CLINICAL STUDY PROTOCOL

Protocol title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Etrasimod in Adult Subjects with Eosinophilic Esophagitis
Protocol number:	APD334-206 (C5041009)
Version:	Amendment 3.0, dated 04 January 2023
Compound name or number:	Etrasimod (APD334)
Study phase:	2
Indication:	Eosinophilic esophagitis
EudraCT number:	2020-003226-23
Sponsor name:	Arena Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer Inc.
Sponsor approval:	This protocol was approved by the Sponsor's Responsible Medical Officer or delegate. The electronic signature manifest is appended.

Confidentiality Statement

PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 3.0	Global	04 January 2023
Amendment 2.1	Regional	22 October 2021
Amendment 2.0	Global	20 October 2021
Amendment 1.1	Regional	24 March 2021
Amendment 1.0	Global	24 September 2020
Original 0.0	Not applicable	10 July 2020

PROTOCOL SYNOPSIS

Sponsor: Arena Pharmaceuticals, Inc.

Name of Investigational Study Drug: APD334 (etrasimod)

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Etrasimod in Adult Subjects with Eosinophilic Esophagitis

Protocol Number: APD334-206

Phase: 2

Countries/Regions (planned): North America, European Union, Australia

Objectives:

Primary:

- To evaluate the effects of etrasimod on esophageal eosinophilia in adult subjects with active eosinophilic esophagitis (EoE)
- To evaluate the dose-response relationship of 2 doses of etrasimod versus placebo in adult subjects with active EoE
- To select an etrasimod dose based on efficacy and safety for continued development

Secondary:

- To evaluate the effect of etrasimod on dysphagia symptoms in adult subjects with active EoE

Study Design:

This Phase 2, randomized, double-blind, multi-center study will evaluate the efficacy, safety, and pharmacokinetics (PK) of etrasimod compared with placebo in adults with active EoE.

The study will consist of a Screening Period of up to 35 days, 24 weeks of double-blind treatment (Double-Blind Treatment Period), 28 weeks of active extended treatment (Extension Treatment Period), and 4 weeks of follow-up (Safety Follow-Up Period) for a total study duration of up to 61 weeks.

Eligible subjects will be randomized in a double-blind fashion (3:3:2 ratio) to etrasimod 1 mg, etrasimod 2 mg, or matching placebo once daily. Randomization will be stratified by baseline history of esophageal dilation (yes/no) and concurrent proton pump inhibitor (PPI) therapy (yes/no).

All subjects who complete the Double-Blind Treatment Period and meet eligibility criteria for the Extension Treatment Period may enter the Extension Treatment Period. Subjects who were in the etrasimod 1 mg or etrasimod 2 mg groups in the Double-Blind Treatment Period will continue the same etrasimod dose in the Extension Treatment Period. Subjects who were in the placebo group during the Double-Blind Treatment Period will be re-randomized (1:1 ratio) to etrasimod 1 mg or etrasimod 2 mg at entry into the Extension Treatment Period.

Subjects will have follow-up visits at 2 and 4 weeks after the last dose of study treatment after Week 52 or the Early Termination (ET) Visit.

Number of Subjects (planned):

Approximately 96 subjects are planned to be enrolled.

Eligibility Criteria for the Double-Blind Treatment Period:

Key Inclusion Criteria (Full Inclusion Criteria Are Provided in the Protocol)

- Men or women between 18 and 65 years of age at the time of informed consent (IC)
- Have an EoE diagnosis prior to screening and histologically active disease with an esophageal peak eosinophil count (PEC) of ≥ 15 eosinophils (eos)/high power field (hpf) (~60 eos/mm^2) from any level (proximal, mid, or distal) of the esophagus at the Screening esophagogastroduodenoscopy (EGD)
- Have dysphagia, defined as solid food going down slowly or getting stuck in the throat with an average frequency of ≥ 2 episodes per week over 2 weeks (as documented using the Dysphagia Symptom Questionnaire (DSQ) during the Screening period)

Key Exclusion Criteria (Full Exclusion Criteria Are Provided in the Protocol)

- History of any of the following non-EoE conditions or procedures that may interfere with the evaluation of or affect the histologic, endoscopic, or symptom endpoints of the study:
  a. Conditions that substantially contribute to esophageal eosinophilia (eg, eosinophilic gastritis or enteritis [ie, eosinophilic duodenitis or colitis] with esophageal involvement, achalasia, hypereosinophilic syndrome, Crohn's disease [CD] with esophageal involvement, esophageal infection [fungal, viral], eosinophilic granulomatosis with polyangiitis (formally known as Churg-Strauss Syndrome), pemphigus, with esophageal involvement, pill esophagitis, graft versus host disease, Mendelian disorders [eg, Marfan syndrome Type II, hyper-immunoglobulin E (IgE) syndrome, phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome, Netherton syndrome, severe atopy metabolic wasting (SAM) syndrome])
  b. Conditions that interfere with the evaluation of the esophagus (eg, esophageal varices with risk of spontaneous bleed, high-grade esophageal stenosis where an 8- to 10-mm endoscope could not pass through the stricture without dilation at the time of Screening EGD)
  c. Conditions or procedures that substantially contribute to dysphagia (eg, histologically active Barrett's esophagitis, active erosive esophagitis Los Angeles Grade B or above, significant hiatal hernia [≥ 4 cm], esophageal resection)
- Undergone dilation of an esophageal stricture within 12 weeks prior to Screening EGD.
- Use of corticosteroids for the treatment of EoE within 8 weeks prior to Screening EGD.
- Discontinue, initiate, or change dosing (dosage/frequency) of the following therapies for EoE within 8 weeks prior to Screening EGD. Subjects on any of the following therapy need to stay on a stable regimen during study participation:

d. Elemental diet
e. EoE food trigger elimination diet
f. PPI therapy

- Used any immunotherapy/desensitization including oral immunotherapy (OIT) or sublingual immunotherapy (SLIT) within 12 months prior to the Screening EGD. Note: Stable (ie, ≥ 6 months prior to the Screening EGD) subcutaneous immunotherapy (SCIT) is permitted. Subjects on SCIT need to stay on a stable treatment during study participation.
- Used any of the following immunomodulatory therapies within the timeframes prior to Baseline as indicated below. The Medical Monitor should be consulted with any questions related to prior use of unlisted immunomodulatory therapies.

Time Frame	Therapies
Within 2 weeks	Antimetabolites (eg, AZA, 6-MP, MTX, 6-TG), calcineurin inhibitors (eg, cyclosporine, tacrolimus), MMF
Within 12 weeks (or 5 half-lives if shorter)	Anti-IL-5 antibodies (eg, mepolizumab, reslizumab, benralizumab), anti-IL-4/13 antibodies (eg, dupilumab), anti-IgE antibodies (eg, omalizumab), TNFα inhibitors (eg, infliximab), JAK inhibitors (eg, tofacitinib, oclacitinib)
Within 24 weeks	Anti-CD20 antibodies (eg, rituximab, ocrelizumab), anti-CD52 antibodies (eg, alemtuzumab), other cell-depleting therapies (eg, bone marrow transplantation, total body irradiation)
Any time prior to Baseline	Sphingosine 1-phosphate receptor modulators (eg, fingolimod, siponimod, ozanimod), natalizumab

AZA, azacytidine; IgE, immunoglobulin E; IL-4/13, interleukin-4/13; IL-5, interleukin-5; JAK, Janus kinase; 6-MP, 6-mercaptopurine; MMF, mycophenolate mofetil; MTX, methotrexate; 6-TG, 6-thioguanine; TNFα, tumor necrosis factor alpha

Eligibility Criteria for the Extension Treatment Period:

Inclusion Criteria

- Completion of the Week 24 study visit (including EGD) including subjects who discontinued study treatment due to lack of clinical efficacy and started rescue therapy between Weeks 16 and 24. Rescue therapy must be discontinued on the day etrasimod is initiated in the Extension Treatment Period.
- Compliance with study procedures during the Double-Blind Treatment Period as assessed by the Investigator
- No notable safety concerns during the Double-Blind Treatment Period, as determined by the Investigator
- Willing to comply with all study visits and procedures for the Extension Treatment Period

Test Product, Dose, and Mode of Administration:

Etrasimod 1 mg and 2 mg tablets taken once daily by mouth in the Double-Blind Treatment Period and the Extension Treatment Period.

Duration of Study:

The overall duration of the study will be up to 61 weeks, including:

- Up to 5-Week Screening Period
- 24-Week Double-Blind Treatment Period
- 28-Week Extension Treatment Period
- Safety Follow-Up Visits 2 and 4 weeks after the last dose of study treatment

Reference Therapy, Dose, and Mode of Administration

Matching placebo tablets taken once daily by mouth in the Double-Blind Treatment Period. There is no reference therapy (no placebo) during the Extension Treatment Period.

Efficacy Assessments:

Esophageal peak eosinophil count (PEC), EoE Histology Scoring System (HSS), DSQ, Food Avoidance Question (FAQ); Eosinophilic Esophagitis Endoscopic Reference Score (EREFS), Adult Eosinophilic Esophagitis Quality of Life (EoE-QOL-A), the Patient Global Impression of Change (PGIC), and Patient Global Impression of Severity (PGIS).

Primary efficacy endpoint:

- Percent change from Baseline in esophageal PEC at Week 16

Secondary efficacy endpoints:

- Absolute change from Baseline in DSQ score at Week 16
- Absolute change from Baseline in esophageal PEC at Week 16
- Proportion of subjects with esophageal PEC < 15 eos/hpf at Week 16
- Proportion of subjects with esophageal PEC ≤ 6 eos/hpf at Week 16

A complete list of efficacy endpoints and definitions, as well as analysis methods will be provided in the Statistical Analysis Plan (SAP).

Pharmacokinetic Assessments:

Etrasimod plasma concentrations will be determined on Day 1 (predose and 4 hours ± 15 minutes postdose) and before dosing at subsequent study visits and at the follow-up visits.

Collected blood for PK 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.

Safety Assessments:

Safety will be assessed through the incidence of adverse events (AEs), clinical laboratory findings, 12-lead electrocardiograms (ECGs) (for first-dose monitoring, on treatment re-initiation after a defined period of treatment interruption, and at the start of the Extension Treatment Period, to be done predose and at 4 hours following the first dose), physical examinations, vital signs (measured hourly for at least 4 hours following the first dose), pulmonary function tests (PFTs), ophthalmoscopy and optical coherence tomography (OCT).

Statistical Methods:

CCI [redacted]

Testing Strategy:

Unadjusted p-values for any hypothesis tests related to the comparisons of etrasimod dose group versus placebo will be reported. Estimated difference between etrasimod dose group and placebo as well as the associated 95% confidence intervals will be reported.

Statistical Analysis:

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

The endpoints of percentage change in esophageal PEC from Baseline to Week 16 and Week 24 will be analyzed using analysis of covariance (ANCOVA) model based on rank scores due to the skewed distribution of the data and possible outliers. The ANCOVA model will include treatment group and randomization stratification factors as factors and Baseline eosinophil PEC as a covariate. PEC after rescue medication/rescue procedure uses will be set to missing; all missing data will be imputed in the FAS using multiple imputation (MI) procedure as appropriate. Multiple results of ANCOVA (least square [LS] mean rank scores and LS mean rank score difference from placebo) for each MI dataset will be analyzed and reported along with final p-value using Rubin's method [1]. In addition, a descriptive summary of percentage change in esophageal PEC from baseline as well as the difference between treatment groups will be presented by treatment group. When applying the same ANCOVA model to key secondary continuous variables, no rank transformation will be used.

Proportion-based secondary endpoints (eg, histologic responders or symptomatic responders) at Week 16 will be analyzed in the FAS; subjects who use rescue medication or have a rescue procedure, or with missing data for any reason will be considered a "nonresponder" or "failure." The analyses will be performed using the Cochran-Mantel-Haenszel (CMH) method adjusted for randomization stratification factors. The number and percentage of subjects achieving the goal and the difference in proportion between treatment groups achieving the goal, along with p-value and the 95% CIs will be reported.

Longitudinal continuous endpoints will also be analyzed up to Week 24 using a linear mixed effects model. The model will include treatment group, visit, interaction of treatment-by-visit, and randomization stratification factors as factors and Baseline measure value as covariates. An unstructured covariance matrix will be specified for the within-subject measurements. LS means and LS mean differences between treatment group with unadjusted p-values and corresponding 95% CIs will be reported at each scheduled visit.

No hypothesis tests between treatment groups will be performed for endpoints measured during the Extension Treatment Period. Only descriptive statistics will be provided.

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

Subjects receiving any rescue therapy will have efficacy assessments after rescue therapy set to missing (continuous variable) or considered as treatment failures/non-responders at subsequent timepoints (dichotomous variables). Details and handling of rescue therapy for analysis will be contained in the protocol and SAP.

Safety Analysis:

All safety data will be listed and summarized by treatment group. All treatment-emergent AEs (TEAEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by System Organ Class and Preferred Term. Incidence of AEs, serious adverse events, adverse events of special interest, and AEs leading to study treatment discontinuation will be summarized and presented in descending order of frequency. In addition, details regarding risk-based safety analyses (eg, risk difference, hazard ratio) and exposure adjusted incidence rates will be described in the SAP. 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. 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.

Pharmacokinetic Analysis:

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

Interim Analysis:

No formal interim analyses for efficacy are planned. Full details of the efficacy, safety, and PK analysis will be provided in the SAP.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AV	atrioventricular
AZA	azacytidine
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
bpm	beats per minute
CBC	complete blood count
CD	Crohn's disease
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CMH	Cochran-Mantel-Haenszel
CMP	Clinical Monitoring Plan
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury

Abbreviation	Explanation
DLCO	diffusing capacity of the lungs for carbon monoxide
DNA	deoxyribonucleic acid
DSQ	Dysphagia Symptom Questionnaire
ECC	Emergency Contact Card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eDiary	electronic diary
EEn	eosinophilic enteritis
EG	eosinophilic gastritis
EGD	esophagogastroduodenoscopy
eGFR	estimated glomerular filtration rate
EGID	eosinophilic gastrointestinal disease
EoE	eosinophilic esophagitis
EoE-HSS	Eosinophilic Esophagitis Histology Scoring System
EoE-QOL-A	Adult Eosinophilic Esophagitis Quality of Life
eos	eosinophils
EREFS	Eosinophilic Esophagitis Endoscopic Reference Score
ET	Early Termination
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FA	fluorescein angiogram
FAQ	Food Avoidance Question
FAS	Full Analysis Set
FCS	fully conditional specification
FDA	Food and Drug Administration
FEV_1	forced expiratory volume at 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	gamma glutamyl transferase

Abbreviation	Explanation
GI	gastrointestinal
GWAS	genome-wide association studies
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hpf	high power field
HR	heart rate
HSS	Histology Scoring System
IAC	independent adjudication committee
IB	Investigator's Brochure
IC	informed consent
ICD	Informed Consent Document
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IL	interleukin
IMID	immune-mediated inflammatory disorder
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IWRS	Interactive Web Response System
JAK	Janus kinase
LFT	liver function test
LS	least square
6-MP	6-mercaptopurine
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set

Abbreviation	Explanation
MI	multiple imputation
MMF	mycophenolate mofetil
MQI	Medically Qualified Individual
MTX	methotrexate
NASH	nonalcoholic steatohepatitis
OCT	optical coherence tomography
OIT	oral immunotherapy
PD	pharmacodynamic(s)
PEC	peak eosinophil count
PFT	pulmonary function test
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHE	public health emergency
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PPI	proton pump inhibitor
PPI-REE	proton pump inhibitor-responsive esophageal eosinophilia
PRES	posterior reversible encephalopathy syndrome
PT	prothrombin time
PTEN	phosphatase and tensin homolog
qd	once daily
QOL	quality of life
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RNA	ribonucleic acid
S1P	sphingosine 1-phosphate
$S1P_{1,4,5}$	sphingosine 1-phosphate receptors 1, 4, 5
SAE	serious adverse event
SAM	severe atopy metabolic wasting
SAP	Statistical Analysis Plan
SCIT	subcutaneous immunotherapy
SD	standard deviation

Abbreviation	Explanation
SLIT	sublingual immunotherapy
SOP	standard operating procedure
SpO_2	arterial oxygen saturation
SRSD	Single Reference Safety Document
6-TG	6-thioguanine
T bili	total bilirubin
TBNK	T, B, NK, CD4+ T cell and CD8+ T cell count (absolute number and percentage)
TEAE	treatment-emergent adverse event
TGF-β	transforming growth factor-beta
Th2	type 2 helper T
TNFα	tumor necrosis factor alpha
TSLP	thymic stromal lymphopoietin
UC	ulcerative colitis
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman of child-bearing potential

1. INTRODUCTION

1.1. Background

1.1.1. Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic and progressive, allergen-driven, immune-mediated disease of the esophagus. Histologically, EoE is characterized by the accumulation of eosinophils in the lining of the esophagus, a tissue that under normal conditions lacks these cells [2-4]. The presence of these unwelcome eosinophils has been shown to have a direct effect on immune function and tissue damage [3]. The eosinophilic predominant inflammation characteristic of EoE results in a variety of symptoms including but not limited to difficulty swallowing (dysphagia and/or odynophagia) and regurgitation, central chest pain, upper abdominal pain, food impaction, food refusal, and malnutrition [2,5,6]. Endoscopic abnormalities common to patients with EoE include esophageal linear furrows with loss of vascularity, trachealization, a small-caliber lumen, strictures, and mucosal exudates [2,3]. If left untreated, the natural course of disease ultimately progresses from chronic esophageal inflammation to fibrostenosis in the esophageal lining that increases tissue dysmotility and rigidity [7-9]. Spontaneous remission or development of tolerance to food allergies appears to be uncommon [9,10] and the disease commonly relapses in the absence of maintenance treatment [11-13]. Both pediatric and adult populations can develop EoE, however, the disorder is most common in individuals between the ages of 20 and 40 years old [14]. EoE also exhibits a strong hereditability pattern and predominance for males and for Caucasians, and principally affects those in socioeconomically developed countries [3,8,14]. Risk factors for EoE include atopy and other allergic diseases, including asthma, allergic rhinitis, and atopic dermatitis [2,15].

