Title Page

SUB STUDY

A PHASE 1, OPEN-LABEL, SINGLE DOSE, FIXED-SEQUENCE CROSSOVER SUB STUDY TO DETERMINE THE PHARMACOKINETICS USING TASSO DEVICE AND SAFETY AND TOLERABILITY USING WEARABLE MONITORING DEVICES FOLLOWING SINGLE ORAL DOSES OF ETRASIMOD 2 MG IR TABLETS IN HEALTHY ADULT PARTICIPANTS IN A HYBRID DECENTRALIZED CLINICAL TRIAL DESIGN

Study Intervention Number:	PF-07915503
Study Intervention Name:	Etrasimod
US IND Number:	125154
EudraCT/EU CT Number:	2023-508119-22-00
ClinicalTrials.gov ID:	Not applicable
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5041050
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Sub Study to Learn About the Study Medication Called Etrasimod Tablets in a Hybrid Decentralized Clinical Trial Setting

Document History

Document	Version Date
Sub Study Protocol Amendment 2 (C5041050)	06 Nov 2023
Sub Study Protocol Amendment 1	12 Oct 2023
Sub Study Protocol	11 Sep 2023
Amendment 1 (C5041034)	02 Jun 2023
Original Protocol (C5041034)	03 Apr 2023

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any global protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Sub Study Protocol Amendment 2 (06 Nov 2023)

Overall Rationale for the Amendment: The Sub Study Protocol was amended to change the protocol number as summarized below:

Description of Change	Brief Rationale	Section # and Name
Non-substantial Modification(s)		
Change of protocol number for the DCT Sub Study from C5041034 to C5041050.	Since the initial approval, the DCT Sub Study protocol (including Amendment 1) is set up as a stand-alone document. The Sub Study protocol (EudraCT/EU CT No. 2023-508119-22-00) was approved with the same protocol number C5041034 as the main study protocol (EudraCT/EU CT No. 2023-504411-32-00). However, to align with the requirements of Pfizer SOPs and data management systems, a separate unique protocol number was required for the Sub Study. This Amendment 2, reflecting the new protocol number, is planned to be implemented in advance of the first participant first visit (FPFV) milestone for the Sub Study. These changes do not affect the main study C5041034 protocol.	Title Page, Header, Section 1.1 Regulatory Agency Identification Number(s)

Description of Change	Brief Rationale	Section # and Name
Protocol number added to Document History Table	For clarification and tracking.	Document History Table

Sub Study Protocol Amendment 1 (12 Oct 2023)

Overall Rationale for the Amendment: The Sub Study Protocol was amended to address queries from EU regulators following submission of an initial clinical trial application; the changes are summarized below:

Description of Change	Brief Rationale	Section # and Name
Non-substantial Modification(s)		
Exclusion Criterion #1, changed the time frame prior to study intervention from ≤8 weeks to ≤6 months.	According to the IB, etrasimod is contraindicated in patients who in the last 6 months have experienced a myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or New York Heart Association Class III/IV heart failure.	Section 5.2. Exclusion Criteria and Section 2.3.1. Risk Assessment
Specify ophthalmologic examination by ophthalmologist as part of physical examination	According to the IB, macular edema is an important identified risk which requires specific ophthalmologic monitoring. Therefore, an ophthalmologic examination by an ophthalmologist is included at baseline (Screening) and for clinical monitoring of any signs or symptoms throughout the trial, as needed.	Section 1.3. Schedule of Activities, Section 2.3.1. Risk Assessment, and Section 8.3.1. Physical Examinations

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 1, Open-Label, Single Dose, Fixed-Sequence Crossover Sub Study to Determine the Pharmacokinetics Using Tasso Device and Safety and Tolerability Using Wearable Monitoring Devices Following Single Oral Doses of Etrasimod 2 mg IR Tablets in Healthy Adult Participants in a Hybrid Decentralized Clinical Trial Design

Brief Title:

A Sub Study to Learn About the Study Medication Called Etrasimod Tablets in a Hybrid Decentralized Clinical Trial Setting

Regulatory Agency Identification Number(s):

US IND Number:	125154
EudraCT/EU CT Number:	2023-508119-22-00
ClinicalTrials.gov ID:	Not applicable
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5041050
Phase:	1

Rationale:

This sub study is being conducted to assess the feasibility of conducting a Phase 1 etrasimod study as a hybrid decentralized clinical trial with dosing by study personnel at the CRU and remote collection of PK, safety and tolerability data. The specific objectives of the sub study are to determine the pharmacokinetics (PK) and to assess the safety and tolerability of etrasimod clinical immediate release (IR) tablets 2 mg under fasted conditions in healthy adult participants in a hybrid decentralized clinical trial (DCT) design.

This study is being conducted under the main study C5041034 as a sub study for the following reasons. The assessments and the objectives of this study are distinctly different from the main study; however, the analysis plan of the sub study includes comparison of the results of the sub study conducted as a hybrid DCT design with corresponding results of the main study conducted at the CRU.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To compare the PK of etrasimod 2 mg clinical IR tablets under fasted conditions in healthy participants using Tasso PK micro samples taken by participants only (Treatment G) vs. CRU staff and participants (Treatment F) in a hybrid DCT design	• Plasma $AUC_{24\ hr}$, $AUC_{24hr\text{-}last}$, AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of etrasimod
Secondary:	**Secondary:**
• To compare the PK of etrasimod 2 mg clinical IR tablets under fasted conditions in healthy participants using Tasso PK micro samples taken by participants only (Treatment G) vs. CRU staff and participants (Treatment F) in a hybrid DCT design vs. venous PK samples taken by CRU staff in conventional design of main study (Treatment A)	• Plasma $AUC_{24\ hr}$, $AUC_{24hr\text{-}last}$, AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of etrasimod
• To evaluate the safety and tolerability of etrasimod 2 mg clinical IR tablets in healthy participants using mobile wearable devices in a hybrid DCT design	• Assessment of first dose HR reduction, TEAEs, clinical laboratory abnormalities, vital signs, PEs, and ECGs

Abbreviations: AUC_{24hr} = area under the plasma concentration-time profile from time zero to 24 hr; $AUC_{24hr\text{-}last}$ = area under the plasma concentration-time profile from time 24 hr to the time of the last quantifiable concentration; AUC_{inf} = area under the concentration-time curve from time zero extrapolated to infinity; AUC_{last} = area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration; C_{max} = maximum observed concentration; DCT = decentralized clinical trial; CRU = Clinical Research Unit; ECG = electrocardiogram; HR = heart rate; IR = immediate release; PE = physical examination; PK = pharmacokinetic(s); TEAE = treatment emergent adverse event.

