, and 4 (± 15 minutes) postdose as part of the first dose cardiac monitoring procedure for Day 1 and Week 24 (Section 10.5.7.4).
[m] Performed prior to randomization for Day 1, predose for Week 24, and at Hour 4 (± 15 minutes) postdose as part of the first dose cardiac monitoring procedure for Day 1 and Week 24 (Section 10.5.7.4).
[n] Holter monitoring is required at visits indicated and any time a subject escalates from 2 mg to 3 mg etrasimod. A Holter monitor will be placed on the subject at the study site and continuous Holter recording should begin approximately 15 minutes before in-clinic dosing. Subjects will be instructed how to remove and store the Holter monitor at Hour 8, record the time the device is removed, and to return the device for analysis at the next in-person study visit. Additional details are provided in Section 10.5.7.5.
[o] On study visit days, subjects should be instructed not to take their dose until after their study visit assessments have been completed. On study visit days when plasma samples for PK are being collected, subjects should wait to take their assigned dose at the study site after predose blood samples for PK have been drawn and after all predose assessments and procedures have been completed (Section 6.3). Of note, in case of dose interruption, an unscheduled visit may be planned to re-initiate study drug (Section 6.3.2).
[p] PFTs/DLCO and ophthalmoscopy/OCT may be conducted between Day −28 and Day −1 for the Screening Visit, within 14 days for the Week 24 Visit, and ± 10 days for all other post-screening visits (Section 10.5.5 and Section 10.5.6). Unscheduled PFT assessments should be performed for subjects reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the same day (Section 10.5.5). PFT assessment may be required at the 4-Week Follow-Up Visit if PFT results at the last on-treatment study visit or ET Visit demonstrate a clinically significant decrease relative to Baseline. Unscheduled ophthalmoscopy/OCT assessments may also be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (Section 10.5.7.7).
[q] Photographs of the full scalp will be taken for all subjects, of the eyebrows and eyelashes for subjects who have hair loss in these areas at Screening and Baseline, and of the fingernails for subjects with fingernail changes related to AA (eg, pitting, white spots, and roughness) at Baseline (Section 10.3.2).
[r] Collected predose (within 60 minutes prior to dosing) and at 4 hours (± 15 minutes) postdose (after ECG) on Day 1 and Week 24; predose (trough; within 60 minutes prior to dosing) at Weeks 1, 2, 4, 8, 12, 16, 20, 25, 28, 36, and 44; anytime at Week 52 or at the ET visit, and the follow-up visits, as applicable; and if possible, at the time of any SAE, AE leading to study drug discontinuation, or AESI.
[s] PRO measures include AASIS and AA-QLI (Section 10.3.4).

AA, alopecia areata; AASIS, Alopecia Areata Symptom Impact Scale; AA-QLI, Alopecia Areata Quality of Life Index; AE, adverse event; AESI, adverse event of special interest; BP, blood pressure; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; HR, heart rate; I/E, inclusion and exclusion criteria; OCT, optical coherence tomography; PFT, pulmonary function test; PK, pharmacokinetic; PRO, patient-reported outcome; SAE, serious adverse event; SALT I, Severity of Alopecia Tool I; SFU, Safety Follow-Up; TB, tuberculosis

APPENDIX 3: TUBERCULOSIS SCREENING

Review of the subject's medical history must include specific questions about a history of tuberculosis (TB) infection or known occupational or other personal exposure to individuals with active TB. Subjects should be asked about past testing for TB, including results of interferon-gamma release assay (IGRA) (eg, QuantiFERON-TB or equivalent assay) or response to tuberculin skin test (TST), history of Bacillus Calmette–Guérin vaccination, and chest radiograph to rule out active pulmonary TB. Study sites may be required to use a TB screening checklist to perform the TB screen for subjects who reside in a high TB burden or high multi-drug resistance (MDR) TB burden country.