Though the etiology of EoE is not yet completely understood, EoE is considered a type 2 helper T (Th2) cell-mediated atopic disease. EoE onset is thought to arise from a multifactorial interaction between genetic susceptibility and inappropriate immune-driven inflammatory responses to food antigens (predominantly non-immunoglobulin E [IgE]-mediated), aeroallergens, and environmental factors [2,5,16,17]. A genetic predisposition to disturbed barrier function, which is observed in esophageal tissue from EoE patients, permits allergenic molecules easy entry through the epithelium and subsequent Th2-driven allergic hypersensitivity [3,8,16]. Dendritic cells localized within the esophageal epithelium sample allergenic molecules and induce the activation and maturation of Th2 cells [4]. This Th2 cell-mediated activity leads to cytokine production (including interleukin [IL]-4, IL-5, and IL-13) and subsequent eosinophil activation and recruitment to the esophagus (eosinophilic inflammation) where the eosinophils release harmful secretory products that cause esophageal symptoms, further reinforcing the inflammatory cycle [3,8,18]. Thus, medical intervention that reduces esophageal inflammation, restores epithelial barrier integrity, and induces histologic remodeling can result in symptom improvement [7].

Genome-wide association studies (GWAS) have identified candidate genes involved in the pathogenesis of EoE including, but not limited to, thymic stromal lymphopoietin (*TSLP*) and calpain 14 (*CAPN14*), that when overexpressed can disrupt barrier integrity and increase allergic inflammation [5,8]. GWAS have also identified links between EoE and overexpression of eotaxin-3, an eosinophil-specific chemoattractant [3,17]. This genetic profile therefore supports an allergic etiology for EoE where a genetic predisposition enhances inappropriate immune responses to potential triggering events [8,16].

Diagnostic criteria currently required for the diagnosis of EoE include 1) symptoms of esophageal dysfunction; 2) eosinophilic esophageal inflammation with at least 15 eosinophils per high power field (hpf) affecting the esophagus alone; and 3) exclusion of other causes of esophageal eosinophilia. The other causes may include non-EoE eosinophilic gastrointestinal diseases (EGIDs) such as eosinophilic gastritis (EG) or eosinophilic enteritis (EEn), Crohn's disease (CD), infection, achalasia, and hypereosinophilic syndrome [6,9,16,19].

The differential diagnosis for EoE has historically included gastroesophageal reflux disease (GERD) and proton pump inhibitor (PPI)-responsive esophageal eosinophilia (PPI-REE), where responsiveness to an 8-week PPI study was considered an exclusion of an EoE diagnosis [5,6,20]. However, research suggested that EoE and GERD were not necessarily mutually exclusive and that PPIs may have an acid-independent anti-inflammatory effect that promotes the reduction of esophageal eosinophilia [5,6,21]. With the similarities in phenotypic, molecular, and pathophysiologic characteristics and responses to treatment, PPI-REE emerged rather as a subtype of EoE in some patients. Based on these findings, PPI trial requirement was removed from the diagnostic algorithm [6] and PPIs are considered a treatment option, although off-label, for EoE.

Current treatment options for EoE may be dietary, pharmacologic, or endoscopic in nature. These treatments are subject to a variety of disadvantages including difficulty in adhering to dietary therapy, potential negative side effects associated with systemic corticosteroids, partial efficacy of topical steroids, and invasiveness and risks of endoscopic treatment, including esophageal dilation [7,21,22]. In 2018, budesonide was approved in Europe as orodispersible tablet formulation [23] for the treatment of EoE, but there are no Food and Drug Administration (FDA) approved medications for the treatment of EoE. Therefore, long-term safe and effective treatments are greatly needed.

Sphingosine 1-phosphate (S1P) receptor modulators have a primary mechanism of action of reducing peripheral lymphocytes. Given that immune system dysregulation is a pathophysiological feature of many immune-mediated inflammatory disorders (IMIDs) [24,25], synthetic small molecule S1P receptor modulators have the potential to act across a wide range of such diseases. S1P receptor modulators have been shown to reduce inflammation and induce clinical remission in multiple sclerosis (fingolimod, ozanimod, ponesimod, siponimod) [26-28], psoriasis (ponesimod) [29], and ulcerative colitis (UC [ozanimod, etrasimod]) [30,31]. Therefore, S1P receptor modulators, such as etrasimod, may have similar effects in EoE.

1.1.2. Etrasimod

Etrasimod (APD334) is an orally administered, synthetic, selective modulator of S1P receptors 1, 4, 5 ($S1P_{1,4,5}$) that is being developed to treat IMIDs.

$S1P_1$ is a cell surface expressed G protein-coupled receptor that has been shown to regulate lymphocyte migration out of lymphoid tissues. 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 [32]. Nonclinical and clinical studies with S1P receptor modulators induce the anticipated $S1P_1$-mediated reduction in peripheral lymphocytes. Nonclinical studies of S1P receptor modulators have shown a reduction in tissue-infiltrating Th2 cells, cells expressing the pro-inflammatory cytokines IL-4,

IL-5, IL-13, and those cells implicated in active disease, including eosinophils [33-36]. In theory, a reduction in the number of circulating lymphocytes translates to reduced infiltration of inflammatory cells into the tissue and less release of pro-inflammatory cytokines which mediate tissue damage and eosinophil infiltration[32,37]. S1P receptor modulators have been shown to be clinically beneficial in other T cell mediated diseases including, but not limited to, inflammatory bowel disease, and multiple sclerosis [26,29,31,32]; etrasimod is therefore thought to be a potential therapeutic approach to the management of EoE.

Consistent with this hypothesis, etrasimod demonstrated positive results in a Phase 2, randomized, double-blind, placebo-controlled study in subjects with moderately to severely active UC in Study APD334-003 [38] and its open-label extension, Study APD334-005 [39]. 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 [30,40-42]. Etrasimod 2 mg administered orally once daily for up to 46 weeks (per Amendment 2 of Study APD334-005 a subset of subjects received treatment for 52 weeks) was generally safe and well tolerated in subjects with UC.

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

The need for a safe, long-term, oral, efficacious non-steroid treatment for EoE is illustrated by the lack of FDA approved medications for the treatment of EoE, and potential negative side effects or compliance difficulty associated with many currently available treatments.

The potential benefit to subjects who enroll in this study is clinical improvement in EoE symptoms as a result of reduced local inflammation in the esophagus through modulation of both T cell infiltration into the tissue and subsequent eosinophil accumulation (Section 1.1.2). As of 08 June 2020, etrasimod has been found to be generally safe and well-tolerated in approximately 736 adult subjects treated at various doses. 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 (qd) without dose-escalation and up to 4 mg qd with dose escalation. Etrasimod has previously demonstrated beneficial effects in another autoimmune inflammatory disease, UC. In a Phase 2 dose-ranging Study APD334-003, once daily treatment with 2 mg etrasimod for 12 weeks led to clinically meaningful and statistically significant endoscopic and symptomatic improvements versus placebo [38]. Sustained beneficial effects of etrasimod were observed for up to 46 weeks in the subsequent open-label extension Study APD334-005 (per Amendment 2 of Study APD334-005 a subset of subjects received treatment for 52 weeks) [39]. Although UC and EoE have different pathophysiology, they are Th2-driven immune-mediated inflammatory diseases where modulation of the S1P/S1P receptor axis is anticipated to provide therapeutic benefit to patients (Section 1.1.2). Therefore, it is reasonable to hypothesize that etrasimod may offer similar clinical benefits to EoE patients with active disease as UC patients. The clinical investigation proposed herein is necessary to affirm or reject this hypothesis.

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 receptor

modulators such as fingolimod and siponimod in multiple sclerosis, monitoring for these specific safety parameters is planned for this study [43,44]. This monitoring includes PFTs, cardiac monitoring at first dose 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. Thus, serial assessment of white blood cell (WBC) count and differential will be performed to assess the risk for serious and atypical infections and study subjects will be closely monitored by Investigators. Subjects with low lymphocyte count in circulation, or who have active infections will be excluded in this study.

S1P receptor modulators are associated with an expected, on-target, dose-dependent effect of reducing heart rate (HR) upon first dosing with HR recovery to predose baseline thereafter [45]. 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. An $S1P_1$-mediated HR reduction is maximal on the first day of dosing with etrasimod and 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) 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 [38]. Therefore, a dose-escalation regimen is not necessary for doses up to 2 mg.

To protect vulnerable subjects, those with certain cardiac risks or pre-existing cardiac conditions (eg, recent myocardial infarction, cardiac conduction delay, recurrent symptomatic bradycardia or syncope) will be excluded from the study. Vital signs will be monitored closely during the study, and direct observation will be performed after the subject receives the first dose of etrasimod in each treatment period (at Day 1 [Double-Blind Treatment Period] and Week 24 [Extension Treatment Period]) or at treatment re-initiation after a defined period of treatment interruption (refer to Section 10.6.7.4 for additional information on Day 1 monitoring).

As additional safety measures, subjects with elevated liver enzymes, abnormal pulmonary function or pulmonary disease requiring 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 for etrasimod are provided in the current edition of the IB.

The safety profile of etrasimod coupled with a potent effect on the lymphocyte count demonstrate that etrasimod may be an effective oral treatment option for IMIDs such as EoE. Based on the favorable clinical safety and efficacy data that has been generated from etrasimod studies in healthy adults and subjects with UC, the precautions outlined above, and the current lack of safe and effective long-term oral medications for the treatment of EoE, the benefit/risk assessment justifies the further clinical development of etrasimod in subjects with EoE and the current Phase 2 study multi-center, randomized, double-blind, placebo-controlled study.

2. OBJECTIVES

Primary:

- To evaluate the effects of etrasimod on esophageal eosinophilia in adult subjects with active EoE
- To evaluate the dose-response relationship of 2 doses of etrasimod versus placebo in adult subjects with active EoE
- To select an etrasimod dose based on efficacy and safety for continued development

Secondary:

- To evaluate the effect of etrasimod on dysphagia symptoms in adult subjects with active EoE

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3. STUDY DESIGN

3.1. Overall Design

This Phase 2 randomized, double-blind, multi-center study will evaluate the efficacy, safety, and PK of etrasimod compared with placebo for 24 weeks in adults with active EoE.

The study will consist of a Screening Period of up to 35 days, 24 weeks of double-blind treatment (Double-Blind Treatment Period), 28 weeks of active extended treatment (Extension Treatment Period), and 4 weeks of follow-up (Safety Follow-Up Period) for a total study duration of up to 61 weeks.

Eligible subjects will be randomized in a double-blinded fashion (3:3:2 ratio) to etrasimod 1 mg, etrasimod 2 mg, or matching placebo once daily. Randomization will be stratified by baseline history of esophageal dilation (yes/no) and concurrent PPI therapy (yes/no).

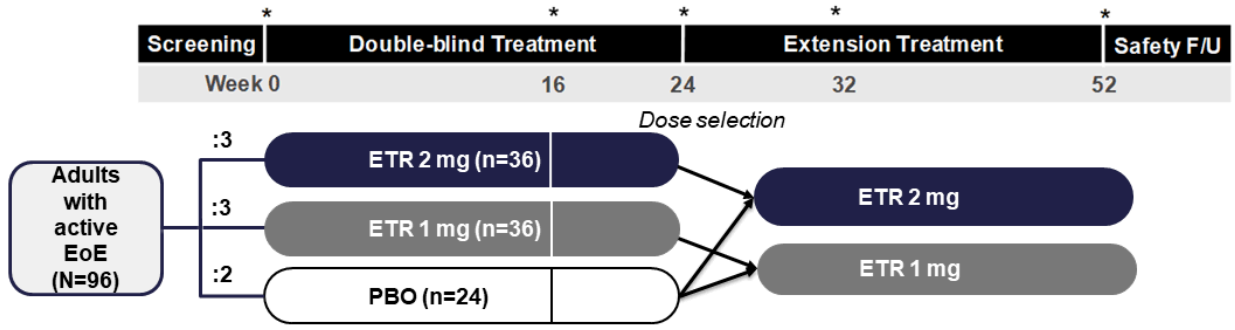
All subjects who complete the Double-Blind Treatment Period and meet eligibility criteria for the Extension Treatment Period may enter the Extension Treatment Period.

Subjects who were in etrasimod 1 mg or etrasimod 2 mg groups in the Double-Blind Treatment Period will continue the same etrasimod dose in the Extension Treatment Period. Subjects who were in the placebo group during the Double-Blind Treatment Period will be re-randomized (1:1 ratio) to etrasimod 1 mg or etrasimod 2 mg at entry into the Extension Treatment Period.

Subjects will have follow-up visits at 2 and 4 weeks after the last dose of study treatment after Week 52 or the Early Termination (ET) Visit.

A study design schematic is shown in Figure 1.

Figure 1: Study Design



*Esophagogastroduodenoscopy
EoE, eosinophilic esophagitis; ETR, etrasimod; F/U, follow-up; PBO, placebo.
Numbers preceded by colons represent the randomization ratio.

3.2. Discussion and Scientific Rationale for Study Design

This Phase 2, randomized, double-blind study is designed to evaluate the safety and efficacy of etrasimod (1 mg and 2 mg) versus placebo for 24 weeks for the treatment of adult subjects with active EoE.

As previously described, EoE is a chronic, immune/antigen mediated disorder characterized histologically by esophageal inflammation with intraepithelial eosinophils and clinically by symptoms of esophageal dysfunction in adult patients (eg, dysphagia or food impaction). Therefore, to confirm eligibility, all subjects will undergo esophagogastroduodenoscopy (EGD) with biopsy and record their EoE symptoms during the Screening period. The target study population will comprise adult subjects with histologically active (ie, esophageal peak eosinophil count [PEC] ≥ 15 eosinophils [eos]/hpf) and sufficiently symptomatic EoE (ie, average of ≥ 2 episodes of dysphagia per week over 2 weeks). Treatment options for EoE include medications, dietary elimination, and esophageal dilation [46]. From a clinical standpoint, the goal of treatment is to decrease or eliminate symptoms, improve or normalize the endoscopic appearance, and decrease or resolve the disease.

Treatment assignment will be blinded to minimize evaluation and reporting biases. Due to limited EoE treatment options, etrasimod will be compared with placebo. This will permit accurate characterization of the effects of investigational etrasimod relative to the placebo effect (ie, background effect related to fluctuations in dysphagia symptom, the natural course of EoE disease, regression to the mean, or response bias due to the subject's reporting of subjective symptoms).

The endpoints of treatment for EoE include improvement of esophageal eosinophilic inflammation and clinical symptoms [47]. Therefore, several histologic primary and secondary efficacy endpoints will be used to characterize the effect of etrasimod on EoE including change (percent and absolute) in esophageal PEC and histologic response as defined by an esophageal PEC of < 15 or ≤ 6 eos/hpf. Eosinophil density is an objective, quantifiable, and highly reproducible measure that is also intrinsic to the disease definition. A symptom-based secondary efficacy endpoint (ie, change in dysphagia frequency and/or severity) will be assessed using the Dysphagia Symptom Questionnaire (DSQ), a validated and qualified patient-reported outcome

measure that has been successfully used in clinical studies investigating the efficacy and safety of novel treatments for EoE.

The primary efficacy endpoint is the percent change from baseline in esophageal PEC at Week 16. The treatment effects of 2 etrasimod doses on the reduction of esophageal tissue eosinophils will be characterized. The secondary endpoints include measures of histologic, endoscopic, and symptomatic improvement for further elucidation of the effects of etrasimod on EoE disease activities.

These primary and secondary endpoints will be assessed at Week 16, and treatment will be continued in the Double-Blind Treatment Period until Week 24. The Week 16 timepoint was selected for primary and secondary efficacy assessments based on meaningful clinical and endoscopic improvements observed in UC patients following treatment with etrasimod. Data from Phase 2 studies APD334-003 and APD334-005 in adult subjects with moderately to severely active UC demonstrated that treatment with etrasimod 2 mg once daily for up to 46 weeks (n = 31) resulted in maximal improvements in the 2 cardinal symptoms of active UC, rectal bleeding and stool frequency, by Week 16, which were sustained through Week 46 [38,39]. Although there are notable differences between EoE and UC, both are IMIDs of the gastrointestinal (GI) tract. Based on etrasimod's mechanism of action and extrapolation on the time from etrasimod treatment initiation to observed clinical effects in patients with active UC, it is hypothesized that 16 weeks of etrasimod treatment will provide sufficient time to elicit the clinical effects of etrasimod in the treatment of patients with active EoE. Study treatment will be administered over 24 weeks in a double-blinded fashion and evaluation of histologic and patient-reported outcomes will occur at Weeks 16 and 24. Ultimately, a comparison of treatment effects observed at Week 16 compared to Week 24 will be performed to confirm that Week 16 is the timepoint at which the maximal treatment effects of etrasimod are observed in subjects with active EoE.

Subjects who complete the Week 24 visit will be eligible to enter the Extension Treatment Period, where etrasimod treatment will continue for up to an additional 28 weeks. In the Extension Treatment Period, subjects treated with placebo in the Double-Blind Treatment Period will have the opportunity to receive etrasimod, and subjects who tolerated etrasimod during the Double-Blind Treatment Period may continue etrasimod therapy. The maintenance or durability of treatment effects and longer-term safety profile of etrasimod will be characterized in the subset of subjects who continue etrasimod therapy over 52 weeks. Thus, the use of an Extension Treatment Period in this study provides study subjects with ongoing access to study treatment and the opportunity to evaluate the longer-term efficacy and safety profile of etrasimod.

Finally, off-treatment safety data will be collected at 2 and 4 weeks after the last dose of study treatment is administered.

3.3. Rationale for Dose Selection

Etrasimod doses selected for evaluation in the proposed study is based on pharmacodynamic (PD) and safety data from single- and multiple-ascending dose studies conducted in healthy adult subjects, Studies APD334-001 and APD334-002, respectively, and on safety, clinical efficacy, and PD data from a Phase 2 parent Study APD334-003 and extension Study APD334-005 in adult subjects with active UC.

Study APD334-001 evaluated single doses of etrasimod 0.1, 0.35, 1, 3, and 5 mg. Dose-limiting treatment-emergent adverse events (TEAEs) of transient, asymptomatic first- or second-degree AV block, both with and without HR decrease, were observed in 3 subjects treated with 5 mg dose. No adverse events (AEs) of bradycardia or AV block were reported at doses < 5 mg. Thus, the 5 mg dose was discontinued in subsequent clinical studies. In Study APD334-002, etrasimod doses of 0.7, 1.35, and 2 mg were administered once daily for 21 days. Additionally, several dose escalation paradigms were evaluated in some subjects; these subjects received either 0.35 or 0.5 mg for 7 days followed by 2 or 3 mg for 14 days, respectively. PD data from single- and multiple-ascending dose studies demonstrated a dose-dependent decrease in the peripheral lymphocyte count. Overall, etrasimod doses 0.35 to 3 mg were well-tolerated for up to 21 days.