Overall Design:

This is a Phase 1, open-label, single-dose, fixed-sequence, crossover sub study in a single cohort of approximately 8 healthy male or female participants conducted using a hybrid DCT design.

The study will consist of 2 treatments. Participants will receive the two Treatments F and G in a fixed sequence as shown below.

Fixed Treatment Sequence (n=8)	Period 1	Period 2
	F	G

Treatment F: Single oral dose of etrasimod 2 mg, DCT with practice sessions* (Reference)
Treatment G: Single oral dose of etrasimod 2 mg, DCT without practice sessions** (Test)
* Practice of Tasso and Wearable Monitoring Devices on Day 2 at CRU; participant self-assessment remotely for vitals and ECG (Days 3-5) and PK samples (Days 3-8)
** Participant self-assessment using Tasso and Wearable Monitoring Devices on Days 1-2 at CRU; and remotely on Days 3-8

Following are the key elements of the design of this hybrid decentralized clinical trial. Participants will be discharged from the clinical research unit (CRU) on Day 2 of each

Period, following practice sessions (Period 1 only) with the use of Tasso for serum PK sampling and wearable devices for safety monitoring, and the completion of all assessments that are planned to be performed at the CRU. The Tasso OnePlus, high-volume liquid blood collection device, will be used for micro-PK sampling and the blood samples collected by participants will be sent to the CRU within 72 hours of collection for processing of serum. The BioBeat Patch and PCA500 wearable monitoring devices will be used for collection of vitals and ECGs, respectively, in Periods 1 and 2. Each treatment period is 8 days that includes dosing, PK sampling, safety assessments, and practice (Period 1 only) with use of wearable devices and Tasso sampling. The PK and safety (ECGs and vitals) assessments through Day 2 of Period 1 will be performed by the CRU staff. Following practice with the Tasso and wearable monitoring devices on Day 2 of Period 1, the assessments on Days 3 to 8 (remote) of Period 1 and on Days -1 to 2 (at CRU) and 3 to 8 (remote) of Period 2 will be self-performed by the participants. Participants will be discharged from the CRU on Day 2 of Periods 1 and 2. Participants will receive an emergency card for contacting the CRU and will be provided detailed instructions to call PCRU for reporting of an AE. Additionally, the participants will be provided with diaries to record information about PK sampling times, concomitant medication(s) and AEs during the self-assessment phase following discharge on Day 2 of Periods 1 and 2. The participants will be provided instructions for returning the wearable devices and other study related materials study following completion of all assessments on Day 8 of Period 2. The total planned duration of participation from the screening visit to the last follow-up phone call, is approximately 9 weeks.

Number of Participants:

A total of 8 participants will be assigned to study intervention in a fixed sequence of two single-dose treatments.

Participants who withdraw from the study or whose study data are determined to be non-analyzable may be replaced at the discretion of the investigator upon consultation with the sponsor.

Note: “Enrolled” means a participant’s agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Male and female participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening who are overtly healthy as determined by medical evaluation including a detailed medical history, full physical

exam, which includes blood pressure (BP) and pulse rate measurement, clinical laboratory tests, temperature, and 12-lead ECG.

2. Body mass index (BMI) of 16 to 32 kg/m^2; and a total body weight >50 kg (110 lb).

3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

4. Capable of giving signed informed consent.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, anaphylactic, ophthalmologic disorder (such as macular edema, uveitis, retinopathy), or allergic disease.

2. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

3. Known immunodeficiency disorder, including positive serology for human immunodeficiency virus (HIV), or a first degree relative with a hereditary immunodeficiency.

4. Infection with hepatitis B or hepatitis C viruses according to protocol specific testing algorithm history.

5. Participants with any of the specified acute or chronic infections or infection history.

6. History of febrile illness within 5 days prior to the first dose of study intervention.

7. History of any lymphoproliferative disorder such as Epstein-Barr virus (EBV) related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs or symptoms suggestive of current lymphatic or lymphoid disease.

8. Known present or a history of malignancy other than a successfully treated or excised nonmetastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

9. Evidence of untreated or inadequately treated active or latent Mycobacterium tuberculosis (TB) infection.

Study Arms and Duration:

Participants will receive a single dose of etrasimod 2 mg on Day 1 of each period. The total planned duration of participation from the screening visit to the last follow-up phone call, is approximately 9 weeks.

Study Intervention(s)	
Intervention Name	Etrasimod clinical IR tablets, 2 mg Reference product
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	Coated tablets containing 2 mg etrasimod each
Unit Dose Strength(s)	2 mg/tablet
Route of Administration	Oral

Abbreviations: AxMP = auxiliary medicinal product; IMP = investigational medicinal product; IR = immediate release; NIMP = noninvestigational medicinal product.

Study Arm(s)		
Arm Title	Period 1	Period 2
Arm Description	Participants will receive a single dose of etrasimod on Day 1 of each period. Participants will be assigned to a fixed crossover sequence to receive single-dose Treatments F and G in Periods 1 and 2, respectively. In each period, etrasimod 2 mg clinical IR tablet will be administered with 240 mL water under fasting conditions.	