a. Subjects without a history of TB infection and have a negative screening IGRA or TST result are eligible to enroll in the study
b. Subjects with a history of active TB, regardless of treatment status, are excluded from the study
c. Subjects with a history of latent TB must have documentation of a TB prophylaxis treatment course or must have started a TB prophylaxis treatment course for ≥ 2 weeks prior to randomization in order to qualify for enrollment. Active pulmonary TB must be ruled out. It is the responsibility of the Investigator to verify the adequacy of TB prophylaxis treatment and provide appropriate documentation, including the work-up for active TB
d. Acceptable TB prophylaxis treatment for latent TB is defined according to local country guidelines. If no local country guidelines for the treatment of latent TB exist, WHO Guidelines must be followed (2018 WHO Updated and Consolidated Guidelines for Programmatic Management; http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/)
e. A subject with a history of latent TB infection, regardless of treatment status, who resides in a country identified by WHO as having a high MDR TB burden (eg, China, India, the Russian Federation, South Africa, Thailand, Ukraine) should be excluded from study participation due to the high risk of infection with MDR TB (2018 WHO Updated and Consolidated Guidelines for Programmatic Management; http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/)
f. IGRA and TST interpretation:

- An indeterminant IGRA test result should be repeated and if the second IGRA test result is also indeterminate, the subject's chest X-ray taken ≤ 6 months before screening shows no evidence of active/old TB, and the subject has no additional risk factors for TB, as determined by the Investigator or the infectious disease consultant or physician TB expert, the subject may be enrolled without treatment for latent TB
  - For subjects residing in a high TB burden or high MDR TB burden country, the chest computed tomography scan should be performed to rule out current/past pulmonary TB in the event that the chest X-ray reading is equivocal
- If the IGRA is not considered a validated test or is not registered for use in the subject's country, a negative TST result is required to rule out latent TB infection
- A positive TST reaction is ≥ 10 mm of induration, or ≥ 5 mm of induration for subjects receiving > 15 mg/day of prednisone or its equivalent for any medical

conditions and subjects residing in countries identified by WHO as a high TB burden country (eg, Brazil, China, India, the Russian Federation, South Africa, Thailand) or MDR TB burden country

APPENDIX 4: GRADING OF CLINICAL AND LABORATORY ADVERSE EVENTS

All clinical and clinically significant laboratory abnormalities will be graded according to the CTCAE Scale for Severity of Adverse Events and Laboratory Abnormalities.

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

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

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

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

Table 11: Example of CTCAE Terms and Grading for Laboratory Abnormalities and Pulmonary Functions Tests

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

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

APPENDIX 5: GUIDANCE FOR THE MANAGEMENT OF CLINICAL AND LABORATORY ADVERSE EVENTS

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

Uniform guidance for the management of AEs is provided in Figure 3.

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

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

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

Any questions regarding adverse event management should be directed to the Medical Monitor.

APPENDIX 6: GUIDANCE FOR THE ASSESSMENT OF POTENTIAL PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

If a subject exhibits signs and symptoms suspicious for progressive multifocal leukoencephalopathy (PML), the Investigator must interrupt study drug and perform a targeted neurologic examination to assess for signs of PML, which are diverse, progress over days to weeks, and may include progressive weakness on 1 side of the body or clumsiness of limbs or difficulty with walking or writing or fine motor skills, disturbance of vision, changes in thinking, memory and orientation leading to confusion and personality changes, paresthesia/anesthesia (of any domain: peripheral to central), dysarthria (expressive aphasia), and/or agnosia (receptive aphasia). Consultation with a local neurologist may be warranted, as presented in the PML case evaluation algorithm in Figure 4.

The Medical Monitor should be informed of any suspected cases of PML and, if needed, will facilitate Investigator/local neurologist consultation with PML medical experts on the independent adjudication committee.

APPENDIX 7: INVESTIGATOR SIGNATURE

Protocol 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: APD334-205

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

Investigator Signature	**Date**

Investigator Name and Credentials - Printed
Institution Name - Printed