Similarly, in Phase 2 Study APD334-003, a dose-dependent reduction in peripheral lymphocyte counts were observed as early as Week 1 in adult subjects with active UC treated with etrasimod 1 mg or 2 mg, and lymphocyte counts stabilized at Week 4. Dose-dependent symptomatic and endoscopic improvements (ie, the Modified Mayo Score) were also observed; however, only favorable clinical effects of etrasimod 2 mg (and not 1 mg) demonstrated a statistically significant difference compared with placebo. The efficacy and safety profile of etrasimod 2 mg was characterized over 46 weeks across the originating Study APD334-003 and extension Study APD334-005. In the subset of subjects exposed to etrasimod 2 mg for up to 46 weeks, no clinically significant safety concerns were identified.

In summary, the PD and favorable longer-term safety profile of etrasimod 2 mg in adults with moderately to severely active UC suggest that it is safe to evaluate doses of etrasimod up to 2 mg as a chronic therapy in adult subjects with active EoE. It is hypothesized that by evaluating etrasimod 1 mg and 2 mg, an efficacious and safe dose for the treatment of active EoE will be identified for continued development.

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, 4-Week Safety Follow-Up Visit). 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 the following inclusion criteria to be eligible for enrollment into the study.

1. Men or women between 18 to 65 years of age at the time of informed consent (IC)
2. Provide signed IC and willing to comply with all protocol-specified assessments and procedures
3. Have an EoE diagnosis prior to screening and histologically active disease with an esophageal PEC of ≥ 15 eos/hpf (~60 eos/mm^2) from any level (proximal, mid, or distal) of the esophagus at the Screening EGD.
4. Have dysphagia, defined as solid food going down slowly or getting stuck in the throat with an average frequency of ≥ 2 episodes per week over 2 weeks (as documented using the DSQ during the Screening period)

4.2. Exclusion Criteria

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

Note: A confirmed result means there have been 2 consecutive assessments showing consistent findings meeting exclusionary values. For criteria requiring confirmed results, the 2nd assessment is needed only if the first assessment result was exclusionary.

Exclusion criteria related to medications, therapies, or GI and eosinophilic disease

1. History of any of the following non-EoE conditions or procedures that may interfere with the evaluation of or affect the histologic, endoscopic, or symptom endpoints of the study:
    a. Conditions that substantially contribute to esophageal eosinophilia (eg, eosinophilic gastritis or enteritis [ie, eosinophilic duodenitis or colitis] with esophageal involvement, achalasia, hypereosinophilic syndrome, CD with esophageal involvement, esophageal infection [fungal, viral], eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss Syndrome), pemphigus with esophageal involvement, pill esophagitis, graft versus host disease, Mendelian disorders [eg, Marfan syndrome Type II, hyper-IgE syndrome, phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome, Netherton syndrome, severe atopy metabolic wasting (SAM) syndrome])
    b. Conditions that interfere with the evaluation of the esophagus (eg, esophageal varices with risk of spontaneous bleed, high-grade esophageal stenosis where an 8- to 10-mm endoscope could not pass through the stricture without dilation at the time of Screening EGD)
    c. Conditions or procedures that substantially contribute to dysphagia (eg, histologically active Barrett's esophagitis, active erosive esophagitis Los Angeles Grade B or above, significant hiatal hernia [≥ 4 cm], esophageal resection)
2. Undergone dilation of an esophageal stricture within 12 weeks prior to Screening EGD.
3. Use of corticosteroids for the treatment of EoE within 8 weeks prior to Screening EGD.
4. Discontinue, initiate, or change dosing (dosage/frequency) of the following therapies for EoE within 8 weeks prior to Screening EGD. Subjects on any of the following therapy need to stay on a stable regimen during study participation:
    a. Elemental diet
    b. EoE food trigger elimination diet
    c. PPI therapy
5. Used any immunotherapy/desensitization including oral immunotherapy (OIT) or sublingual immunotherapy (SLIT) within 12 months prior to the Screening EGD
   Note: Stable (ie, ≥ 6 months prior to the Screening EGD) subcutaneous immunotherapy (SCIT) is permitted. Subjects on SCIT need to stay on a stable treatment during study participation.
6. Used any of the following immunomodulatory therapies within the timeframes prior to Baseline as indicated in Table 1. The Medical Monitor should be consulted with any questions related to prior use of unlisted immunomodulatory therapies.

Table 1: Required Washout Period of Immunomodulatory Therapies

Time Frame	Therapies
Within 2 weeks	Antimetabolites (eg, AZA, 6-MP, MTX, 6-TG), calcineurin inhibitors (eg, cyclosporine, tacrolimus), MMF
Within 12 weeks (or 5 half-lives if shorter)	Anti-IL-5 antibodies (eg, mepolizumab, reslizumab, benralizumab), anti-IL-4/13 antibodies (eg, dupilumab), anti-IgE antibodies (eg, omalizumab), TNFα inhibitors (eg, infliximab), JAK inhibitors (eg, tofacitinib, oclacitinib)
Within 24 weeks	Anti-CD20 antibodies (eg, rituximab, ocrelizumab), anti-CD52 antibodies (eg, alemtuzumab), other cell-depleting therapies (eg, bone marrow transplantation, total body irradiation)
Any time prior to Baseline	Sphingosine 1-phosphate receptor modulators (eg, fingolimod, siponimod, ozanimod), natalizumab

AZA, azacytidine; IgE, immunoglobulin E; IL-4/13, interleukin-4/13; IL-5, interleukin-5; JAK, Janus kinase; 6-MP, 6-mercaptopurine; MMF, mycophenolate mofetil; MTX, methotrexate; 6-TG, 6-thioguanine; TNFα, tumor necrosis factor alpha

7. Use of moderate or strong inducers or inhibitors that inhibit or induce at least 2 of the following: cytochrome P450 (CYP) 2C8, CYP2C9, and CYP3A4 (eg, fluconazole, rifampin, enzalutamide) (Section 6.7.3) within 4 weeks prior to Baseline
8. Use of any investigational agent or device within 12 weeks prior Baseline
9. Have a known hypersensitivity to etrasimod or any of the excipients.

Exclusion criteria related to other medical history

10. Have any of the following conditions or risk factors:
    a. Primary or secondary immunodeficiency syndromes (eg, hereditary immunodeficiency syndrome, acquired immunodeficiency syndrome)
    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
    e. Test positive for human immunodeficiency virus (HIV [positive HIV antibody]), hepatitis B virus (positive hepatitis B surface antigen [HBsAg]), or active hepatitis C (HCV [positive hepatitis C antibody with detectable HCV RNA]) at Screening

    Note: If the Investigator suspects false positive hepatitis serology results, such as an antibody pattern indicating acute hepatitis infection, but no corresponding elevated liver enzymes and no signs or symptoms of liver disease, an infectious disease expert may be consulted. If the infectious disease expert finds no evidence of acute or chronic hepatitis infection and considers the serology results false positive and not clinically relevant, the Investigator may document (in source data and in the electronic case report form [eCRF]) that the serology results are considered false positive and may randomize the subject.

11. Have a serious infection that requires hospitalization or treatment with intravenous (IV) medications within 4 weeks prior to Baseline
12. Received a live-attenuated virus vaccine (except for recommended and age-appropriate influenza, measles/mumps/rubella, or varicella vaccine) within 4 weeks prior to Baseline
13. 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 regardless of whether there is evidence of local recurrence or metastases
14. Have active epilepsy
15. Have a history of cirrhosis
16. 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 prior to Baseline
    b. Second-degree or third-degree AV block, sick sinus syndrome without a functional pacemaker, or periods of asystole for > 3 seconds without an implanted cardiac pacemaker
    c. Recurrent symptomatic bradycardia or recurrent cardiogenic syncope
    d. Confirmed Screening and Day 1 baseline vital signs (taken in the sitting position) with a HR < 50 bpm OR systolic blood pressure (BP) < 90 mm Hg OR diastolic BP < 55 mm Hg.
    e. Confirmed Screening and Day 1 baseline ECG with PR interval ≥ 200 ms or Friderica's corrected QT interval (QTcF) ≥ 450 ms in males or ≥ 470 ms in females.
    f. Receiving Class Ia or Class III anti-arrhythmic drugs
    g. Start, stop, or change dosage of Class Ib, II, or IV anti-arrhythmic drugs within 1 week prior to Baseline
17. Have active diabetic retinopathy, uveitis, retinitis pigmentosum, macular edema, or had an intraocular surgery within 12 months prior to Baseline. Refer to Appendix 11 for modification in the event that coronavirus disease 2019 (COVID-19) or similar public health emergency (PHE)-related restrictions limit the capacity to perform non-essential ophthalmoscopy with OCT.
18. Have a confirmed forced expiratory volume at 1 second (FEV_1) or forced vital capacity (FVC) of < 70% predicted (prior to the administration of a short-acting bronchodilator) on Screening PFTs. Refer to Appendix 11 for modification in the event that COVID-19 or similar PHE-related restrictions limit the capacity to perform non-essential PFTs.

Exclusion criteria related to test or laboratory results (performed by central laboratory)

19. Have confirmed absolute lymphocyte count (ALC) < 0.8×10^9 cells/L at Screening
20. Have 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

21. Have confirmed moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] < 60 mL/min/m^2)

General exclusionary criteria

22. Lactating female who is breastfeeding
23. Females who are pregnant, evidenced by a positive serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at Screening and/or urine dipstick pregnancy test at Day 1, or females who do not meet criterion a or agree with criterion b below, or males who do not agree with criterion c below
    a. A female who is not of child-bearing potential must meet 1 of the following:
        – Postmenopausal, defined as no menses for 12 months without an alternative medical cause and confirmed by follicle-stimulating hormone (FSH) within postmenopausal range according to local standards
        – Had permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, or bilateral oophorectomy
    b. A female who is of child-bearing potential must agree to using a highly effective contraception method during treatment and for 4 weeks 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; sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments). 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, or post-ovulation methods) is not acceptable
    c. A male with pregnant or non-pregnant woman of child-bearing potential (WOCBP) partner must agree to use condoms during treatment and for 4 weeks following the last dose of study treatment
24. Any acute illness or medical condition including 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), confound interpretation of study results, or interfere with the subject's ability to comply with protocol-specified procedures or assessments.

Testing positive for COVID-19 is NOT exclusionary on its own if other exclusion criteria (#11 or #24) are not met. If a subject screen fails due to COVID-19, the subject may be re-screened for the study when their COVID-19 symptoms have improved or resolved but no sooner than 10 days after the first date of COVID-19 symptom onset. Subjects who are asymptomatic after COVID-19 recovery are not required to show a negative COVID-19 viral or serology test in order to qualify for re-screening.

For subjects who have not received the COVID-19 vaccine, it is recommended that COVID-19 vaccination is completed 14 days prior to randomization.

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

4.3. Eligibility Criteria for the Extension Treatment Period

Inclusion Criteria:

1. Completion of the Week 24 study visit (including EGD) including subjects who discontinued study treatment due to lack of clinical efficacy and started rescue therapy between Weeks 16 and 24. Rescue therapy must be discontinued on the day etrasimod is initiated in the Extension Treatment Period.
2. Compliance with study procedures during the Double-Blind Treatment Period as assessed by the Investigator
3. No notable safety concerns during the Double-Blind Treatment Period, as determined by the Investigator
4. Willing to comply with all study visits and procedures for the Extension Treatment Period

5. SUBJECT RESTRICTIONS

Prohibited concomitant therapies are described in Section 6.7.3. Subjects should be instructed to abstain from consuming herbal remedies containing St John's wort during the study as these may interfere with the metabolism of etrasimod.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Study treatments include the investigational medicinal product(s), defined as a pharmaceutical form of the active substance being tested (etrasimod) and a reference therapy (placebo). Study treatment is outlined in Table 2.

Table 2: Study Treatments

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

NA, not applicable; qd, once daily

6.2. Identity of Study Treatments

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 (pH = 8.9) at 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 and 2 mg. The etrasimod drug product is manufactured, packaged, tested, and released in compliance with cGMP. Placebo tablets are identical in appearance to the active drug tablets as described above.

6.2.2. Placebo

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

6.3. Dosage and Administration

One tablet (etrasimod 1 mg, 2 mg, or placebo, assigned as described in Section 6.4) is to be taken once daily with water (either with or without food) at approximately the same time each day, preferably in the morning.

On study visit days with blood draws, subjects should wait to take their assigned dose after PK blood samples have been drawn and after all predose assessments and procedures have been completed. The time of PK sample collection and subsequent dosing should be documented.

6.3.1. Instructions for Missed Dose(s)

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

Subjects who do not take the study treatment for ≥ 2 consecutive days within the first week of either treatment period (ie, Week 1 [Double-Blind Treatment Period] or Week 24 [Extension Treatment Period]) or for ≥ 7 consecutive days after the first week of either treatment period must be instructed to contact the Investigator to discuss treatment re-initiation under direct supervision and are required to return to the study site at the time they take their next dose of study treatment. The subject must take the next dose of study treatment at the study site, and cardiac monitoring should be performed as outlined in Section 10.6.7.4.

6.3.2. Dose Interruptions

Temporary withholding of study treatment, if deemed necessary by the Investigator, is permitted for up to 6 days (after Week 1) without obtaining prior approval from the Medical Monitor. If ≥ 7 days of study treatment interruption is required for a medical reason, the Investigator must contact the Medical Monitor as soon as this is anticipated.

The instruction for missed dose(s) is outlines in Section 6.3.1.

6.4. Method of Assigning Subjects to Treatment

Subjects will be centrally assigned to randomized study drug using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each study site.

On Day 1 of the Double-Blind Treatment Period, subjects will be randomly assigned to 1 of 3 treatment groups (etrasimod 2 mg, etrasimod 1 mg, or placebo) in a 3:3:2 ratio. Randomization will be stratified by baseline history of esophageal dilation (yes/no) and ongoing PPI therapy at study entry (yes/no).

At the start of the Extension Treatment Period, subjects who were randomized to either etrasimod 1 mg or 2 mg during the Double-Blind Treatment Period will be assigned to the same treatment as their Double-Blind Treatment Period treatment. Subjects who were randomized to placebo during the Double-Blind Treatment Period will be re-randomized to etrasimod 1 mg or 2 mg (1:1 ratio) for the Extension Treatment Period.

6.5. Blinding

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

Site staff including investigators will be blinded to the following laboratory results while subject is on study treatment: WBC count, WBC differential (percentage and absolute number), and TBNK panel (T, B, NK, CD4+ T cell, and CD8+ T cell count [absolute number and percentage]). The monitoring of WBC count, WBC differential, and TBNK panel during the study are described in Section 10.6.7.2. Additionally, post-baseline esophageal histologic outcomes including eosinophil counts and Eosinophilic Esophagitis Histology Scoring System (EoE-HSS) scores will be blinded to site staff until the end of the study.

Treatment assignments in the Double-Blind Treatment Period and Extension Treatment Period should remain blinded for Sponsor, site staff, and subjects until the Week 24 dose selection analysis, unless that knowledge is necessary to determine a subject's emergency medical care. At the time of the 24-week Double-Blind Treatment Period analysis, the sponsor staff will be un-blinded to the initial treatment assignments, but subjects, investigators and site staff will remain blinded. During the Extension Treatment Period, subjects, investigators, and site staff will be

aware that active treatment is being provided; however, they will remain blinded to the dose assignments.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. The IWRS is programmed with blind-breaking instructions to guide the Investigator on how to obtain treatment assignment in the event of an emergency unblinding. The Investigator is requested to contact the Medical Monitor promptly in case of any treatment unblinding. 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.

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.

6.6. 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. Tablet counts per bottle < 80% or > 120% of the expected value between visits should be documented as a protocol deviation.

6.7. Concomitant Therapy

Concomitant therapy refers to all medications (over the counter and prescribed) that are taken by subjects and all procedures that are performed from Day 1 (the date of the first dose of study treatment) through the safety reporting period. Concomitant therapy (medications and procedures) information 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.

6.7.1. Required Concomitant Therapy

Not applicable

6.7.2. Permitted Therapy

Stable treatment, dosage and/or dosing frequency of the following therapies:

- PPIs
- SCIT

- Diet therapy (eg, elimination diet, elemental diet)
- Inhaled/intranasal corticosteroids for the treatment of allergic comorbidities (eg, asthma, allergic rhinitis)
- Short course (eg, 7 days) or pulse corticosteroid therapy for exacerbation of a respiratory illness (eg, asthma)
- COVID-19 vaccines that are not categorized as live or live-attenuated viral vaccines and are approved or granted emergency use authorization

The Investigator must contact the medical monitor to discuss any changes to concomitant medications not listed here that could impact the outcome of the study.

6.7.3. Prohibited Concomitant Therapy

The following therapies or procedures are prohibited during the study while on study treatment However, in the event of an emergency, any needed medications may be prescribed without prior approval, but the Medical Monitor must be notified of the use of any prohibited medications immediately.