Etrasimod will be supplied as clinical IR tablet to the CRU in bulk in high-density polyethylene (HDPE) bottles.

Statistical Methods:

Sample Size Estimation

A sample size of 8 participants will provide adequate precision to estimate the relative bioavailability (rBA) of etrasimod across studies. These estimates are based on the assumption that standard deviations are 0.281 and 0.305 for $\ln AUC_{inf}$ and $\ln C_{max}$, respectively, as obtained from studies APD334-007 and APD334-114.

Primary Endpoints

PK parameters will be summarized descriptively by treatment, in accordance with Pfizer data standards. Plasma concentrations will be listed and summarized descriptively by nominal PK sampling time and treatment. Individual participant and median profiles of the plasma concentration-time data will be plotted by treatment using actual and nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales.

Natural log transformed AUC_{24hr}, $AUC_{24hr\text{-}last}$, AUC_{inf}, AUC_{last}, and C_{max} will be analyzed using a mixed effect model with treatment as fixed effect and participant within the sequence as a random effect. Treatment F (etrasimod 2 mg, DCT Tasso PK micro samples taken by CRU staff and participants) will be the Reference treatment while Treatment G (etrasimod 2 mg, DCT Tasso PK micro samples taken by participants only) will be the Test treatment.

Additionally, natural log transformed AUC_{24hr}, $AUC_{24hr\text{-}last}$, AUC_{inf}, AUC_{last}, and C_{max} will be analyzed using a mixed effect model with treatment as a fixed effect. Treatment A (etrasimod 2 mg, Main study, venous PK samples) will be the Reference treatment while Treatment F (etrasimod 2 mg, DCT Tasso PK micro samples taken by CRU staff and participants) and Treatment G (etrasimod 2 mg, DCT Tasso PK micro samples taken by participants only) will be the Test treatments.

Secondary Endpoints

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Ethical Considerations:

Etrasimod, an investigational, oral, and once daily sphingosine 1-phosphate (S1P) receptor modulator, is not expected to provide any clinical benefit to healthy participants. In this study, etrasimod will be administered as a single dose of 2 mg in each period of the study.

The sub study is being conducted to assess the feasibility of conducting a Phase 1 etrasimod study as a hybrid decentralized clinical trial [1,2] with dosing by study personnel at the CRU and remote collection of PK, safety and tolerability data. DCTs have the potential to expand

[1] FDA. Decentralized clinical trials for drugs, biological products, and devices. May 2023. Available from: Decentralized Clinical Trials for Drugs, Biological Products, and Devices | FDA. Accessed: 09 Aug 2023.

[2] EMA. Recommendation paper on decentralised elements in clinical trials. Version 01, 13 Dec 2022. Available from: mp_decentralised-elements_clinical-trials_rec_en.pdf (europa.eu). Accessed: 09 Aug 2023.

access to more diverse patient populations and improve trial efficiencies. [3] Advances in clinical care using electronic communications and information technology to interact with trial participants in different locations (ie, telehealth) allow for fewer in-person visits to clinical trial sites. Digital health technologies (DHTs), for example, have expanded the types of trial-related data that can be obtained remotely from trial participants. By enabling remote participation, DCTs may enhance convenience for trial participants, reduce the burden on caregivers, and facilitate research on rare diseases and diseases affecting populations with limited mobility or access to traditional trial sites. This may help improve trial participant engagement, recruitment, enrollment, and retention of a meaningfully diverse clinical population.

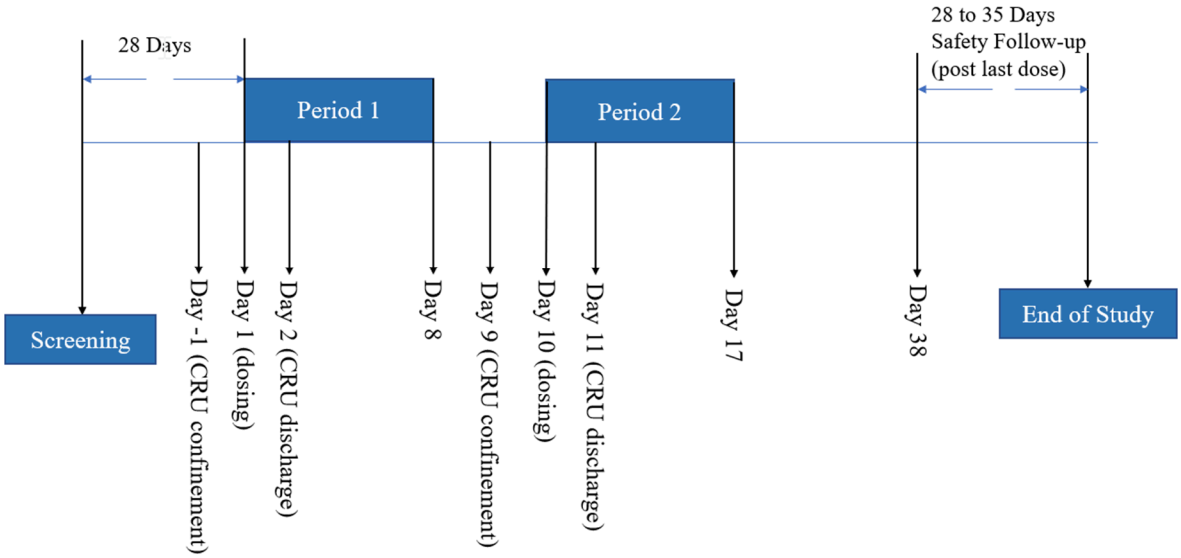
Etrasimod 2 mg was determined to be well tolerated and to have an acceptable safety profile in both healthy participant and diseased clinical studies.

Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants of childbearing potential must agree to use appropriate contraception methods. Participants should avoid vaccination with live attenuated replication-competent vaccines. It is recommended that participants keep their diet habits constant throughout the study.