- Esophageal dilation
- Systemic corticosteroids (except pulse corticosteroid therapy, refer to Section 6.7.2)
- Oral or swallowed corticosteroids (for the treatment of EoE)
- SLIT or OIT
- Immunomodulatory agents
  - Examples: Antimetabolites (eg, azacytidine [AZA], 6-mercaptopurine [6-MP], methotrexate [MTX], 6-thioguanine [6-TG]), calcineurin inhibitors (eg, cyclosporine, tacrolimus), mycophenolate mofetil [MMF], S1P receptor modulators (eg, fingolimod, siponimod), anti-interleukin (IL)-5 antibodies (eg, mepolizumab, reslizumab, benralizumab), IL-4 and IL-13 antagonists (dupilumab), anti-IgE antibodies (omalizumab), anti-tumor necrosis factor alpha (TNFα) antagonists (eg, infliximab), anti-integrin antibodies (vedolizumab, natalizumab), Janus kinase (JAK) inhibitors (eg, tofacitinib, oclacitinib), anti-CD20 antibodies (rituximab, ocrelizumab), anti-CD52 antibodies (alemtuzumab)
- Any investigational drug other than the study treatment
- Class Ia (eg, quinidine, procainamide) and Class III (eg, sotalol, amiodarone) anti-arrhythmic drugs
- Live-attenuated virus vaccine (except for recommended and age-appropriate influenza, measles/mumps/rubella, or varicella vaccine) while on study treatment and within 4 weeks after the last dose of study treatment
- Moderate/strong inhibitors or inducers that inhibit or induce at least 2 of the following: CYP2C8, CYP2C9, and CYP3A4 (eg, fluconazole, rifampin, enzalutamide); for additional information refer to United States Food and Drug

Administration (FDA) *Drug development and drug interactions: Table of substrates, inhibitors and inducers* [48]

- Blood donations during the study and for 30 days after the last dose of study treatment
- Sperm or oocytes donation during the study and for 30 days after the last dose of study treatment

6.7.4. Rescue Therapy

Any new medication or procedure used to treat new or worsened EoE symptoms is considered a rescue therapy. Rescue therapy should not be withheld if, in the opinion of the Investigator, failure to use/implement them would compromise the safety of the subject.

Subjects who discontinue between Week 16 and Week 24 due to lack of clinically meaningful efficacy will be provided the option to remain in the study. For these subjects, rescue therapy may be given until the end of the Double-Blind Treatment Period but must be discontinued upon entry in the Extension Treatment Period during which all subjects receive active treatment.

7. STUDY TREATMENT MATERIALS MANAGEMENT

7.1. Packaging and Labeling

Study drug will be provided in induction-sealed, high-density polyethylene bottles with child-resistant screw caps and desiccant canisters. Each bottle will be labeled as required per country requirement. Subjects will be instructed to take 1 tablet qd as described in Section 6.3.

7.2. Storage and Handling

Bottles 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

Subjects will be instructed to record tablet self-administration daily and to document the time of their last dose prior to each study visit in an electronic diary (eDiary) that will be reviewed at each study visit by study site staff.

At each site visit, subjects will return all dispensed medication bottles and any remaining tablets to study site staff; remaining tablets will be collected and counted by the Investigator or qualified staff to confirm subject compliance. The number of remaining tablets in the bottle may be counted by visual inspection via videoconferencing for virtual assessment. In this scenario, all bottles and any remaining tablets must be returned at the next study site visit.

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

7.5. Retention and Disposal

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

8. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

8.1. Discontinuation of Study Treatment

Study medication must be discontinued in the following instances:

- Unacceptable TEAE or TEAE that, in the judgment of the Investigator, is considered to not be in the best interest of the subject to continue study medication, including:
  - Suspected drug induced liver injury as defined by the 2009 FDA Guidance for Industry [49] and described in Section 10.6.7.1
  - Sustained decrease in absolute lymphocyte count (ALC < 0.2×10^9 cells/L) with treatment re-initiation or re-challenge after study treatment interruption due to a confirmed ALC < 200 cells/μL, as described in Section 10.6.7.2
- Intolerance associated with first-dose cardiac effects (Section 10.6.7.4)

Study medication may be discontinued for the following reasons:

- Lack of clinical improvement or therapeutic benefit by Week 32, as determined by the Investigator
- Loss of clinical response after initial treatment response, as determined by the Investigator, at any time during the Extension Treatment Period
- Subject non-compliance

The Medical Monitor should be notified when a subject is discontinued from study treatment.

8.2. Reasons for Discontinuation from the Study

The reason(s) for study discontinuation must be determined by the Investigator and recorded in the source documents and on the eCRF. If a subject discontinues for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

- AE
- Withdrawal by subject
- Study termination by Sponsor
- Pregnancy
- Non-compliance
- Lost to follow-up

- Lack of efficacy
- Death
- Other

All patients should be encouraged to complete the study. However, 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 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 and date of last study drug intake.

Subjects who discontinue treatment prematurely, regardless of the reason, should be instructed to return for an Early Termination and Follow-Up Visits. Refer to Section 9.6 and Section 9.5 for description of ET and follow-up procedures, respectively.

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 study site for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 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 eCRF

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 Independent Ethics Committees

(IECs)/Institutional Review Boards (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 the ICH guideline for GCP

9. STUDY PERIODS

9.1. General Instructions

Study procedures and their timing are summarized in the Schedules of Assessments (Appendix 1; Table 7 and Table 8). Protocol waivers or exemptions are not allowed unless specified otherwise.

- Results of all protocol required procedures must be recorded in the eCRF.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the Schedules of Assessments, is essential and required for study conduct.
- Study visits should be scheduled in the morning, whenever possible.
- All laboratory assessments required by the protocol will be performed by a central laboratory unless otherwise stated.
- On study day visits with blood draws, subjects should take their study treatment after predose assessments and procedures (eg, PK sample collection) have been completed.

The Investigator will maintain a screening log and enrollment log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

9.2. Screening

Subjects must sign the informed consent form (ICF) and meet study eligibility criteria before any study-specific procedure can be performed (Section 12.2).

All screening evaluations should be completed and reviewed within 35 days prior to Day 1 to confirm subject eligibility. In some cases, the screening visit window for a given subject may be extended by 2 business days beyond the date the Investigator receives the screening histopathology report to confirm subject eligibility. Note that only extension of the screening visit window due to a legitimate delay in the reporting of screening histopathology report will be approved by the Medical Monitor and will not be considered a protocol deviation.

Refer to Appendix 11 for modification in the event that COVID-19 or similar PHE-related restrictions limit the capacity to perform certain Screening assessments.

The Medical Monitor should be consulted to see whether repeat testing is needed if the subject is planned to be enrolled > 35 days from the signing of the ICF.

The Screening EGD should be performed early in the screening period (preferably within the first 7 days of the screening period) to allow sufficient time for central reading to confirm eligibility by histology.

During Screening, subjects will record daily presence of dysphagia to solid food in their eDiary, according to the question-answer format of the DSQ. Subjects will begin daily eDiary entries starting on the first day of Screening after the eDiary training is completed. eDiary device and training should be provided at Screening to ensure capturing of entries within the required 14-day period. Study site staff will monitor the eDiary compliance. At least 8 DSQ daily entries in the last 2 weeks prior to Day 1 visit as well as completion of Patient Global Impression of Severity (PGIS) are needed for randomization.

9.3. Double-Blind Treatment Period

9.3.1. Day 1 Pre-Randomization and Predose

The day of administration of the first dose is defined as Day 1.

The following procedures/assessments must be performed and assessed again on Day 1 to confirm eligibility before randomization:

- HR and BP, followed by 12-lead ECG
- Pregnancy test for all WOCBP

If the subject remains eligible based on HR, BP, and 12-lead ECG parameters, and has a negative pregnancy test result (WOCBP only), then blood samples for laboratory and PK assessments will be collected, after the 12-lead ECG assessment is completed.

Subjects will also complete selected questionnaires to assess baseline status.

9.3.2. Day 1 Randomization and Postdose

After the eligibility criteria have been confirmed and the Day 1 predose assessments (Section 9.3.1) are completed, subjects will be enrolled and randomly assigned to treatment.

First dosing of study treatment will be given, and cardiac monitoring will take place under direct observation for at least 4 hours. HR and ECG measurements will be performed according to Table 5 and the subject will be assessed for discharge at 4 hours postdose. Refer to Section 10.6.7.4 for detailed guidance on first-dose cardiac monitoring and subject discharge criteria postdose.

Additional blood sample for PK assessment will be taken 4 hours (± 15 minutes) postdose after the Hour 4 ECG.

9.4. Extension Treatment Period

9.4.1. Week 24 Visit

The Week 24 visit will be used to assess eligibility for the Extension Treatment Period and is considered the beginning of the Extension Treatment Period. During this visit, eligibility for

entry into the Extension Treatment Period will be confirmed (ie, meets eligibility criteria; Section 4.3).

At the Week 24 visit, vital signs should be measured first, followed by ECG, predose PK sample collection, study drug dosing at the study site, and first-dose cardiac monitoring (direct observation) for at least 4 hours in all subjects continuing in the Extension Treatment Period. Cardiac monitoring is required because there is a subset of subjects who will transition from placebo in the Double-Blind Treatment Period to an etrasimod dose in the Extension Treatment Period. Refer to Section 10.6.7.4 for detailed guidance on first-dose cardiac monitoring and subject discharge criteria postdose.

9.5. Follow-Up/End of Study

All subjects will have follow-up visits for safety assessment at 2 and 4 weeks after the last dose of study treatment. All AEs should be recorded for 30 days after last dose of study medication (Section 10.6.8.1.9). Refer to Section 10.6.7.2 for details on the post-treatment follow up assessments and procedures for subjects who experience an ongoing AE of decreased lymphocyte count or infection.

In the event that a subject fails to attend any 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.

9.6. Early Termination

Subjects who discontinue the study prior to the end of the 24-week Double-Blind Treatment Period or the 28-week Extension Treatment Period (Week 52) will return to the study site for an ET Visit. The ET Visit should occur within 7 days of last dose and before initiation of any new treatments.

Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible, including an EGD, if not done within 4 weeks, and PFTs and ophthalmic and OCT testing. If a subject discontinues due to pregnancy, they may not be required to complete the EGD and biopsy.

9.7. Telehealth and Hybrid Visits

Study visits may be conducted as a Telehealth Visit, Home Health Visit or a Hybrid Visit. Refer to Section 10.1 for details on virtual and in-person assessments and procedures. These types of study visit will reduce direct human-to-human contact time, an important public health strategy to reduce COVID-19 transmission.

Study visits that may be conducted as a Telehealth Visit are designated in the Schedules of Assessments (Appendix 1; Table 7 and Table 8). All other study visits may be conducted as a Hybrid Visit.

9.7.1. Telehealth Visits

A Telehealth Visit refers to a visit consisting only of virtual assessments.

Telehealth visits may be used to assess subject safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the subject and the investigator to

communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record study drug(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 10.6.8.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the subject is adhering to the contraception method(s) required in the protocol. Refer to Section 4.2.

Study subjects must be reminded to promptly notify site staff about any change in their health status.

9.7.2. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits. Home health visits include a healthcare provider conducting selected in-person study assessments at the subject's location, rather than an in-person study visit at the site. The following may be performed during a home health visit (see the SoA):

- Review and record study drug (s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 10.6.8.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the subject is adhering to the contraception method(s) required in the protocol. Refer to Section 4.2.

9.7.3. Hybrid Visits

A Hybrid visit refers to a visit consisting of both virtual assessments and in-person assessments that may be performed on different days within the study visit window.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1. Virtual and In-Person Assessments

Virtual assessment refers to an assessment conducted by phone or video-conferencing where the study site staff (including the Investigator) and subject are not physically present with each other. In-person assessment refers to assessments that require physical presence of both the subject and Investigator or delegated study staff. For in-person assessments, subjects may visit the study site

or the Investigator or delegated study staff may arrange to visit the subject (ie, Home Health Visit).

Assessments or procedures that may be conducted virtually include the following: The informed consent process including obtaining written informed consent, medical history and concomitant medication query to assess eligibility criteria, review of demographic information, social and family history, AE query, review of concomitant medications, eDiary training and compliance review/monitoring including study drug administration and questionnaires, and the urine pregnancy testing (for WOCBP).

- AE Assessment: During the virtual assessment, a subject may report an AE that requires a follow-up symptom-focused physical exam or diagnostic testing, as determined by the Investigator. In this scenario, the Investigator may have the subject return to the study site for an unscheduled study visit to perform the assessment.
- Pregnancy Test: Pregnancy test results (for WOCBP) should be visually inspected, when possible, via video conferencing when it is a virtual assessment.
- Study Drug Dispensation: Study drug may be dispensed by secure mail per country-specific guidance prior to the Telehealth Visit. Alternatively, a future supply of study medications may be dispensed to the subject at a site visit to cover study medications to be dispensed at the Telehealth Visit. In-person dispensation of study drug is preferred.
- Study Drug Accountability: Medication bottle(s) and remaining tablets may be visually inspected and counted on video conferencing. Subjects must return dispensed bottle(s) and any remaining tablets to the study site at the next site visit.

Subjects will visit the study site or a specialist (eg, ophthalmologist) for the following in-person assessments: EGD, full or focused physical exam, first-dose cardiac monitoring, and ophthalmic exam with OCT. Other in-person assessments (eg, vital signs, blood collections for serum pregnancy test, clinical laboratory tests, and PK sampling) may be performed by delegated study staff deployed to visit the subject.

Guidance on mitigating challenges that may occur as a result of COVID-19-related limitations, restrictions, or local/national public health official mandates is provided in Appendix 11.

10.2. Subject Informed Consent

The Investigator, or a person designated by the Investigator, will obtain written IC [50] from each subject before any study specific activity is performed (refer to Section 12.2 for additional details). A digital IC document may be used to provide information usually contained in a physical IC document, and the electronic signature may be used to document the subject's signed informed consent. The IC process may take place at the study site with both the Investigator and subject physically in the same location, or it may take place over the phone or by video conferencing, where the Investigator and subject are in different locations. The Investigator or the person designated by the Investigator will administered the IC process and answer the subject's questions in the same manner, whether the process is done in person, by phone or using other telehealth communication technology. The virtual process may be used where permitted by local regulations.

10.3. Screening and Eligibility

10.3.1. 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.

10.3.2. Social and Family History

A history of current tobacco and/or alcohol use at Screening will be recorded.

Family history of eosinophilic, atopic (eg, eczema, asthma, and rhinoconjunctivitis), and other GI diseases will also be collected at Screening.

10.3.3. Prior Therapies

Prior or current use of the following therapies, if applicable, will be recorded in the eCRF.

- Elemental diet (specify name, year start and stop, reason for discontinuation of elemental diet, if applicable).
- Trigger food elimination diet (name of EoE food triggers, year start and stop, reason for discontinuation of elimination diet, if applicable).
- EoE medical therapies (eg, PPIs, swallowed topical steroids, investigational EoE therapies accessed through a clinical trial): name of medication, dosage, dosing frequency, route of administration, side effects or intolerance, start and stop dates (month and year), the reason(s) for treatment discontinuation (eg, initial inadequate response, initial response followed by loss of response, or intolerance). Record the Investigator's characterization of the subject's responsiveness to PPIs and/or swallowed topical steroid therapy as responsive, refractory, or not applicable.
- Esophageal dilation (month and year of first procedure and most recent procedure). If more than 1 dilation has been performed, record the duration of time (in months) between the last 2 dilation procedures and the impact of dilation on EoE symptoms (eg, complete or partial resolution of dysphagia to solid food).
- Any history of immunotherapies for allergies (eg, OIT, SLIT, SCIT): Type of immunotherapy, name of specific food or aeroallergen, start and stop date (month and year) of immunotherapy, if applicable.

All medications (eg, prescribed medications, over-the-counter medications, vitamins, and herbal supplements) received within 30 days prior to the Baseline visit (Day 1) will be recorded in the eCRF as follows: Name of medication, dosage, dosing frequency, indication, and start and stop date (month and year), if applicable. The name of any live-attenuated vaccines received within 30 days prior to the Baseline visit will also be recorded.

10.3.4. Medical History

The following EoE medical history will be recorded in the eCRF: Year of EoE diagnosis, known food triggers of EoE disease, last known esophageal PEC and location (proximal, mid, and or distal esophagus), known endoscopic findings (eg, fixed rings, exudates, furrows, edema, strictures), dominant EoE symptoms (eg, dysphagia, food impaction, and/or specific food

avoidance), and EoE histopathologic phenotype (eg, inflammatory, fibrostenosis with or without strictures).

If a subject has a history of esophageal dilation, any prior complications related to dilation procedure should be noted.

History of atopic comorbidities (eg, allergic rhinitis, bronchial asthma, atopic dermatitis, IgE-mediated food allergies, other eosinophilic diseases), exclusionary comorbidities (refer to Section 4.2), and all prior hospitalizations and surgeries (reason and year) will also be recorded.

10.3.5. Pregnancy Testing

The following instructions on pregnancy testing apply to all WOCBP. Women who are surgically sterile or who are postmenopausal are not considered to be of child-bearing potential. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause and confirmed by an FSH level in the postmenopausal range. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm postmenopausal state.

At Screening a serum pregnancy test for β-hCG will be performed to determine eligibility. On Day 1, urine pregnancy test must be performed and negative pregnancy must be documented prior to dosing.

After Day 1, urine pregnancy tests (β-hCG) should be performed monthly either at home per country-specific guideline or at the study site and documented in the eDairy or eCRF. Monthly home urine pregnancy tests will be supplied to subjects as needed. Negative pregnancy test results for the respective month must be verified prior to in-person dosing for Hybrid Visits. Visual inspection of the pregnancy test result via videoconferencing is recommended for virtual assessments and it should be documented. Subjects should be instructed to immediately report any positive result to the study site, and the subject will have study treatment 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 treatment and all the necessary follow-up will be conducted as per Section 10.6.9. If the serum test is negative, the subject may resume study treatment.

10.3.6. Esophagogastroduodenoscopy

Planned timepoints for the EGD with biopsy collection are provided in the Schedules of Assessments (Appendix 1; Table 7 and Table 8).

To ensure quality data and standardization, the same trained endoscopist at each site should be used throughout the study wherever possible.

Endoscopic findings will be assessed by the trained personnel performing the EGD using the Eosinophilic Esophagitis Endoscopic Reference Score (EREFS; Section 10.4.2.1).

Biopsy collection (Section 10.3.6.1) and histopathology assessments by central reading will include eosinophil count (Section 10.4.1.1) and histologic characterization using the EoE-HSS (Section 10.4.1.2).

10.3.6.1. Biopsy Collection

Biopsies will be obtained at each endoscopy to support assessment of the histopathology and, where permitted, for the assessment of [redacted].

At the Screening EGD (Baseline), biopsies from 3 levels of esophagus as well as the gastrum and duodenum will be obtained for all subjects to determine eligibility criteria. If any of these assessments are missing, the subject will not be eligible. If the Screening EGD identifies eosinophilia in the stomach and/or duodenum, the subject will be excluded from the study. At each subsequent EGD, only esophageal biopsies will be taken.