[redacted]

[3] FDA. Guidance for industry: enhancing the diversity of clinical trial populations - eligibility criteria, enrollment practices, and trial designs. November 2020. Available from: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry | FDA. Accessed: 09 Aug 2023.

1.2. Schema


28 Days
Period 1
Period 2
28 to 35 Days
Safety Follow-up
(post last dose)
Screening
Day -1 (CRU confinement)
Day 1 (dosing)
Day 2 (CRU discharge)
Day 8
Day 9 (CRU confinement)
Day 10 (dosing)
Day 11 (CRU discharge)
Day 17
Day 38
End of Study

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Study Schedule of Assessment

Visit Identifier **Abbreviations used in this table may be found in Appendix 10**	**Screen**	**Periods 1-2**				**F/U Telephone Contact**	**ET**	**Notes**
Days Relative to Day 1 in Each Period	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Days 3-8**	**Days 28-35***		• Participants will be screened within 28 days of the first dose of study intervention. • * Follow-up contact will occur by telephone and must occur at least 28 to 35 days after the last administration of etrasimod (Day 1 of Period 2 if dosing completed).
Period 1 Study Days	**-28 to -2**	**-1**	**1**	**2**	**3-8**			Participants will be discharged from CRU on Day 2 of Period 1
Period 2 Study Days		**9**	**10**	**11**	**12-17**			• Minimum 8-day washout period between dosing in Periods 1 and 2 • Participants will be discharged from CRU on Day 2 of Period 2.
Check In		X						
Informed consent	X							
Inclusion/exclusion criteria	X	X						• Inclusion/exclusion criteria should be reviewed and updated on Day -1 of Period 1 only.
CRU confinement		X	→					• Participants will be discharged from CRU on Day 2 of Periods 1 and 2
Demography	X							• Including measurement of height and weight
Medical/medication history, drug, tobacco, and alcohol history	X	X						• Include history of alcohol abuse, tobacco/nicotine containing products, licit and illicit drug use or dependence within 6 months of screening. • For Day -1, records should be reviewed or updated only.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen	Periods 1-2				F/U Telephone Contact	ET	Notes
Days Relative to Day 1 in Each Period	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Days 3-8**	**Days 28-35***		• Participants will be screened within 28 days of the first dose of study intervention. • * Follow-up contact will occur by telephone and must occur at least 28 to 35 days after the last administration of etrasimod (Day 1 of Period 2 if dosing completed).
Period 1 Study Days	**-28 to -2**	**-1**	**1**	**2**	**3-8**			Participants will be discharged from CRU on Day 2 of Period 1
Period 2 Study Days		**9**	**10**	**11**	**12-17**			• Minimum 8-day washout period between dosing in Periods 1 and 2 • Participants will be discharged from CRU on Day 2 of Period 2.
Physical exam	X	X						• See Section 8.3.1 • Must be conducted at screening or upon admission on Day -1 Period 1 only.
Ophthalmology exam	X							• See Section 8.3.1 • Further ophthalmologic assessment will be arranged for any ophthalmic adverse event throughout the trial
Safety laboratory	X	X		X			X	• Safety laboratory screening testing must be collected, reported, and reviewed within 28 days prior to first administration of study intervention. • Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed. Participants should fast for at least 4 hours prior to any safety blood collection. Additional laboratory assessments may be performed if deemed necessary by the investigator. • If labs are not within normal range on Day 2 of Period 2, unscheduled follow-up visits will occur per protocol. • Refer to Table 4 for full list of assessments
Urine drug testing	X	X						
Pregnancy test (WOCBP only)	X	X						• See Table 4 for more details.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10	Screen	Periods 1-2				F/U Telephone Contact	ET	Notes
Days Relative to Day 1 in Each Period	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Days 3-8**	**Days 28-35***		• Participants will be screened within 28 days of the first dose of study intervention. • * Follow-up contact will occur by telephone and must occur at least 28 to 35 days after the last administration of etrasimod (Day 1 of Period 2 if dosing completed).
Period 1 Study Days	**-28 to -2**	**-1**	**1**	**2**	**3-8**			Participants will be discharged from CRU on Day 2 of Period 1
Period 2 Study Days		**9**	**10**	**11**	**12-17**			• Minimum 8-day washout period between dosing in Periods 1 and 2 • Participants will be discharged from CRU on Day 2 of Period 2.
Contraception check	X	X		X		X	X	• The contraception check is to confirm that contraception, if applicable, is used consistently and correctly.
12-Lead ECG	X		X	X	X		X	• Assessments using standard ECG machine at screening. • Assessments using wearable device for Periods 1 and 2. • On Day 1 of each period perform ECGs pre-etrasimod dose and every hour up to 6 hours, and at 8 and 24 hours post-etrasimod dose (in Period 1 by staff and in Period 2 by participants). The pre-etrasimod dose ECGs will be done in triplicate. • On Days 3-5 of each period, perform ECGs at approximately the same clock time as etrasimod dose on Day 1 (in both Periods by participants). • Refer to Section 8.3.3 for additional details
Blood pressure, pulse rate, temperature	X		X	X	X		X	• Assessments using standard methodology (BP, PR and temperature) at screening. • Assessments using standard methodology (temperature) in Periods 1 and 2. ○ Temperature will only be performed predose on Day 1.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screen**	**Periods 1-2**				**F/U Telephone Contact**	**ET**	**Notes**
Days Relative to Day 1 in Each Period	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Days 3-8**	**Days 28-35***		• Participants will be screened within 28 days of the first dose of study intervention. • * Follow-up contact will occur by telephone and must occur at least 28 to 35 days after the last administration of etrasimod (Day 1 of Period 2 if dosing completed).
Period 1 Study Days	**-28 to -2**	**-1**	**1**	**2**	**3-8**			Participants will be discharged from CRU on Day 2 of Period 1
Period 2 Study Days		**9**	**10**	**11**	**12-17**			• Minimum 8-day washout period between dosing in Periods 1 and 2 • Participants will be discharged from CRU on Day 2 of Period 2.
								• Assessments using wearable device (BP, PR) in Periods 1 and 2. o On Day 1 of each period PR and BP vital signs will be performed at predose (baseline) and every hour up to 6 hours, and at 8 and 24 hours post-etrasimod dose (in Period 1 by CRU staff and in Period 2 by participants). o On Days 3-5 of each period, PR and BP will be taken at approximately the same clock time as etrasimod dose on Day 1 (in both Periods by participants). • ECG will be taken first followed by vital signs.
HIV, HbsAg, HbcAb, HbsAb, HCVAb	X							• If HbsAg is negative and HbcAb is positive, HbsAb should be evaluated.
COVID-19 related procedures		X						• Performed per local procedures
TB (QuantiFERON® Gold Test)	X							
Study intervention administration			X					• Participants assigned to receive study intervention under fasted must be fasted for at least 10 hours pre dosing and 4 hours postdosing. • See Section 6.1.1 for additional details