- For esophageal biopsy collection, approximately 4 specimens will be collected from each esophageal level (proximal, mid and distal) targeting areas of apparent inflammation, when possible, to increase the diagnostic yield [6]
- For gastric biopsy collection, approximately 2 specimens will be collected from antrum and from fundus or body of the stomach each
- For duodenal biopsy collection, approximately 4 specimens will be collected from the second (descending) portion of the duodenum

Detailed instructions for endoscopic biopsies (eg, number of biopsies, anatomic site, normal or inflamed mucosa) will be provided in the Histopathology Manual.

All esophageal biopsy samples will be processed by a central laboratory. Biopsy specimen transfer, processing, slide preparation, and digitization procedures will be detailed in a Histopathology Manual.

10.3.7. Rescreening

If a subject fails Screening, 1 rescreening attempt during a new Screening Period may be made at the Investigator's discretion. Additional screening attempts beyond the first should be approved by the Medical Monitor prior to rescreening. Each subject must be reconsented prior to each screening attempt.

The results from the Screening EGD, ophthalmoscopy with OCT or PFTs from the first Screening Period may be used to confirm eligibility for rescreening if the results were obtained within 90 days prior to Day 1 (Baseline).

10.4. Efficacy Assessments

The efficacy assessments (esophageal PEC, EoE Histology Scoring System [HSS], DSQ, Food Avoidance Question [FAQ], EREFS, Adult Eosinophilic Esophagitis Quality of Life [EoE-QOL-A], Patient Global Impression of Change [PGIC] and Patient Global Impression of Severity [PGIS]) will be performed according to the Schedules of Assessments (Appendix 1; Table 7 and Table 8).

10.4.1. Histology

Details on biopsy collection are provided in Section 10.3.6.1.

10.4.1.1. Esophageal Peak Eosinophil Count

Eosinophils will be counted in the areas of greatest eosinophil density. Counts will be reported as the number of eos/hpf and multiple hpfs will be analyzed until the PEC is clearly identified after taking into account all biopsies from all esophageal levels.

The esophageal PEC will be determined by a central reader who is blinded to the identity of treatment assignment and EGD collection timepoints (except for the Screening EGD). Eligibility based on PEC will be made available to the study sites.

A subject with a PEC of ≥ 15 eos/hpf at any levels (proximal, mid, or distal) of the esophagus will be eligible to enroll in the study. Change from baseline (percentage and absolute) in PEC and histologic response (yes/no) based on pre-defined PEC timepoints will be used to characterize histologic efficacy as described in Section 11.5.

10.4.1.2. Eosinophilic Esophagitis Histology Scoring System

The EoE-HSS is a method to objectively assess histologic changes in the esophageal mucosa beyond eosinophil number. It describes changes in 8 histologic features of the esophageal mucosa: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis [51]. The severity (grade) and extent (stage) of abnormalities are scored using a 4-point scale (0 normal; 3 maximum change).

The EoE-HSS will be used to characterize the baseline esophageal histopathologic severity of EoE disease and changes with treatment intervention. Histopathologic scoring by EoE-HSS will be performed by a central reader who is blinded to treatment allocation and EGD collection timepoints. The EoE-HSS is further defined in Appendix 2.

10.4.2. Endoscopy

10.4.2.1. Eosinophilic Esophagitis Endoscopic Reference Score

The EREFS will be used to characterize the baseline endoscopic severity of EoE and changes with treatment.

The presence and severity of esophageal endoscopic features (eg, edema, rings, exudates, furrows, and strictures) will be characterized using the EREFS [52]. Endoscopic scoring by EREFS will be performed by the local endoscopist, who is blinded to the subject's treatment assignment. Grading severity and respective description of each endoscopic feature is detailed in Appendix 3.

10.4.3. Clinical Outcome Assessments

Completion of the following questionnaires will be monitored by site staff.

10.4.3.1. Dysphagia Symptom Questionnaire

The DSQ is a validated patient-reported outcome questionnaire that captures the presence and severity of dysphagia to solid food in patients with EoE. Subjects record whether they have eaten solid food since waking up, any dysphagia to solid food on that day, dysphagia severity based on relief strategies utilized during the dysphagia episode and the severity of the worst daily pain related to swallowing, if there is any [47,53]. The DSQ will be used to characterize baseline dysphagia severity and changes with treatment intervention.

Questions 1 and 2 of the DSQ from the subject's daily eDiary entries will be used to determine the eligibility regarding active dysphagia during the Screening Period. One episode of dysphagia is counted when a subject responds "yes" to questions 1 and 2 of the DSQ. Subjects must have at least an average of 2 episodes of dysphagia per week over 2 weeks during the Screening Period.

During the study, the DSQ will be completed daily in the evening after the last meal of the day.

The DSQ will be scored over a 14-day period, and a minimum of 8 DSQ daily eDiary entries out of the 14-day period preceding the date of scoring are required to calculate DSQ score. The DSQ total score range is 0 to 84.

Daily dysphagia symptom diary questions are provided in Appendix 4.

10.4.3.2. Food Avoidance Question

The FAQ assesses the reason(s) why a subject did not try to eat solid food in a given day: 1) Because of EoE, or 2) Because of other reasons. The FAQ will be administered daily via the eDiary, after the subject completes the DSQ diary questions. Only the subjects who did not eat solid food on the respective day will complete the FAQ.

The FAQ is provided in Appendix 5.

10.4.3.3. EoE-QOL-A

The EoE-QOL-A questionnaire is a disease-specific measure of health-related quality of life (QOL) in adults with EoE [54]. It measures 5 domains: eating/dietary impact, social impact, emotional impact, disease anxiety and choking anxiety. Subjects will complete the questionnaire, if available, via the eDiary on Day 1 (Baseline) and at Weeks 16, 24, 32, and 52.

10.4.3.4. Patient Global Impression of Severity

The PGIS is a current-state, 4-point Likert scale that captures the subject's overall impression of EoE symptom severity over the past week. The PGIS will be administered via eDiary on Day −8 and Day −1 of the Screening Period which will serve as the baseline and at Weeks 15, 16, 23, 24, 31, 32, 51, and 52.

The PGIS is provided in Appendix 6.

10.4.3.5. Patient Global Impression of Change

The PGIC is a 5-point Likert scale that captures the subject's overall impression of change in EoE symptoms from Baseline. The recall period is 16 to 52 weeks. The PGIC will be administered via eDiary at Weeks 16, 24, 32, and 52.

The PGIC is provided in Appendix 7.

10.5. Pharmacokinetic Assessments

Blood samples 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 and at 4 hours (± 15 minutes) postdose (after ECG) on Day 1
- Predose (trough; within 60 minutes prior to dosing) at Weeks 4, 8, 16, 24, 28, 32, 46, and 52 or at the ET Visit, if applicable

- At the 4-Week Safety Follow-Up Visit (28 days [± 3 days] after the last dose of study drug)
- If possible, at the time of an AE leading to study drug discontinuation or when there is a significant AE such as a severe or atypical infection (including but not limited to systemic infections like sepsis) and severe drug induced liver injury that meets Hy's criteria [49]. The time of the last study treatment dose should be documented.

Subjects should be instructed to document the time of their last dose prior to the study visit (Section 7.4) and the time must be recorded in the eCRF. The time of PK sample obtained predose and when study drug is administered during the study visit must also be recorded in the source.

Blood samples will be processed for collection of plasma fractions for determination of the concentrations of etrasimod and, if warranted, metabolites of interest. Blood samples collected for PK analyses 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.

No urine samples will be collected for PK analysis.

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; Table 7 and Table 8).

10.6. Safety Assessments

Planned timepoints for all safety assessments are provided in the Schedules of Assessments (Appendix 1; Table 7 and Table 8).

10.6.1. Vital Signs

Resting vital signs measurements will be made 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.

10.6.2. Physical Examinations

Full physical examination includes the following assessments:

- General inspection, including height (Day 1 only) and weight
- Head/ears/eyes/nose/throat examination
- Cardiac examination
- Auscultation of lungs
- Abdominal examination (liver, spleen)
- Neurological assessment
- Musculoskeletal assessment
- Dermatologic assessment

Full physical examinations will be performed on Day 1 and Week 52 or at the ET Visit. For visits where a full physical examination is not required, symptom-directed physical examination should assess clinically significant changes from prior study visits including the baseline physical examination or any new signs or symptoms. Symptom-directed physical examination may be performed at the Investigator's discretion at any time during the study.

10.6.3. Electrocardiography

All 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 ECGs will be recorded with subjects in supine position.

Intervals to be provided on the confirmed read for each safety ECG are RR, PR, QRS, QT, QTcB (Bazett's corrected QT interval), and QTcF.

The Investigator or designee will be responsible for review and interpretation of ECGs on site and assessing if the ECG is normal, abnormal clinically insignificant, or abnormal clinically significant. Findings will be documented in the eCRF.

Specific guidance on cardiac monitoring including ECG assessment following the first dose of study treatment is provided in Section 10.6.7.4.

10.6.4. 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 or warranted due to special circumstances (eg, inability to ship to central laboratory due to COVID-19 restrictions, Appendix 11). Refer to Table 3 for the list of clinical laboratory tests to be performed.

Clinical safety laboratory tests should be completed predose. The Investigator must review the laboratory report, document the review, and record any clinically relevant changes in the AE section of the eCRF (results of the white blood cell differential including ALC will be reviewed and monitored as described in Section 10.6.7.2). The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal (ie, those that are AEs) during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal range, have stabilized, or are no longer considered clinically significant by the Investigator. If such values do not return to normal or stabilized, or otherwise resolve to a non-clinically significant value within a reasonable period of time, as judged by the Investigator, the etiology should be identified, and the 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), 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 8 and Appendix 9. See Appendix 12 for suggested actions and follow-up assessments in the event of potential DILI.

Table 3: Clinical Laboratory Tests

<table>
<tr><td><u>Infectious Disease</u>
HIV-1 and -2 antibody, HBsAg, total anti-HBc, HCV antibody (if positive, reflex to HCV RNA quantification)</td><td rowspan="2"><u>Coagulation</u>
International normalized ratio (INR)
Activated partial thromboplastin time</td></tr>
<tr><td><u>Pregnancy and Postmenopausal Status Testing</u>
Serum pregnancy test for β-hCG (Screening or if positive urine pregnancy test; WOCBP only)
Urine pregnancy test for β-hCG (Day 1 and monthly post-Day 1; WOCBP only)
FSH (Screening; postmenopausal women only)</td></tr>
<tr><td colspan="2"><u>CBC with Differentials</u>
Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell count
WBC[a] count
WBC differential count (absolute and %): lymphocytes, neutrophils, eosinophils, monocytes, basophils</td></tr>
<tr><td colspan="2"><u>TBNK</u> Panel[a]
T, B, NK, CD4+ T cell and CD8+ T cell count (absolute number and percentage)</td></tr>
<tr><td><u>Serum Chemistry</u>
Albumin
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatinine</td><td>Glucose
Potassium
Sodium
Total bilirubin
Total protein</td></tr>
<tr><td colspan="2">CCI [redacted]</td></tr>
</table>

[a] WBC count, WBC differential count, and TBNK panel will be assessed by an independent Medical Monitor during treatment (ie, after Day 1) until completion of the Double Blind Treatment Period dose selection analysis at Week 24 or subject discontinues study treatment (whichever occurs first) while the Investigators will assess the results of these lab parameters during Screening, on Day 1, and during the post treatment follow-up (refer to Section 10.6.7.2).

β-hCG, beta-human chorionic gonadotropin; CBC, complete blood count; FSH, follicle-stimulating hormone; HBsAg, hepatitis B surface antigen; anti-HBc, hepatitis B core antibody; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; TBNK, T, B, NK, CD4+ T cell, and CD8+ T cell count (absolute number and percentage); WBC, white blood cell; WOCBP, woman of child-bearing potential

10.6.5. Pulmonary Function Test

PFTs will be performed according to the Schedules of Assessments (Appendix 1; Table 7 and Table 8). Where locally available, diffusing capacity of the lungs for carbon monoxide (DLCO) measurements will also be performed (sites where DLCO is not available should consult the Sponsor or Sponsor's delegate). 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. All DLCO values will be corrected for hemoglobin concentration (ie, hemoglobin-adjusted diffusion capacity) in the study.

PFTs and DLCO (or other acceptable pulmonary function methods) 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 [55-57]. Concern has been raised that pulmonary function testing could represent a potential avenue for COVID-19 transmission due to the congregation of patients with lung disease and because of the potential for coughing and droplet formation surrounding pulmonary function testing procedures. Refer to Appendix 11 for modifications in the event that COVID-19 or similar PHE-related restrictions limit the capacity to perform non-essential PFTs.

Patient respiratory history will be collected at the Screening Visit, and any condition that might affect the outcome of PFT, 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 patient 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. Smoking status (including ecigarettes) will be collected and recorded in the eCRF each time a PFT assessment is conducted.

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 function is provided in Section 10.6.7.5.

10.6.6. Ophthalmoscopy and Optical Coherence Tomography

A complete ophthalmoscopy and OCT assessment will be performed according to the Schedules of Assessments (Appendix 1; Table 7 and Table 8) and all ophthalmic findings should be recorded in eCRF.

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.

The ophthalmologist should be provided with a study referral letter explaining the reason for the referral along with information about the study, the investigational drug, and the ophthalmic clinical data to be collected for the study.

At the Screening and Post-Screening Visits, eye examination performed by an ophthalmologist 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
  - A dilated fundus exam should be performed in all subjects at the Screening Visit and as needed at subsequent visits in subjects with significant abnormalities identified on the screening exam. Subjects should be advised to wear sunglasses after pupil dilation and arrange for a driver to transport them after the exam
- Retinal photographs (only if evidence of clinically significant abnormalities)
- OCT for the measurement of central foveal thickness (recorded in micrometers)
- Fluorescein angiogram (FA) (at the discretion of the ophthalmologist) if there is a suspicion of macular edema by ophthalmoscopy and increased central foveal thickness by OCT

Subjects experiencing unexpected ophthalmic symptoms without a known suspected etiology or experiencing a relevant ophthalmic AE may need to have repeat ophthalmoscopy and OCT testing performed.

Additional guidance on clinical monitoring of ophthalmic symptoms is provided in Section 10.6.7.6.

10.6.7. Safety Monitoring Guidance

10.6.7.1. Drug-Induced Liver Injury

There is no published consensus on exactly when to stop a drug in the face of laboratory abnormalities and the decision may be affected by the clinical status of the patient and many other factors. The following can be considered a basic guide. When there is no alternative etiology for persistently elevated liver enzymes, discontinuation of study treatment should be considered, consistent with the United States FDA guidance [49], if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN **and** (total bilirubin > 2 × ULN **or** INR > 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%)

See Appendix 12 for suggested actions and follow-up assessments in the event of potential DILI. Information on the grading and management of laboratory abnormalities according to assessed severity is provided in Appendix 8 and Appendix 9.

10.6.7.2. Guidance on Management of Lymphocyte, Neutrophil, and White Blood Cell Counts, and Monitoring for 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. Site staff including investigators will be blinded to the WBC count, WBC differential (percentage and absolute number), and the TBNK panel cell count while subjects are on study treatment. During this time, WBC count, WBC differential, and the TBNK panel results will be assessed by an independent Medical Monitor (not involved in any other aspects of study conduct or data analysis) and will direct Investigators on specific actions to take. Blinded values may be released to treating physicians and Investigators as deemed medically necessary to monitor the risk of infection and/or aid in diagnostic work-up as clinically indicated, and/or as a tool to assess the effectiveness of therapeutic interventions for an infection.

ALC

The independent Medical Monitor will notify Investigators when the subject has an absolute lymphocyte count (ALC) $< 0.2 \times 10^9$ cells/L. In this scenario, the Investigator will be asked to have the subject return for a repeat CBC with differential within 7 days to confirm the ALC. If the ALC is confirmed to be below 0.2×10^9 cells/L, study treatment should be interrupted. While study treatment is interrupted, the Investigator will repeat the CBC with differentials weekly until ALC is $> 0.5 \times 10^9$ cells/L. Re-initiation of the study treatment can be considered when ALC is $> 0.5 \times 10^9$ cells/L. ALC recovery is expected to occur within 7 to 10 days after study treatment interruption.

When there is a sustained decreased in ALC $< 0.2 \times 10^9$ cells/L, defined as having a second confirmed ALC $< 0.2 \times 10^9$ cells/L with treatment rechallenge (after the initial study treatment interruption due to a low ALC), study treatment must be permanently discontinued.

Subjects with an ongoing AE of decreased lymphocyte count or infection at the post-treatment 4 Week Follow-Up Visit will continue to have weekly CBC with differential until ALC recovery is achieved (defined as ALC return to within the normal range or to at least 80% of the pre-treatment value).

ANC and WBC

In addition, the independent Medical Monitor will notify Investigators when there is at least 1 measurement of ANC $< 1.0 \times 10^9$ cells/L or WBC count $> 20 \times 10^9$ cells/L.

Investigators will repeat the CBC with differentials weekly until ANC $> 1.0 \times 10^9$ cells/L or the increased WBC count trends downward (on 2 separate days), respectively.

Refer to Section 10.6.7.3 for information on monitoring for signs and symptoms of infections and diagnostic work-up and treatment of infections.

10.6.7.3. Guidance on Monitoring Subjects for Infections

Low lymphocyte counts with the use of other S1P receptor modulators in patients with multiple sclerosis have been associated with serious and atypical infections [43,44]. 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 treatment (ie, the 28-day posttreatment 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 10 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.

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

Cardiac monitoring following treatment initiation applies to the first dose administered in the Double-Blind Treatment Period (Day 1) and in the Extension Treatment Period (Week 24). The lowest predose HR measurement (by vital signs) will be used for comparison to the postdose measurement (by vital signs). Subjects should receive the first dose of study treatment before 12:00 PM (noon).

First-Dose Heart Rate Monitoring

Cardiac monitoring of at least 4 hours following the first dose (Day 1 and Week 24) will include the following (Table 4):

- Full baseline vital signs (HR, BP, body temperature, and respiratory rate) and 12-lead ECG will be assessed predose (ie, Baseline)
- After the first dose of study treatment (Day 1 and Week 24), subjects must remain under direct observation at the study site for at least 4 hours.
- At Hours 1, 2, and 3 (± 15 minutes) postdose, the 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 evaluate cardiac rhythm by 12-lead ECG to identify any clinically relevant ECG changes.
- At the Hour 4 (± 15 minutes) discharge assessment, HR and BP will be assessed with the subject in the seated position and a 12-lead ECG in the supine position will also be performed. Subjects may be discharged from the study site after the Hour 4 assessment if they meet the discharge criteria described in Table 5. Subjects not meeting the discharge criteria will require extended monitoring as described below.
- Subjects experiencing a treatment-related symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope) associated with reduction of the HR together with clinically relevant 12-lead ECG changes at any time during the 4-hour monitoring period should be discontinued from study treatment.