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 10	**Screen**	**Periods 1-2**				**F/U Telephone Contact**	**ET**	**Notes**
Days Relative to Day 1 in Each Period	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Days 3-8**	**Days 28-35***		• Participants will be screened within 28 days of the first dose of study intervention. • * Follow-up contact will occur by telephone and must occur at least 28 to 35 days after the last administration of etrasimod (Day 1 of Period 2 if dosing completed).
Period 1 Study Days	**-28 to -2**	**-1**	**1**	**2**	**3-8**			Participants will be discharged from CRU on Day 2 of Period 1
Period 2 Study Days		**9**	**10**	**11**	**12-17**			• Minimum 8-day washout period between dosing in Periods 1 and 2 • Participants will be discharged from CRU on Day 2 of Period 2.
PK blood sampling (Periods 1 and 2)			X				X	• Venous PK sample blood collection (for Tasso results comparison) will be at the following timepoints: predose and at 2 and 4 hours postdose.
PK micro sampling (Periods 1 and 2)			X	X	X			• Micro sampling PK sample collection will be on the day of dosing at the following timepoints: predose and at 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose • Micro PK sampling for Period 1 (Treatment F) will be performed by CRU staff up to 24 hours postdose (at CRU) and by the participants 48-168 hours post dose (remote) • Micro PK sampling for Period 2 (Treatment G) will be performed by the participants at the CRU (up to 24 hours postdose) and remote (48-168 hours postdose) • Micro PK sampling occurs after venous PK blood sampling; samples to be taken from the alternate arms from one sampling time to the next.

Table 1. Study Schedule of Assessment

Visit Identifier **Abbreviations used in this table may be found in Appendix 10**	**Screen**	**Periods 1-2**				**F/U Telephone Contact**	**ET**	**Notes**
Days Relative to Day 1 in Each Period	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Days 3-8**	**Days 28-35***		• Participants will be screened within 28 days of the first dose of study intervention. • * Follow-up contact will occur by telephone and must occur at least 28 to 35 days after the last administration of etrasimod (Day 1 of Period 2 if dosing completed).
Period 1 Study Days	**-28 to -2**	**-1**	**1**	**2**	**3-8**			Participants will be discharged from CRU on Day 2 of Period 1
Period 2 Study Days		**9**	**10**	**11**	**12-17**			• Minimum 8-day washout period between dosing in Periods 1 and 2 • Participants will be discharged from CRU on Day 2 of Period 2.
CRU discharge				X				• The participants will be discharged on Day 2 of each Period.
Participant Training for Micro PK Sampling, and Wearable Monitoring Devices, and recording of PK sampling times, concomitant medications and AEs				X#				• # On Day 2 of Period 1, prior to discharge, participants will be trained on 1) use of devices (PCA500, BioBeat and Tasso) and provided with instruction materials for self-assessment of ECGs, vitals and PK samples, and 2) completion of diaries to record PK sampling times, concomitant medications and AEs • In both Periods, participants will be provided with adequate supply of devices and diaries for remote self-assessment following discharge on Day 2
Serious and nonserious AE monitoring	X	→	→	→	→	X	X	• See Section 8.4.3 for follow up AE and SAE assessments. • AEs during Days 3-8 of both study Periods will be recorded on CRF by participants and if needed, reported to CRU by telephone.

2. INTRODUCTION

Etrasimod is an orally administered, selective, synthetic $S1P_{1,4,5}$ modulator that is being developed to treat immune-mediated inflammatory disorders, including UC, AA, AD, and EoE. The $S1P_1$ is a cell surface expressed protein 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. Modulation of the S1P/S1P receptor axis is thought to be a potential therapeutic approach to the management of immune-mediated inflammatory disorders.

2.1. Study Rationale

This sub study is being conducted to assess the feasibility of conducting a Phase 1 etrasimod study as a hybrid decentralized clinical trial with dosing by study personnel at the CRU and remote collection of PK, safety and tolerability data. The specific objectives of the sub study are to determine the PK and to assess the safety and tolerability of etrasimod clinical IR tablets 2 mg under fasted conditions in healthy adult participants in a hybrid DCT design.

This study is being conducted under the main study C5041034 as a sub study for the following reasons. The assessments and the objectives of this study are distinctly different from the main study; however, the analysis plan of the sub study includes comparison of the results of the sub study conducted as a hybrid DCT design with corresponding results of the main study conducted at the CRU.

2.2. Background

The pharmacology, safety pharmacology, PK, metabolism, toxicology and clinical dose-ranging efficacy and safety of etrasimod oral administration had been comprehensively studied. A summary of relevant, currently available data is provided in this protocol. Additional details and further information for this compound could be found in the current IB.

The sub study is being conducted to assess the feasibility of conducting a Phase 1 etrasimod study as a hybrid decentralized clinical trial [1,2] with dosing by study personnel at the CRU and remote collection of PK, safety and tolerability data. DCTs have the potential to expand access to more diverse patient populations and improve trial efficiencies.[3] Advances in clinical care using electronic communications and information technology to interact with trial participants in different locations (ie, telehealth) allow for fewer in-person visits to clinical trial sites. DHTs, for example, have expanded the types of trial-related data that can be obtained remotely from trial participants. By enabling remote participation, DCTs may enhance convenience for trial participants, reduce the burden on caregivers, and facilitate research on rare diseases and diseases affecting populations with limited mobility or access to traditional trial sites. This may help improve trial participant engagement, recruitment, enrollment, and retention of a meaningfully diverse clinical population.

2.2.1. Nonclinical Pharmacology

A summary of the nonclinical investigational programs can be found in the current IB.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

Etrasimod is eliminated primarily hepatically by extensive metabolism involving oxidation of etrasimod, along with dehydrogenation and conjugation, and showed no human specific metabolite(s) compared to those observed in the toxicology species. The main CYP enzymes involved in the oxidative metabolism of etrasimod are CYP2C8 (38%), CYP2C9 (37%), and CYP3A4 (22%), and with CYP2C19 and CYP2J2 being minor contributors (1% each). There are no major circulating metabolites and etrasimod is the primary circulating drug entity.

Additional information of the nonclinical PK and metabolism of etrasimod is available in the current IB.

2.2.3. Nonclinical Safety

Etrasimod was well tolerated across the general toxicity program conducted in CD-1 mice, Sprague Dawley rats, and beagle dogs, with no etrasimod-induced mortality following repeat administration up to 91-days, 6-months, and 9-months at 20, 150, and 15 mg/kg/day in mice, rats, and dogs, respectively. Most etrasimod-related findings were considered nonadverse, reversible upon cessation of treatment, and/or readily monitorable in the clinic. One of the most common adverse effects across species was decreased body weight and/or body weight gain, with associated decreases in food consumption. The primary target organs identified across all species were lymphoid tissues, lung, and liver. In addition, the heart was identified as a target organ in the dog. When administered at doses within and above the therapeutic range (up to 858 × in rats and 380 × in dogs over the total C_{max} exposure at the proposed human dose for the treatment of UC) in safety pharmacology studies, etrasimod showed no effect on CNS, respiratory, or cardiovascular function.

The potential effects of etrasimod on the cardiovascular system were investigated in a series of in vitro and in vivo studies. In vitro, etrasimod increased hERG currents by 31.4% at 1 mm and 58.9% at 3 mm. These concentrations are approximately 193 × and 578 × over the free C_{max} exposure at the proposed human dose for the treatment of UC. An IC_{50} for hERG current inhibition could not be established for etrasimod since only increases in hERG channel current, rather than inhibition, were observed. Based on the G protein receptor signaling associated with the primary PD activity, etrasimod was observed to activate GIRK currents in vitro. GIRK1 and GIRK4 are the 2 homologous subunits of I_{KACh} that interact with Gβγ to mediate the activation of the potassium channel.[4] G-protein signaling via GIRK I_{KACh} channel activation in cardiac cells is considered to be responsible for the transient cardiovascular effects seen with first dose of S1P receptor modulators.[5, 6, 7] At I_{KACh} in primary human atrial cardiomyocytes, etrasimod exhibited an EC_{50} of 29.9 nM and there was no difference between S1P and etrasimod in the time course of I_{KACh} activation. The maximal current induced by etrasimod, however, was 90% of that observed with carbachol and was 10 × lower (based on EC_{50}) than S1P itself.

Etrasimod was not mutagenic or clastogenic in in vitro genetic toxicity studies and is not considered genotoxic in rats or to pose a genotoxic risk to humans. There were no etrasimod-related effects on spermatogenesis or fertility in males at any dose level evaluated. In the embryo-fetal development studies in rats and rabbits, administration of etrasimod during the period of organogenesis resulted in increased post implantation loss and decreased mean litter numbers and proportions of viable fetuses in both species. The embryo lethality and fetal malformations noted with etrasimod in the rat and rabbit embryo-fetal development studies are consistent with similar findings observed with approved S1P modulators[8, 9, 10, 11] and are believed to be a result of the important role of $S1P_1$ in embryogenesis, including vascular and neural development.[12]

Further details of the nonclinical safety program are provided in the current IB.

2.2.4. Clinical Overview

Safety, tolerability and PK of etrasimod were evaluated in 15 Phase 1 studies in healthy adult participants. Efficacy and safety of etrasimod was evaluated in 3 completed Phase 2, 6 ongoing Phase 2, 4 completed Phase 3 and 1 ongoing Phase 3 studies across several disease indications. Clinical pharmacology data established the PK properties of etrasimod with or without food and in specified participant subpopulations (eg, participants with renal or hepatic impairment), and included comprehensive drug interaction studies to inform dosing recommendations.

A complete summary of the clinical data relevant to etrasimod and its study in human participants is provided in the current edition of the IB.

2.2.4.1. Pharmacokinetic Overview of Etrasimod

Etrasimod is absorbed with a median T_{max} of 4 hours after administration as an etrasimod 2 mg IR tablet in the fasted state, and up to 6 hours in the fed state. Food did not affect etrasimod exposure measures (C_{max} and AUC). Plasma C_{max} and AUC values of etrasimod are dose proportional following a single dose of 0.1 to 5 mg. For multiple-doses of etrasimod over a range of 0.7 to 2 mg once daily, steady-state C_{max} increased dose proportionally and steady-state AUC_{0-24} increased slightly greater than dose proportionally. Apparent dose proportional increases were also observed for mean steady-state C_{max} and AUC_{0-24} values from 2 to 4 mg once daily dosing in healthy participants. The time to reach approximate steady-state for etrasimod exposure measures (C_{max}, AUC_{0-24}, C_{trough}) is within 7 days of the first dose. Mean Rac for etrasimod exposure measures are <3-fold with once daily dosing. These observations are consistent with etrasimod's elimination (effective) half-life of approximately 30 hours. The mean oral V_z/F of etrasimod ranged from 50 to 103 L in healthy participants across evaluated single and multiple-dose levels and Phase 1 studies, indicating extravascular distribution. The mean oral plasma CL/F of etrasimod following single and multiple-dose administration of etrasimod was low and ranged from 1.13 to 1.43 L/h and 0.97 to 1.70 L/h, respectively, in healthy participants across evaluated dose levels in the Phase 1 studies.