Table 4: 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 ECG	X		X
Assess discharge criteria			X

[a] Measurements may be taken ± 15 minutes of the scheduled time.
[b] Heart rate is based on vital signs.
ECG, electrocardiogram

Table 5: Discharge Criteria After Cardiac Monitoring

Subjects will be released from the study site after dosing on Day 1 or Week 24 (but no sooner than 4 hours postdose) when they fulfill all of the following discharge criteria:
• Heart rate ≥ 50 bpm or no more than 10 bpm lower than the predose value
• Heart rate is not the lowest value measured during the observation period
• No evidence of second-degree AV block or higher
• No cardiac symptoms (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope)[a]

[a] 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 other discharge criteria, and deemed appropriate by the Investigator.

Note: Subjects should have written instructions on when to return to the study site 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; HR, heart rate

Extended Cardiac Monitoring

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

- Vital signs (BP and HR) will be assessed hourly and a 12-lead ECG may be performed, as clinically indicated, until the subject meets the discharge criteria (Table 5)
- The Medical Monitor should be contacted if the subject does not meet the discharge criteria after ≥ 4 hours of extended cardiac monitoring

If an ECG shows a new onset QTcF interval above 500 ms (CTCAE Grade 3), a repeat ECG is warranted, and, if this abnormal finding is confirmed and is considered related to study treatment, then study treatment must be interrupted. Effective diagnostic and therapeutic strategies should be employed.

Reversible causes of prolonged QTcF interval (eg, electrolyte abnormalities like hypokalemia and hypomagnesemia), should be corrected as clinically indicated. When evaluating a subject with new onset QTcF interval above 500 ms, referral to a physician experienced in treating cardiac conduction disorders should be considered. If treatment is interrupted, re-initiation of study treatment can only be considered if the QTcF interval is < 450 ms (males) or < 470 ms (females), the prolonged QTcF interval is not considered related to study treatment, the individual risk benefit is favorable (as determined by the Investigator, in agreement with the cardiologist), and after discussion with the Medical Monitor. If, after re-initiation, the QTcF interval is again prolonged above 500 ms, then study drug must be discontinued.

Cardiac Monitoring Upon Treatment Re-Initiation Following Dose Interruption

The procedure for first-dose cardiac monitoring as outlined above should be performed any time a subject misses study treatment for:

- ≥ 2 consecutive days within the first week of treatment during the Double-Blind Treatment Period or during Week 24 of the Extension Treatment Period or
- ≥ 7 consecutive days after the first week of treatment during the Double-Blind Treatment Period or after Week 24 of the Extension Treatment Period.

Subjects are not to re-initiate therapy until they return to the study site for dosing with cardiac monitoring.

10.6.7.5. Pulmonary Function Monitoring

Based on changes in pulmonary function observed with the use of S1P receptor modulators such as fingolimod and siponimod, approved for relapsing multiple sclerosis [43,44], pulmonary function will be assessed in this study. PFTs will be performed at the start and conclusion of the study.

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 8. Investigators should consider interruption of study treatment 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 (ADL). The decision to interrupt study treatment 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 treatment can only be considered if the respiratory AE has improved, stabilized, and/or resolved, and is not considered related to study treatment; the individual risk-benefit is favorable (as determined by the Investigator, in agreement with the pulmonologist); and after discussion with the Medical Monitor.

10.6.7.6. Ophthalmic Symptom Monitoring

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 repeat ophthalmoscopy and OCT testing performed.

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:

- 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.

If there is evidence of new onset macular edema considered related to study treatment, then study treatment should be interrupted as appropriate and the subject should be monitored closely with the appropriate diagnostic and clinical work-up.

Subjects with a diagnosis of macular edema considered related to study treatment 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 no less than 3 months).

These evaluations will include repeat 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) 6 to 8 weeks 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.

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.

10.6.8. Adverse Events

10.6.8.1. Definitions

10.6.8.1.1. 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

Additional guidance on the management of AEs according to assessed severity is provided in Appendix 9.

10.6.8.1.2. Serious Adverse Event

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

Fatal:	The AE resulted in death.
Life-threatening:	The AE placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.

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

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

10.6.8.1.3. 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).

10.6.8.1.4. 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 adverse events of special interest (AESIs) will be identified. In addition to appropriate reporting of these events as an AE or SAE, supplementary detailed information may be collected.

Potential AESI for etrasimod include but are not limited to:

- Cardiovascular events (eg, bradycardia, AV conduction delay, and hypertension)
- Macular edema
- Pulmonary events (airflow obstruction or altered gas exchange)
- Infections (severe infections, opportunistic infections, Herpes simplex, and Herpes zoster)
- Liver injury
- PRES
- Malignancies

10.6.8.1.5. Severity

The severity of each AE will be assessed at the onset by medically qualified personnel in accordance with the local or regional requirements in participating countries. 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 (ADL).
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care activities of daily living (ADL) (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 8.

10.6.8.1.6. Relationship

The Investigator is obligated to assess the relationship (causal relationship) between the study treatment and each occurrence of each AE. The AE relationship (causal relationship) to study treatment must be characterized as one 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 treatment administration should be considered and investigated. The Investigator should consult the IB and the Product Information of marketed products within the drug class, when applicable. For each AE/SAE, 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.

10.6.8.1.7. Eliciting, Recording, and Reporting Adverse Events

10.6.8.1.8. 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.

10.6.8.1.9. Recording Adverse Events

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

Investigators are not obligated to actively seek information on AEs or SAEs after the subject has concluded study participation. Any SAE suspected to be related to the study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration.

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

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

For SAEs, events occurring secondary to the primary event should be described on the 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.

10.6.8.1.10. 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.

10.6.8.1.11. Reporting Serious Adverse Events

All SAEs are subject to reporting requirements.

10.6.8.1.12. Serious Adverse Events

All SAEs, whether or not considered related to study drug, must be immediately reported to Pfizer Safety on the CT SAE Report Form upon awareness **and under no circumstances should the time to report exceed 24 hours of becoming aware of the event**.

If additional follow-up information is required or becomes available for a previously reported SAE, entry into eCRF of the new or updated information should be completed and reported to Pfizer Safety on a new CT SAE Report Form **within 24 hours of awareness.**

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

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.

10.6.8.1.13. Serious, Unexpected Adverse Drug Reactions

All ADRs that are both serious and unexpected are subject to expedited reporting to regulatory agencies and will be reported in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. 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:

5. For a medicinal product not yet approved for marketing in a country, the reference safety information section of a company's IB will serve as the source document in that country
6. 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 reference safety information in the IB would be considered "unexpected."

10.6.9. Pregnancy and Lactation

Pregnancy

If at any point any pregnancy test is 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 treatment and until 30 days after the last dose.

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

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported as such (following the SAE reporting process) even if outside the SAE reporting period. Examples of environmental exposure may include oral ingestion of, inhalation of, or skin contact with a tablet that is broken/crushed.

Any such exposures to the study drug under study are reportable to Pfizer Safety within 24 hours of investigator awareness irrespective of whether an AE has occurred.

10.6.9.1. Exposure During Pregnancy

An environmental EDP occurs if:

- A female nonsubject is found to be pregnant while being exposed or having been exposed to study treatment because of environmental exposure.

- A male nonsubject who has been exposed to the study drug then inseminates his female partner prior to or around the time of exposure.

10.6.9.2. Exposure During Breastfeeding

An environmental EDB occurs if:

- A female nonsubject is found to be breastfeeding while being exposed or having been exposed to study drug.

When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the subject enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

10.6.9.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

10.6.10. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE.**

10.6.11. Medication Errors

Medication errors may result from the administration or consumption of the study drug by the wrong subject, or at the wrong time, or at the wrong dosage strength. Medication errors not associated with an AE/SAE should be recorded as a protocol deviation.

A medication error with a potentially associated AE/SAE is recorded in the CRF. Medication errors associated with an SAE (per the Investigator's assessment) should be reported to Pfizer Safety within 24 hours on the CT SAE Report Form. SAEs must be reported to the designated Sponsor Contact via established reporting mechanism within 24 hours of awareness.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

10.7. Procedures for Overdose

The current edition 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:

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

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

10.8. Genetic Testing

Genetics may be evaluated in this study to assess genetic variation that may impact response to treatment, metabolism, and mechanism of action of etrasimod and for consideration of risks of the disease state.

A blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. An additional ICF may be provided to subjects for genetic analyses. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples are provided in the Laboratory Manual.

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10.10. Qualitative Interview

Qualitative interviews may be conducted with a subset of subjects who have consented to participate in the Qualitative Interview component of the study. Participation is optional. Subjects who do not wish to participate in the Qualitative Interview may still participate in the study.

The Qualitative Interview will gather insights about subjects' symptom experience during the study and identify any additional aspects of change that might be important to assess for future studies. Other factors driving subject satisfaction with treatment and perceptions on meaningful change will be asked.

The Qualitative Interview will be conducted via telephone by a trained qualitative research interviewer using a semi-structured interview guide. All interviews will be conducted in the participant's native language and will be audio recorded in accordance with applicable laws of the jurisdictions where the subjects are located. The audio recording will be transcribed for analysis and will be destroyed after evaluation. Interviews will be conducted within 14 days after the Week 24 visit. Failure to complete the optional interview that a subject has consented to will not constitute a protocol deviation. If a potential adverse event is discovered during the interview process, the information will be shared by the interviewer with the Investigator.

11. PLANNED STATISTICAL METHODS

11.1. General Considerations

Details regarding the statistical analyses will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock and unblinding.

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.

For Double Blinded Treatment Period, hypotheses tests will be performed for efficacy endpoints for the comparison of etrasimod dose versus the placebo group. However, these hypotheses tests will not be controlled for type-I error rate. Un-adjusted p-values will be reported.

For the Extension Treatment Period, no hypothesis tests between treatment groups will be performed; only descriptive statistics will be provided.

The SAP will describe an overall plan to address the alignment between the target of efficacy estimation (ie, trial objective, or estimand of interest), the analysis set, the method of estimation, and primary method to handle intercurrent events; along with a plan of sensitivity analysis to evaluate the robustness of findings that can sustain limitations in missing data and intercurrent events of non-adherence to protocol.

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

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11.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined for each treatment period as shown in Table 6.

Table 6: Analysis Sets

Analysis Set	Description
Full Analysis Set (FAS); (Double-Blind Treatment Period)	The FAS will include all randomized subjects in the Double-Blind Treatment Period, who receive at least 1 dose of study treatment. Subjects will be summarized by treatment to which they were randomized, regardless of treatment actually received.
Modified Full Analysis Set (mFAS); (Double-Blind Treatment Period)	The mFAS will include all randomized subjects who receive at least one dose of study medication and 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 one endpoint may differ from another endpoint, based on the baseline and post-baseline data.
Per Protocol Set; (Double-Blind Treatment Period)	The Per Protocol will include all subjects from the FAS without major protocol violations that might affect the evaluation of the effect of study treatment on the primary endpoint. The Per Protocol will be used in sensitivity analyses of the primary and secondary endpoints to evaluate the influence of major protocol violators and protocol deviators on the main efficacy results. Subjects may be excluded from this population if they violate the eligibility criteria or significantly deviate from the study plan. Specific reasons for warranting exclusion from this population will be documented prior to database lock and may include, but are not limited to, study treatment noncompliance, receiving incorrect study treatment, and missing more than a defined number of visits while still on study. The statistical analysis plan, which will be finalized prior to database lock, will be the final documentation for the Per Protocol Set definition.
Pharmacokinetic Set; (Double-Blind Treatment Period)	The Pharmacokinetic Set will include all subjects in the FAS with at least 1 postdose PK measurement.
Safety Set; (Double Blind Treatment Period and Extension Treatment Period)	The Safety Set will include all randomized subjects who received at least one dose of study treatment during the specified treatment period.
Efficacy Evaluable Set: (Extension Treatment Period)	The Efficacy Evaluable Set will include subjects who receive at least one dose of etrasimod and have at least one efficacy measurement in the Extension Treatment Period (endpoint specific)

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

11.4. Missing Data

11.4.1. Primary Methods of Handling Missing Data and Rescue Medication/Rescue Procedure Usage

In order to analyze efficacy endpoints at Week 16 and Week 24 in the Full Analysis Set (FAS), handling missing data and rescue mediation uses are specified as following. For the endpoint of the percent change from Baseline in esophageal PEC at Week 16 and Week 24, PEC after rescue medication/rescue procedure use will be set to missing. All missing PEC at scheduled visits up to Week 24 will be imputed using a multiple imputation (MI) procedure with a fully conditional specification (FCS) method and predictive mean matching for PEC [64-66]. The use of rescue medication/rescue procedure, reasons for early discontinuation (eg, AE), and duration of study treatment prior to early discontinuation will be captured to address and characterize the nature of

missing data in the MI procedure with an FCS method. Detailed MI model descriptions and analysis procedures will be specified in the SAP.

For analysis of dichotomous endpoints (eg, proportion of subjects with esophageal PEC of < 15 and ≤ 6 eos/hpf at Week 16 and Week 24), all subjects in the FAS will be included in the analyses. Subjects in any of the following cases will be considered as a "non-responder" or "failure":

- Use of rescue medications/rescue procedures during the Double-Blind Treatment Period;
- Prematurely discontinue from study due to any reason prior to Week 16 and Week 24; or
- With missing data at Week 16 and Week 24 for any reason

11.4.2. Sensitivity Analyses

In addition to the primary method for handling missing data and rescue medication/rescue procedure use in the FAS described in Section 11.4.1, the following sensitivity analyses will be performed for primary, secondary, and selected CCI [redacted] using alternative methods to handle missing data and/or in alternative analysis populations:

- MI usually assumes that the data are missing at random (MAR) but MAR cannot be verified using the observed data. Therefore, the sensitivity of inferences to departures from the MAR assumption will be examined. For the MI analysis of the primary endpoint of percent change from Baseline in esophageal PEC at Week 16 and Week 24, data MAR within each treatment group will be investigated using tipping point analyses method and results will be described using Rubin's rule [1]
- Percent change in esophageal PEC from Baseline to Week 16 and Week 24 will be analyzed in the modified Full Analysis Set (mFAS), data will be set to missing after rescue medication/rescue procedure uses
- Proportion of subjects with esophageal PEC of < 15 and ≤ 6 eos/hpf at Week 16 and Week 24 will be analyzed in the FAS using PEC imputed by the MI method discussed in Section 11.4.1
- Proportion of subjects with esophageal PEC of < 15 and ≤ 6 eos/hpf at Week 16 and Week 24 will be analyzed in the mFAS using PEC imputed by the MI method discussed in Section 11.4.1
- Observed data analyses in mFAS, regardless of rescue medication/rescue procedure use and without missing data imputation:
  - For longitudinal continuous variables, a linear mixed effects model will be performed and results will be reported by visit.
  - For longitudinal dichotomous measures, logistic regression analysis may be performed by visit
- Completers analyses (also known as complete case) of primary and secondary endpoints for subjects who complete 16 and 24 weeks of study treatment

- Per Protocol Set analyses in subjects who meet the criteria of Per Protocol definition approved prior to database lock

Detailed sensitivity analysis methods will be described in the SAP.

11.5. Efficacy Analyses

For the Double-Blind Treatment Period, the primary and secondary endpoints will be analyzed using the FAS. Other important statistical considerations, such as handling rescue medication/rescue procedure uses during study treatment, missing data imputation strategies, sensitivity analyses, and subgroup analyses will be described in the SAP.

The endpoints of percentage change in esophageal PEC from Baseline to Week 16 and Week 24 will be analyzed using analysis of covariance (ANCOVA) model based on rank scores due to the skewed distribution of the data and possible outliers. The ANCOVA model will include treatment group and randomization stratification factors as factors and Baseline eosinophil PEC as a covariate. PEC after rescue medication/rescue procedure uses will be set to missing; all missing data will be imputed in the FAS using MI procedure as appropriate. Multiple results of ANCOVA (least square [LS] mean rank scores and LS mean rank score difference from placebo) for each MI dataset will be analyzed and reported along with final p-value using Rubin's method [1]. In addition, a descriptive summary of percentage change in esophageal PEC from baseline as well as the difference between treatment groups will be presented by treatment group. When applying the same ANCOVA model to key secondary continuous variables, norank transformation will be used.

For the efficacy endpoints of the percentage change in esophageal PEC from Baseline at Week 16 and Week 24, in the FAS, subjects who have experienced intercurrent events, such as rescue medication/rescue procedure use, early discontinuation of study treatment, etc., will be included in the analysis and their missing data at Week 16 and Week 24 will be imputed using a MI model. The MI model will take into consideration the reason and nature of intercurrent event leading to missing data. A detailed plan for constructing and analyzing the primary estimand will be described in the SAP.

Proportion-based secondary endpoints (eg, histologic responders or symptomatic responders) at Week 16 will be analyzed in the FAS; subjects who use rescue medication or have a rescue procedure, or with missing data for any reason will be considered a "non-responder" or "failure." The analyses will be performed using the Cochran-Mantel-Haenszel (CMH) method adjusted for randomization stratification factors. The number and percentage of subjects achieving the goal and the difference in proportion between treatment groups achieving the goal, along with p-value and the 95% CIs will be reported.

Longitudinal continuous endpoints (Section 11.5.1.2) will also be analyzed up to Week 24 using a linear mixed effects model. The model will include treatment group, visit, interaction of treatment-by-visit, and randomization stratification factors as factors, and Baseline measure as covariates. An unstructured covariance matrix will be specified for the within-subject measurements. LS means and LS mean differences between treatment group with unadjusted p-values and corresponding 95% CIs will be reported at each scheduled visit. This method will also be applied to other score based or continuous measures.