The human mass balance study identified 2 oxidative metabolites, AR503641 (M3) and AR504344 (M6) present in systemic circulation, though minor as they are each <10% of total radioactivity. The oxidation of etrasimod occurs by 3 CYPs (CYP2C8, CYP2C9 and CYP3A4). Etrasimod is primarily eliminated in feces, with no parent drug detected in the urine.

2.2.4.2. Safety Overview of Etrasimod

As of 30 Aug 2022, a total of 2119 participants (419 healthy participants and 1700 participants with disease) have been exposed to etrasimod in clinical development programs. Clinical evidence in participants of healthy status, UC, CD, AD, AA or EoE to date have demonstrated that etrasimod is well tolerated in humans.

Across all clinical studies (Phase 1 to Phase 3), etrasimod caused expected mild, transient, and generally asymptomatic reduction in HR at first dose and very few participants with HR < 50 bpm. These reductions were greatest following first dose and lessened upon repeat dosing due to development of tolerance, allowing HR to return to baseline. The HR effects are related to $S1P_1$ localized on atrial myocytes that activate GIRK channels, which are transient and not clinically adverse or associated with safety findings.

Etrasimod 2 mg administered once daily demonstrated an acceptable safety profile up to 52 weeks in controlled studies and up to 104 weeks in uncontrolled studies. There was a low incidence of SDEIs such as infections, including severe (ie, Grade ≥3) infections, opportunistic infections, and herpes infections (herpes zoster and herpes simplex), cardiac safety events (bradycardia, AV conduction delays, and hypertension), malignancies, liver injury (liver transaminase elevation and bilirubin elevation), macular oedema, and pulmonary disorders (airflow obstruction and decreased gas exchange) in participants who were treated with etrasimod 2 mg.

2.3. Benefit/Risk Assessment

Etrasimod, an investigational, oral, and once daily S1P receptor modulator, is not expected to provide any clinical benefit to healthy participants. In this study, etrasimod will be administered at single doses of 2 mg. This study is being conducted primarily to generate safety, tolerability, pharmacokinetic data for the etrasimod tablets in a hybrid DCT design.

Etrasimod was determined to be well tolerated and to have an acceptable safety profile in both healthy participant and diseased clinical studies.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of etrasimod may be found in the IB, which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Etrasimod		
S1P receptor modulator-related effects (class effect of AEs observed with S1P receptor modulators) may be observed. • cardiovascular events (eg, bradycardia, atrioventricular conduction delay and hypertension) • infections (severe infections, opportunistic infections, Herpes simples and Herpes zoster) • macular edema • pulmonary events (airflow obstruction or altered gas exchange) • liver injury • malignancy	Clinical experience with other S1P receptor modulators for the treatment of MS and UC. • The totality of etrasimod clinical studies (Phase 1, 2 and 3 studies) have shown that 2 mg etrasimod is well-tolerated with no clinically significant safety signals.	Exclusion of participants at risk. Short duration of treatment. Safety labs at screening and baseline and when deemed necessary by the investigator throughout the study. AE monitoring throughout the study.
S1P receptor modulator-specific lymphocyte level decreases.	Dose-dependent reductions in peripheral lymphocyte counts are an expected PD effect of etrasimod. The totality of clinical studies following single dose administration of study intervention is well-tolerated with a return to normal range by Day 7.	Participants with conditions or risk factors related to infection or immune function will be excluded from the study. Participants will be assessed for safety including infections at regular intervals throughout the study to identify and mitigate the potential risks.
First dose cardiac effect	S1P receptor modulators class of drugs is associated with an expected, on-target effect of reducing HR when first dosed. The totality of clinical data up to date across Phase 1 to 3 studies across several indications indicate that etrasimod 2 mg is well-tolerated with modest	Participants with elevated cardiac risk factors will be excluded from participation in the study. Specifically, Section 5.2 Exclusion Criterion #1 is aligned with IB to require “Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	HR reduction that is maximal on the first day of dosing without major clinically relevant cardiac safety events.	hospitalization, or Class III/IV heart failure ≤6 months prior to study intervention." Hourly HR monitoring for the first 6-hours post first dose will be conducted for all dose periods. Participants with cardiac effects associated with first dose will be required to permanently discontinue study intervention.
Reproductive and developmental toxicity.	The effects of etrasimod on human fertility and embryonic development are unknown. Nonclinical reproductive and developmental toxicity studies of etrasimod combined with data and knowledge on the role of $S1P_1$ in vascular embryogenesis demonstrate embryo fetal toxicity of etrasimod if used during pregnancy. Etrasimod is potentially teratogenic in humans with a low genotoxic potential. There is no margin of safety for these findings compared to therapeutic exposure range. Etrasimod should not be given to women who are pregnant, lactating, or breastfeeding.	WOCBP who are pregnant, lactating, or breastfeeding will be excluded from this study. WOCBP will be eligible only if she and her partner(s) agree(s) with the contraceptive method as described in Section 10.4.4 throughout the study period and for at least 28 days after the last dose of etrasimod. Males with female partners of childbearing potential must agree to use contraception throughout the study period and for at least 28 days after the last dose of etrasimod.
Macular Edema.	Macular edema is an identified risk which requires specific ophthalmologic monitoring.	In this study, an ophthalmologic examination by an ophthalmologist is included at baseline (Screening) and for clinical monitoring of any signs or symptoms throughout the trial, as needed.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures Blood Collection for PK		
Extravasation, bruising, local discomfort	Collection of 3 venous PK plasma samples each in Period 1 and 2. Collection of 14 PK micro samples each in Periods 1 and 2.	Use of highly qualified nurses, with venipuncture experience. Use of alternating arms for adjacent time points can provide more resting and healing time for each arm between samplings.