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Endpoints measured during the Extension Treatment Period after Week 24 up to Week 52 will be summarized using descriptive statistics without inferential comparison. Dichotomous remission or response outcomes derived from specific scores will be assessed. Continuous variables will be summarized by visit using the number of observations, mean, SD, median, minimum, and maximum; and categorical variables will be summarized by visit using frequency counts and percentages, with following considerations:

- Four treatment sequence (as listed below) in the Extension Treatment Period will be analyzed, if applicable
  - etrasimod 1 mg-1 mg
  - etrasimod 2 mg-2 mg
  - placebo - etrasimod 1 mg
  - placebo - etrasimod 2 mg
- Change from baseline in continuous variables will be analyzed on change from Baseline in the Double-Blind Treatment Period and change from Baseline in the Extension Treatment Period

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In addition to between group analyses on the primary and secondary endpoints, dose-response relationship will be investigated using exposure-response modeling and the details will be described in the PK/PD analysis document. The PK/PD modeling will be written as a standalone document.

11.5.1. Efficacy Endpoints

11.5.1.1. Primary Endpoint

- Percent change from Baseline in esophageal PEC at Week 16

11.5.1.2. Secondary Endpoints

- Absolute change from Baseline in DSQ score at Week 16
- Absolute change from Baseline in esophageal PEC at Week 16
- Proportion of subjects with esophageal PEC < 15 eos/hpf at Week 16
- Proportion of subjects with esophageal PEC ≤ 6 eos/hpf at Week 16

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11.6. Subgroup Analyses

Subgroup analyses will be performed in primary and secondary endpoints and selected CCI [redacted] for the following baseline demographics and disease characteristics:

- Sex (male, female)
- Race (white, non-white)
- Age (≤ or > median)
- History of dilation (yes or no)
- Duration of disease (≤ or > median)
- Concurrent PPI therapy (yes or no)
- Concurrent atopic comorbidities (yes or no)
- Concurrent elimination diet (yes or no)

- Baseline esophageal PEC (≤ or > median)
- Baseline DSQ score (≤ or > median)
- Baseline EREFS (≤ or > median)
- Baseline swallowed topical steroid treatment refractory status (yes or no)

11.7. Testing Strategy

For Double Blinded Treatment Period, hypotheses tests will be performed for efficacy endpoints for the comparison of etrasimod dose versus the placebo group. However, these hypotheses tests will not be controlled for type-I error rate. Un-adjusted p-values will be reported. The associated 95% confidence intervals will be reported.

For the Extension Treatment Period, no hypothesis tests between treatment groups will be performed; only descriptive statistics will be provided.

11.8. Interim Analysis

No formal interim analyses for efficacy are planned.

11.9. Safety Analyses

All safety data will be listed and summarized by treatment group. All TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by System Organ Class and Preferred Term. Incidence of AEs, SAEs, AESIs, and AEs leading to study treatment discontinuation will be summarized and presented in descending order of frequency. In addition, details regarding risk-based safety analyses (eg, risk difference or hazard ratio) and exposure adjusted incidence rates could be described in the SAP if deemed appropriate. 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. 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.

Safety analyses for the Extension Treatment Period will follow the general considerations used for the Double-Blind Treatment Period with the following exceptions:

- Four treatment sequences (as mentioned in Section 11.5) in the Extension Treatment Period will be analyzed
- Change from Baseline will be analyzed based on change from the Double Blind Treatment Period Baseline and change from Extension Treatment Period Baseline

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, and coagulation)
- Incidence of clinically significant vital sign abnormalities and changes from baseline

11.9.2. Adverse Events

AEs will be coded using the MedDRA.

For each treatment group, the proportion of subjects with TEAEs will be summarized overall, by severity, and by relationship to study treatment. SAEs and AEs leading to study treatment discontinuation will also be summarized by treatment group. AE summaries by System Organ Class and Preferred Term will be presented in descending order of frequency. A TEAE is defined as:

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

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

11.9.3. Extent of Exposure

The duration of time on study and time on study treatment will be summarized for each treatment using descriptive statistics. The number of subjects on treatment for certain time intervals will also be summarized. The 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. Electrocardiograms

ECG rhythms and intervals will be listed by visit and summarized using descriptive statistics. Intervals to be provided for each ECG are RR, PR, QRS, QT, QTcB, 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. Outlier analysis will be performed on all subjects with QTcF values greater than 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).

11.9.6. Vital Signs

Descriptive statistics for vital signs (BP, HR, body temperature, and respiratory rate) will be presented by treatment group. Incidence of abnormal vital signs parameters will be summarized. Details will be provided in the SAP.

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. Pharmacokinetic Analyses

Plasma concentrations of etrasimod and if warranted metabolites of interest will be determined from samples collected prior to dosing and 4 hours (± 15 minutes) postdose (after ECG) on Day 1.

Plasma concentrations of etrasimod will be determined from samples collected prior to dosing (trough) at other post-baseline (Day 1) visits.

11.10.1. Pharmacokinetic Endpoint

- To determine the plasma concentration of etrasimod in subjects with EoE

A descriptive summary of observed plasma concentration will be displayed by time and by treatment group. The Pharmacokinetic Set will be used to analyze plasma levels. Full details of PK analysis will be provided in the SAP.

11.11. Clinical Outcome Assessments

The clinical outcome measures based on questionnaires (DSQ, FAQ, EoE-QOL-A, PGIC, and PGIS) will be summarized by treatment and visit using descriptive statistics.

12. REGULATORY AND ETHICAL CONSIDERATIONS

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

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;

- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

12.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study drug, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

12.2. Informed Consent and Assent

The Investigator will fully inform the subject of all pertinent aspects of the study, including the approval of the study by the IRB/IEC. Before informed consent/assent (parent or legal guardian must provide consent for a minor subject according to local regulations who has assented to participate in the study) 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. If a subject is unable to read, an impartial witness will be present during the entire 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.

12.3. 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.

12.4. 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

An audit of one or more participating study sites 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. The Trial Master File will be maintained by the CRO and the Sponsor.

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

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All changed information, including the date and person performing the corrections, will be available via the audit trail, which will be part of the electronic data capture system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness and acceptability by Sponsor personnel (or their representatives). The Sponsor's 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, endoscopy reports, laboratory data/information, subject eDiaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, ECGs, X-rays, ultrasounds. 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 treatment.

Records will be available for 2 years after marketing application approval, or if the application is not approved or never submitted, 2 years after the appropriate regulatory authorities have been notified of the discontinuation of clinical development of the investigational product, but may be retained for a longer period of time if required by the applicable regulatory requirements. 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 following:

- Location of study documentation
- 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

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 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 IC of each human subject to whom the drug is administered.

15.2. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to their investigator and the sponsor's MQI for study related medical questions or problems, subjects are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study drug identifiers, (b) subject's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the subject and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a subject. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the subject directly; if a subject calls that number directly, they will be directed back to the investigator site.

15.3. Sponsor Responsibilities

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

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APPENDIX 1: SCHEDULES OF ASSESSMENTS

Table 7: Schedule of Assessments – Screening, Double-Blind Treatment Period, and Safety Follow-Up Period

Evaluation	Screening Period	24-Week Double-Blind Treatment Period									Safety Follow-Up Period	
	D –35 to D –1	W0/D1	W2/ D15 (± 3) [Tele-health]	W4/ D29 (± 3)	W8/ D57 (± 5)	W12/ D85 (± 5) [Tele-health]	W16/ D113/ (± 5)	W20/ D141 (± 5) [Tele-health]	W24/ D169[a] (± 5)	ET[b]	2-Week F-U Visit (± 3) [Tele-health]	4-Week F-U Visit (± 3)
Informed consent	X											
Inclusion/ exclusion criteria	X	X							X			
Demographics, social and family history	X											
Medical history[c]	X	X										
Prior and concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X
Virology screen (HIV, HBV, HBsAg, HCV)	X											
Randomization/ re-randomization		X							X			
eDiary training[d]	X											
eDiary monitoring[e]	X	X	X	X	X	X	X	X	X	X		
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[f]	X[f]	X[f]		X	X		X		X	X		X
12-lead ECG[g]	X	X							X	X		
Physical examination[h]		X								X		
Pulmonary function test[i]	X								X	X		X

Evaluation	Screening Period	24-Week Double-Blind Treatment Period									Safety Follow-Up Period	
	D –35 to D –1	W0/D1	W2/ D15 (± 3) [Tele-health]	W4/ D29 (± 3)	W8/ D57 (± 5)	W12/ D85 (± 5) [Tele-health]	W16/ D113/ (± 5)	W20/ D141 (± 5) [Tele-health]	W24/ D169[a] (± 5)	ET[b]	2-Week F-U Visit (± 3) [Tele-health]	4-Week F-U Visit (± 3)
Ophthalmoscopy with OCT[j]	X								X	X		X
Pregnancy test[k]	X	X		X	X	X	X	X	X	X		X
CCI [redacted]		[redacted]										
TBNK panel	X	X		X	X		X		X	X		X
Laboratory tests[l]	X	X		X	X		X		X	X		X
EGD and biopsies[m]	X						X		X	X		
PK assessments[n]		X		X	X		X		X	X		X
CCI [redacted]		[redacted]					[redacted]		[redacted]			
Study drug dispensation[p]		X			X		X		X[q]			
Study drug accountability[r]			X	X	X	X	X	X	X	X		
In-person study drug dosing[s]		X		X	X		X		X			
Qualitative interview (optional)[t]									X			

[a] For subjects who complete Week 24 and are eligible to enter the Extension Treatment Period, the Week 24 visit will be used to assess eligibility for the extension and may also serve as the Day 1 visit of the Extension Treatment Period. Subjects on placebo during the 24-Week Treatment Period will be re-randomized to study drug for the Extension Treatment Period (Section 6.4).

[b] Subjects discontinuing prior to Week 24 should have an ET visit within 7 days of the last study treatment administration and before initiation of any new treatments. Note that safety evaluations (eg, AE query, review of concomitant medications, symptom-directed and focused physical exams as needed and relevant laboratory assessments) will be performed as described in Section 10.6.

[c] Medical history will be collected during Screening and should be updated for any new conditions or medications as needed prior to dosing at the Week 0/Day 1 visit (Section 10.3.4).

[d] eDiary device and training should be provided at Screening to ensure capturing of entries within the required 14-day period.

[e] Study site staff will monitor subject eDiary compliance. During Screening, the completion of the following eDiary questionnaires should be monitored: DSQ (daily), FAQ (daily), PGIS (Day –8 and Day –1). At least 8 DSQ daily entries in the last 2 weeks prior to Week 0/Day 1 (Baseline) visit as well as completion of PGIS are needed for

randomization. During the Treatment Period, the completion of the following eDiary questionnaires should be monitored: DSQ (daily), FAQ (daily), PGIS (Weeks 15, 16, 23, and 24), PGIC (Weeks 16 and 24), EoE-QOL-A (Week 0/Day 1 and Weeks 16 and 24).

[f] Safety vital signs (resting HR and systolic and diastolic BP, body temperature, and respiratory rate) taken with subjects in the sitting position will be performed at Screening and prior to randomization on Week 0/Day 1 (Baseline). Vital signs may be repeated up to 2 times during a visit to confirm abnormal readings (no need for second reading if the first reading is normal). Inclusion and exclusion criteria related to vital signs and ECG must be reviewed and reassessed to confirm eligibility. Vital signs including HR and BP must be measured first, followed by 12-lead ECG. The 12-lead ECGs should be obtained prior to predose blood sample collection. The first-dose cardiac monitoring procedure (Section 10.6.7.4) should be repeated if a subject has a dose interruption of: 1) ≥ 2 consecutive days within the first week of treatment during the Double-Blind Treatment Period or during Week 24; or 2) ≥ 7 consecutive days after the first week of treatment during the Double-Blind Treatment Period or after Week 24.

[g] Safety 12-lead ECGs will be performed with the subject in the supine position prior to blood sample collection and after vital signs are measured at Screening and prior to randomization on Week 0/Day 1 (Baseline), and 4 hours (± 15 minutes) after dosing on Week 0/Day 1. At the Week 24 visit, vital signs should be measured first, followed by ECGs, predose PK sample collection, study drug dosing at the study site, and first-dose cardiac monitoring for subjects continuing in the Extension Treatment Period.

[h] Complete physical examination (including assessments of the skin, head, eyes, ears, nose, throat, thyroid, lungs, heart, abdomen, back, lymph nodes, extremities, body weight, and height [height collected at Week 0/Day 1 Visit only]) should be performed at Week 0/Day 1 and the ET visit.

[i] PFTs include FEV_1 and FVC measurements. Where locally available, DLCO measurements will also be performed (sites where DLCO is not available should consult the Sponsor or Sponsor's delegate). If Week 24 or ET result is abnormal, then testing should be repeated as soon as able. Post-screening PFTs may be performed within7 days of the study visit. Details regarding additional PFTs are provided in Section 10.6.5.

[j] Scheduled non-screening ophthalmoscopy with OCT may be performed within 7 days of the study visit. Screening ophthalmoscopy with OCT is to be conducted with subjects' pupils dilated (Section 10.6.6).

[k] Only for women of child-bearing potential. Serum β-hCG test required at screening. On Day 1, urine pregnancy test must be performed and negative test result verified prior to dosing. Monthly urine pregnancy test either at home or at the study site at all other visits. Visual inspection of the test result via videoconferencing for virtual assessment is recommended. If at any point there is a positive urine β-hCG test, the subject will have study treatment interrupted and a serum sample submitted to the central laboratory for β-hCG testing (Section 10.6.9).

[l] Clinical laboratory tests will include serum chemistry, CBC with differentials, and coagulation. Screening samples should be obtained, and results must be available and reviewed prior to the first dose of study treatment. On other study visits, samples should be obtained prior to the daily dosing. Refer to Section 10.6.4.

[m] Screening EGD (Section 10.3.6) and biopsies (Section 10.3.6.1) should be performed preferably within the first 7 days of the screening period visit to allow sufficient time to confirm histology eligibility. The eosinophil counts from the central reader must be available for confirmation of eligibility. The EREFS will be scored by personnel performing the EGD. If the ET visit is within 4 weeks of the last EGD and biopsy, these procedures do not need to be repeated.

[n] PK blood samples are to be collected predose (for trough level, within 60-minute period prior to dosing) and 4 hours (± 15 minutes) postdose on Week 0/Day 1 (after 12-lead ECG), and predose on all other indicated days. A PK sample should be taken, if possible, at the time of any SAE or AE leading to study treatment discontinuation. For all PK blood draws, the time of the last dose should be documented.

[redacted] CCI

[p] Study drug may be dispensed by secure mail per country specific guidance. Alternatively, a future supply of study medications may be dispensed to the subject at a site visit to cover study medications to be dispensed at the Telehealth Visit.

[q] Study treatment should be dispensed at Week 24 if the subject continues treatment in the Extension Treatment Period. Additionally, subjects who continue on study but do not enter the Extension Treatment Period on the same day as the Week 24 visit may also be dispensed bridging study treatment.

[r] At each site visit, previously dispensed medication bottles and any remaining tablets will be collected and counted by the Investigator or qualified staff. The number of remaining tablets in the bottle may be counted by visual inspection via videoconferencing for virtual assessment. The bottle(s) and any remaining tablets must be returned to the site at the next site visit.

[s] On study visit days with blood draws, subjects should take their dose of study treatment after predose assessments and procedures have been completed.

[t] The visit window is 14 days following Week 24 visit.

AE, adverse event; β-hCG, beta-human chorionic gonadotropin; BP, blood pressure; CBC, complete blood count; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; DSQ, Dysphagia Symptom Questionnaire; ECG, electrocardiogram; eDiary, electronic diary; EGD, esophagogastroduodenoscopy; EoE-QOL-A, Adult Eosinophilic Esophagitis Quality of Life; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; ET, Early Termination; FAQ, Food Avoidance Question; FEV_1, forced expiratory volume at 1 second; F-U, follow-up; FVC, forced vital capacity; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human

immunodeficiency virus; HR, heart rate; OCT, optical coherence tomography assessment; PFT, pulmonary function test; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetics; SAE, serious AE; TBNK, T, B, NK, CD4+ T cell, and CD8+ T cell count (absolute number and percentage); W, week

Table 8: Schedule of Assessments – Extension Treatment Period and Safety Follow-Up Period

Evaluation	28-Week Extension Treatment Period					Safety Follow-Up Period	
	W28/D197 ± 7 Days	W32/D225 ± 7 Days	W46/D323 ± 7 Days	W52/D365 ± 7 Days	Early Termination[a]	2-Week Follow-Up Visit ± 3 Days [Telehealth]	4-Week Follow-Up Visit ± 3 Days
EGD and biopsies[b]		X		X	X		
eDiary monitoring[c]	X	X	X	X	X		
Concomitant therapy[d]	X	X	X	X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X
Vital signs[e]	X	X	X	X	X		X
12-lead ECG[f]				X	X		
Physical examination[g]				X	X		
Pulmonary function test[h]				X	X		X
Ophthalmoscopy with OCT[i]				X	X		X
Pregnancy test[j]	X	X	X	X	X		X
TBNK panel	X	X	X	X	X		X
Laboratory tests[k]	X	X	X	X	X		X
PK assessments[l]	X	X	X	X	X		X
CCI [redacted]		[redacted]		[redacted]			
Study drug dispensation[n]		X	X				
Study drug accountability[o]	X	X	X	X	X		
In-person study drug dosing[p]	X	X	X	X			

[a] Subjects discontinuing the study prior to Week 52/Day 365 should have an ET visit within 7 days of the last study treatment administration and before initiation of any new treatments.

[b] The EREFS will be scored by the personnel performing the EGD. If the ET visit is within 4 weeks of the last EGD and biopsy, these procedures do not need to be repeated.

[c] The completion of the following eDiary questionnaires should be monitored: DSQ (daily), FAQ (daily), PGIS (Weeks 31, 32, 51, and 52), PGIC (Weeks 32 and 52), and EoE-QOL-A (Weeks 32 and 52).
[d] All concomitant medications and procedures should be collected through the safety reporting period (Section 6.7).
[e] Vital signs including HR and BP must be measured first, followed by 12-lead ECG.
[f] Safety 12-lead ECGs will be performed with the subject in the supine position prior to predose blood sample collection and after vital signs are measured.
[g] At the Week 52 or ET visit, a complete physical examination (including assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, back, lymph nodes, extremities, and body weight) should be performed.
[h] PFTs include FEV_1 and FVC measurements. Where locally available, DLCO measurements will also be performed (sites where DLCO is not available should consult the Sponsor or Sponsor's delegate). If Week 52 or ET result is abnormal, then testing should be repeated as soon as able. Post-screening PFTs may be performed within 7 days of the study visit. Details regarding additional PFTs are provided in Section 10.6.5.
[i] Details regarding ophthalmoscopy and OCT assessments and instruction following abnormal results are provided in Section 10.6.6.
[j] Urine pregnancy test only for women of child-bearing potential. Monthly urine pregnancy test should be performed either at home or at the study site. At Weeks 32 and 46, sufficient urine pregnancy test kits should be provided to female subjects for monthly testing until the next study site visit. Visual inspection of the test result via videoconferencing for virtual assessment is recommended. If at any point there is a positive urine β-hCG test, the subject will have study treatment interrupted and a serum sample submitted to the central laboratory for β-hCG testing (Section 10.6.9).
[k] Clinical laboratory tests will include serum chemistry, CBC with differentials and coagulation and should be obtained prior to the daily dosing. Refer to Section 10.6.4.
[l] PK blood samples are to be collected predose (within 60-minutes prior to dosing). A PK sample should be taken, if possible, at the time of any SAE or AE leading to study treatment discontinuation. For all PK blood draws, the time of the last dose should be documented.
[CCI]
[n] Study drug may be dispensed by secure mail per country specific guidance. Alternatively, a future supply of study medications may be dispensed to the subject at a site visit to cover study medications to be dispensed at the Telehealth Visit.
[o] At each site visit, previously dispensed medication bottles and any remaining tablets will be collected and counted by the Investigator or qualified staff. The number of remaining tablets in the bottle may be counted by visual inspection via videoconferencing for virtual assessment. The bottle(s) and any remaining tablets must be returned to the site at the next site visit.
[p] On study visit days with blood draws, subjects should take their dose of study treatment after all predose assessments and procedures have been completed.

AE, adverse event; β-hCG, beta-human chorionic gonadotropin; BP, blood pressure; CBC, complete blood count; D, day; DLCO, diffusing capacity of the lungs for carbon monoxide; DSQ, Dysphagia Symptom Questionnaire; eDiary, electronic diary; ECG, electrocardiogram; EGD, esophagogastroduodenoscopy; EoE-QOL-A, Adult Eosinophilic Esophagitis Quality of Life; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; ET, Early Termination; FAQ, Food Avoidance Question; FEV_1, forced expiratory volume at 1 second; FVC, forced vital capacity; HR, heart rate; OCT, optical coherence tomography; PFT, pulmonary function test; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetics; SAE, serious AE; TBNK, T, B, NK, CD4+ T cell, and CD8+ T cell count (absolute number and percentage); W, week

APPENDIX 2: EOSINOPHILIC ESOPHAGITIS HISTOLOGY SCORING SYSTEM

Table 9: Eosinophilic Esophagitis Histology Scoring System Definitions

Each feature will be scored separately for grade (severity) or stage (extent) of abnormality using a 4-point scale (0 = normal; 3 = most severe or extensive).

Features	Definition
Eosinophilic inflammation	Based on peak eosinophil count
Basal zone hyperplasia	Basal zone occupies more than 15% of total epithelial thickness
Eosinophil abscess	Eosinophil aggregate that disrupts the underlying epithelial architecture
Eosinophil surface layering	Eosinophils align in one or more rows in the upper third of the epithelium
Dilated intercellular spaces	Intercellular bridges are visible in paracellular spaces
Surface epithelial alteration	Surface epithelial cells stain more darkly than normal and eosinophils that may be present among the altered epithelial cells
Dyskeratotic epithelial cells	Epithelial cells with deeply staining cytoplasm and shrunken hyperchromatic nuclei that generally occur singly and may be found anywhere in the epithelium
Lamina propria fibrosis	Coalesced fibrils form fibers of varying diameter

Source: [67].

APPENDIX 3: EOSINOPHILIC ESOPHAGITIS ENDOSCOPIC REFERENCE SCORE

Major features

- Fixed rings (also referred to as concentric rings, corrugated esophagus, corrugated rings, ringed esophagus, trachealisation)
  - Grade 0: none
  - Grade 1: mild (subtle circumferential ridges)
  - Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope (outer diameter 8-9.5 mm))
  - Grade 3: severe (distinct rings that do not permit passage of a diagnostic endoscope)
- Exudates (also referred to as white spots, plaques)
  - Grade 0: none
  - Grade 1: mild (lesions involving < 10% of the esophageal surface area)
  - Grade 2: severe (lesions involving > 10% of the esophageal surface area)
- Furrows (also referred to as vertical lines, longitudinal furrows)
  - Grade 0: absent
  - Grade 1: present
- Edema (also referred to as decreased vascular markings, mucosal pallor)
  - Grade 0: absent (distinct vascularity present)
  - Grade 1: loss of clarity or absence of vascular markings
- Stricture
  - Grade 0: absent
  - Grade 1: present

Minor features

- Crepe paper esophagus (mucosal fragility or laceration upon passage of diagnostic endoscope but not after esophageal dilation)
  - Grade 0: absent
  - Grade 1: present

Source: [52].

APPENDIX 4: DYSPHAGIA SYMPTOM QUESTIONNAIRE

1. **Since you woke up this morning, did you eat solid food?**

Possible responses:

- *Yes*
- *No*

2. **Since you woke up this morning, has food gone down slowly or been stuck in your throat?**

Possible responses:

- *Yes (2)*
- *No (0)*

3. **For the most difficult time you had while swallowing food today, did you have to do anything to make the food go down or to get relief?**

Possible responses:

- *No, it got better or cleared up on its own (0)*
- *Yes, I had to drink liquid to get relief (1)*
- *Yes, I had to cough and/or gag to get relief (2)*
- *Yes, I had to vomit to get relief (3)*
- *Yes, I had to seek medical attention to get relief (4)*

4. **The following question concerns the amount of pain you have experienced when swallowing food. What was the worst pain you had while swallowing food today?**

Possible responses:

- *None, I had no pain (0)*
- *Mild (1)*
- *Moderate (2)*
- *Severe (3)*
- *Very Severe (4)*

The Dysphagia Symptom Questionnaire questions above will be administered via the electronic diary (eDiary), which will be completed daily in the evening after subjects have their last meal of the day.

APPENDIX 5: FOOD AVOIDANCE QUESTION

If you did not try to eat solid food today, what is the primary reason for this? Mark ☒ in applicable box(es).	
☐	Not applicable because I ate solid food today
☐	Because of eosinophilic esophagitis symptoms
☐	Because of other reasons

The Food Avoidance Question will be administered via the electronic diary (eDiary), after subject completes the Dysphagia Symptom Questionnaire diary questions.

APPENDIX 6: PATIENT GLOBAL IMPRESSION OF SEVERITY

Please choose the response below that best describes the severity of your eosinophilic esophagitis symptoms over the past 7 days. Mark ☒ in one box below.	
☐	None
☐	Mild
☐	Moderate
☐	Severe

APPENDIX 7: PATIENT GLOBAL IMPRESSION OF CHANGE

Please choose the response below that best describes the overall change in your eosinophilic esophagitis symptoms since you started taking the study medication.

Mark ☒ in one box below.

☐	Much better
☐	A little better
☐	No change
☐	A little worse
☐	Much worse

If you had a change, was it meaningful to you? ☐ **Yes** ☐ **No**

APPENDIX 8: GRADING OF CLINICAL AND LABORATORY ADVERSE EVENTS

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

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

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

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	–	–
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing.					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self-care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways.					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self-care ADL	–	–
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	–
Definition: A disorder characterized by visual perception of unclear or fuzzy images.					
Blood and lymphatic system disorders					
Anemia	Hgb < LLN–10.0 g/dL; < LLN-6.2 mmol/L; < LLN-100 g/L	Hgb < 10.0-8.0 g/dL; < 6.2-4.9 mmol/L; < 100-80 g/L	Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					

ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; Hgb, hemoglobin

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					
Platelet count decreased	< LLN-75,000/mm^3; < LLN-75.0 × 10^9/L	< 75,000 – 50,000/mm^3; < 75.0-50.0 × 10^9/L	< 50,000-25,000/mm^3; < 50.0-25.0 × 10^9/L	< 25,000/mm^3; < 25.0 × 10^9/L	–
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
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	–	–

ADL, activities of daily living; 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 9: 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 Common Terminology Criteria for Adverse Events.

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

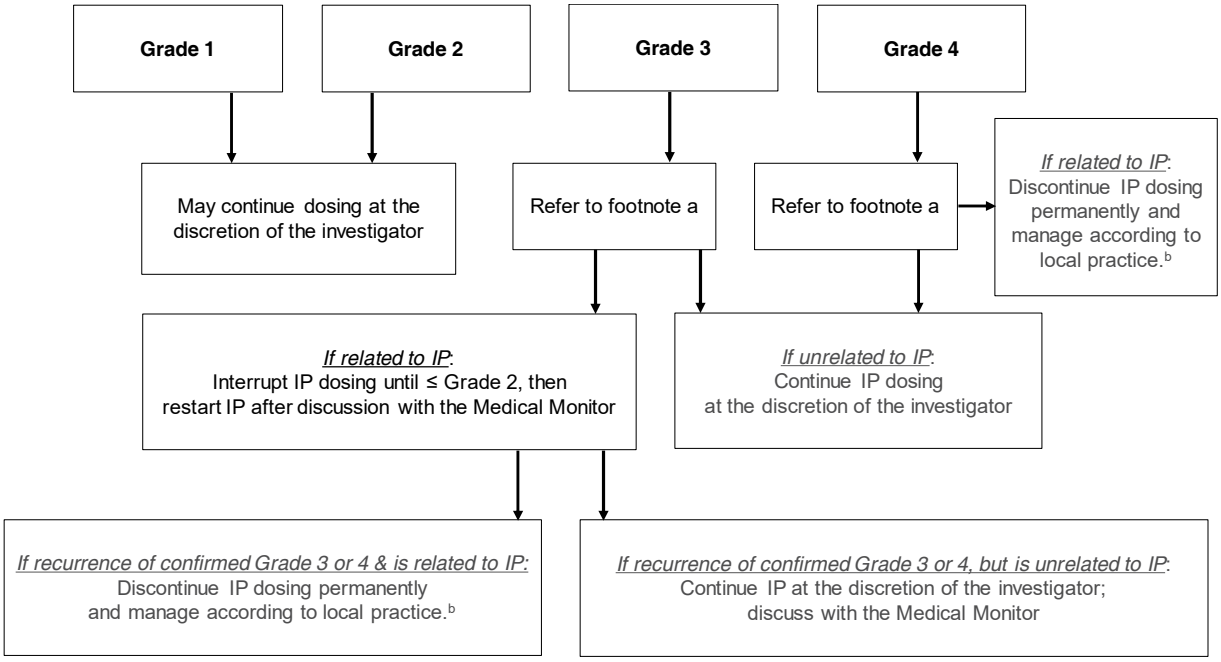
Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational product discontinuation, unless such a delay is not consistent with good medical practice.

A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat 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.

Figure 2: Algorithm for the Management of Clinical and Safety Assessment-Related Adverse Events



AE, adverse event; ECG, electrocardiogram; IP, investigational product; PFT, pulmonary function test.
[a] Repeat lab tests, ECG, or PFT to confirm AE grade. Clinical adverse event(s) may require additional assessment, therapeutic intervention, and/or consultation with relevant expert.
[b] Laboratory and/or clinical AEs should be followed until there is stability, improvement or resolution.

APPENDIX 10: GUIDANCE FOR THE ASSESSMENT OF POTENTIAL PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

To date, there have been no reports of progressive multifocal leukoencephalopathy (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 treatment (ie, the 28-day Safety Follow-Up Period).

If a subject exhibits signs and symptoms suspicious for PML, the Investigator must interrupt study treatment 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 one 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). In the evaluation of suspected PML cases, investigators may consult with a local neurologist or relevant experts, as needed. If PML cannot be ruled out, an Independent Adjudication Committee (IAC) of PML medical experts may be consulted.

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 IAC. Based on the results of investigator/neurologist examination and IAC input, subject may need additional diagnostic tests to exclude or confirm the diagnosis of PML (eg, magnetic resonance imaging of the brain, spinal tap).

Study treatment may resume, and no further evaluation is needed if the investigator assessment reveals no objective signs of PML, the neurologist confirms that the patient does not have PML, or the IAC’s review of the evidence concludes that PML is ruled out.

APPENDIX 11: GUIDANCE ON CLINICAL TRIAL CONDUCT DURING THE COVID-19 PANDEMIC

With a public health emergency (PHE) such as the coronavirus disease 2019 (COVID-19) pandemic, it is recognized that the conduct of clinical trials of medical products may be greatly impacted. However, the investigator will remain responsible for assuring the safety of trial participants, maintaining compliance with Good Clinical Practice, and minimizing risks to trial integrity. Additionally, it is expected that every effort will be made to avoid protocol deviation while abiding with national and local health official mandates related to the control and management of COVID-19.

Consistent with guidance provided by the Food and Drug Administration [68] and European Medicines Agency [69], the following general considerations are provided to illustrate appropriate action(s) that may be implemented should ongoing COVID-19 or similar PHE-related challenges lead to difficulties in adhering to protocol-specified study visits, assessments and/or procedures.

Screening

1. The 35-day Screening Period may be extended on a case-by-case basis to accommodate reasonable delays in specific screening assessments (eg, pulmonary function tests [PFTs], optical coherence tomography [OCT]). The Medical Monitor should be consulted on each case.
2. If significant delay is expected in getting the histology results back, Screening esophageal biopsy specimens may be read locally to determine peak eosinophil count for eligibility verification. The local histology read may be confirmed by a central read at a later timepoint. The Sponsor will determine when it is appropriate to proceed by this alternative route.
3. Depending on local institutional practices or country-specific guidelines, the Investigator may consider having the subject obtain COVID-19 diagnostic testing 5 to 7 days prior to a scheduled esophagogastroduodenoscopy (EGD) (performed by any qualified healthcare provider) and use the result to inform the vigilance of infection control measures to be carried on the day of EGD. COVID-19 testing for this trial that is not covered by the subject's health insurance plan may be invoiced to the Sponsor. Consult your clinical research associate (CRA) on this matter.

Safety Assessments

1. When required in-person safety assessments (eg, clinical safety laboratory tests) can only be performed outside of a study visit window, the investigator should consider whether the safety of the trial participant can be assured with the delayed evaluation.
    - It is recommended that in-person safety assessments (eg, clinical safety laboratory tests) and efficacy assessments (eg, EGD) be performed no later than the timepoint that is halfway between two consecutive study visits.
2. When the subject cannot return to the study site or delegated study staff cannot be deployed to visit the subject for in-person safety assessments (eg, clinical safety laboratory tests) for submission to the central lab, the clinical safety laboratory tests may

be processed and analyzed by a local lab. This option will require prior agreement by the Sponsor.

3. Due to the risk of COVID-19 transmission from dispersion of respiratory droplets, medical societies or local/national public health officials may recommend that pulmonary function testing and DLCO be limited to tests that are essential for immediate treatment decisions.
    - When PFTs cannot be performed, the Sponsor may recommend other methods of monitoring respiratory health including measurement of arterial oxygen saturation (SpO_2) by pulse oximeter at Screening and post-baseline visits. It has been shown that the SpO_2 in patients with chronic obstructive pulmonary disease (COPD) correlates with the forced expiratory volume in 1 second (FEV_1) [70]. A pulse oximeter SpO_2 of ≤ 92% on room air is 100% sensitivity and 86% specificity for detecting hypoxemia [71].
    - When Screening PFTs cannot be performed, Exclusion Criterion 18 may be modified as shown by the text in *italicized* font to identify and exclude subjects with underlying pulmonary disease at Screening: Have an FEV_1 or forced vital capacity (FVC) of < 70% predicted (prior to the administration of a short-acting bronchodilator) on Screening PFTs; *or a Screening pulse oximeter SpO_2 of ≤ 92% on room air when Screening PFTs are not available due to COVID-19-related restrictions or a history of pulmonary disease requiring hospitalization ≤ 6 months prior to Baseline.*
    - Under the scenario above, the missed PFTs and DLCO must be performed no later than 10 days after COVID-19 restrictions are lifted and the PFT lab re-opens.
4. Due to risk of COVID-19 transmission from prolonged contact time between patients and medical staff, medical societies may recommend limiting ophthalmic evaluations to tests that are essential for immediate treatment decisions.
    - When ophthalmoscopy with OCT cannot be performed, Exclusion Criterion 17 may be modified as shown by the text in *italicized* font to identify and exclude subjects with potential macular edema at Screening: "Have active diabetic retinopathy, uveitis, retinitis pigmentosum, history of intraocular surgery ≤ 12 months prior to Baseline, macular edema *or symptoms of blurry or wavy central vision, report colors appearing washed out or different, or have difficulty reading ≤ 6 months prior to Baseline (when Screening ophthalmoscopy with OCT cannot be performed due to COVID-19-related restrictions)*."
    - Under the scenario above, the missed ophthalmoscopy with OCT exam must be performed no later than 10 days after COVID-19 restrictions are lifted and the ophthalmology consultant's office is opened for non-urgent ophthalmic evaluations.

Documentation Guidance

When COVID-19-related restrictions/mandates lead to protocol deviations, the following COVID-19-related reasons should be documented for each deviation and each subject.

- Specific local restrictions (eg, mandated quarantines, mandated travel limitations) and/or
- Site-specific circumstances (eg, limitation on the number of patients that can be seen in at a clinic/investigative site at any one time due to social distancing parameters) and/or
- Patient-specific circumstances (eg, patient with COVID-19)

Valid COVID-19-related reasons will be taken into considerations when determining the corrective action for the protocol deviation.

Ask your CRA and/or the Medical Monitor for guidance on any alternative safety monitoring approaches that are not described above.

APPENDIX 12: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Subjects who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For subjects with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

  - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

Document Approval Record

Document Name:	C5041009 (APD334-206) Protocol Amendment 3.0 04 January 2023
Document Title:	C5041009 (APD334-206) Protocol Amendment 3.0 04 January 2023

Signed By:	Date(GMT)	Signing Capacity
PPD	05-Jan-2023 06:44:44	Author Approval
PPD	05-Jan-2023 13:26:17	Manager Approval