2.3.2. Benefit Assessment

Etrasimod is not expected to provide any clinical benefit to healthy participants. This sub study is designed primarily to assess the feasibility of conducting a Phase 1 etrasimod study as a hybrid decentralized clinical trial with dosing by study personnel at the CRU and remote collection of PK, safety and tolerability data. In this study, etrasimod will be administered at single doses of 2 mg.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with etrasimod are justified by the anticipated benefits that may be afforded to participants with UC.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To compare the PK of etrasimod 2 mg clinical IR tablets under fasted conditions in healthy participants using Tasso PK micro samples taken by participants only (Treatment G) vs. CRU staff and participants (Treatment F) in a hybrid DCT design	• Plasma $AUC_{24\ hr}$, $AUC_{24hr\text{-}last}$, AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of etrasimod
Secondary:	**Secondary:**
• To compare the PK of etrasimod 2 mg clinical IR tablets under fasted conditions in healthy participants using Tasso PK micro samples taken by participants only (Treatment G) vs. CRU staff and participants (Treatment F) in a hybrid DCT design vs. venous PK samples taken by CRU staff in conventional design of main study (Treatment A)	• Plasma $AUC_{24\ hr}$, $AUC_{24hr\text{-}last}$, AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} of etrasimod
• To evaluate the safety and tolerability of etrasimod 2 mg clinical IR tablets in healthy participants using mobile wearable devices in a hybrid DCT design	• Assessment of first dose HR reduction, TEAEs, clinical laboratory abnormalities, vital signs, PEs, and ECGs
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To compare the concentrations of etrasimod in PK samples collected using micro sampling device against those using venous blood sampling.	• Plasma concentrations of etrasimod obtained via micro sampling compared to venous sampling at pre-dose and at 2 and 4 hrs post-dose.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, single-dose, fixed-sequence, crossover sub study in a single cohort of approximately 8 healthy male or female participants conducted using a hybrid DCT design.

The study will consist of 2 treatments. Participants will receive the two Treatments F and G in a fixed sequence as shown below.

Fixed Treatment Sequence (n=8)	Period 1	Period 2
	F	G

Treatment F: Single oral dose of etrasimod 2 mg, DCT with practice sessions* (Reference)
Treatment G: Single oral dose of etrasimod 2 mg, DCT without practice sessions** (Test)
* Practice of Tasso and Wearable Monitoring Devices on Day 2 at CRU; participant self-assessment remotely for vitals and ECG (Days 3-5) and PK samples (Days 3-8)
** Participant self-assessment using Tasso and Wearable Monitoring Devices on Days 1-2 at CRU; and remotely on Days 3-8

Following are the key elements of the design of this hybrid decentralized clinical trial. Participants will be discharged from the CRU on Day 2 of each Period, following practice sessions (Period 1 only) with the use of Tasso for serum PK sampling and wearable devices for safety monitoring, and the completion of all assessments that are planned to be performed at the CRU. The Tasso OnePlus, high-volume liquid blood collection device, will be used for micro-PK sampling and the blood samples collected by participants will be sent to the CRU within 72 hours of collection for processing of serum. The BioBeat Patch and PCA500 wearable monitoring devices will be used for collection of vitals and ECGs, respectively, in Periods 1 and 2. Each treatment period is 8 days that includes dosing, PK sampling, safety assessments, and practice (Period 1 only) with use of wearable devices and Tasso sampling. The PK and safety (ECGs and vitals) assessments through Day 2 of Period 1 will be performed by the CRU staff. Following practice with the Tasso and wearable monitoring devices on Day 2 of Period 1, the assessments on Days 3 to 8 (remote) of Period 1 and on Days -1 to 2 (at CRU) and 3 to 8 (remote) of Period 2 will be self-performed by the participants. Participants will be discharged from the CRU on Day 2 Periods 1 and 2. Participants will receive an emergency card for contacting the CRU and will be provided detailed instructions to call PCRU for reporting of an AE. Additionally, the participants will be provided with diaries to record information about PK sampling times, concomitant medication(s) and AEs during the self-assessment phase following discharge on Day 2 of Periods 1 and 2. The participants will be provided instructions for returning the wearable devices and other study related materials study following completion of all assessments on Day 8 of Period 2. The total planned duration of participation from the screening visit to the last follow-up phone call, is approximately 9 weeks.

Since etrasimod has a half-life approximately 30 hours, there will be an 8-day washout between each dose.

In both Periods 1 and 2, capillary blood samples (using micro sampling Tasso device) for PK analysis will be collected at predose and at 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 hours postdose (SoA). Venous blood samples for PK analysis will be collected predose and at 2 and 4 hours postdose (SoA). Micro PK sampling occurs after venous PK blood sampling; samples will be taken from the alternate arms from one sampling time to the next.

Participants will be screened within 28 days of the first dose of study intervention and if all entry criteria are fulfilled, the participants will report to the CRU on the day prior to Day 1 dosing (Day -1). On Day 1 of each period, participants will receive a single dose of study intervention at the CRU. Administration of etrasimod will be oral via dosing of clinical IR

tablet 2 mg with water as per dosing instructions. Participants will be fasted for at least 10 hours predosing and 4 hours postdosing.

Participants will be confined in the CRU for a total of at least 2 days and discharged on Day 2 of each Period. A follow-up phone call will be made at least 28 calendar days and up to 35 calendar days after the last administration of the study intervention to capture any potential AEs and confirm appropriate contraceptive usage.

Tolerability and safety will be assessed for all treatments by monitoring AEs. Participants who withdraw from the study or whose PK samples are determined to be non-analyzable may be replaced at the discretion of the of the investigator upon consultation with the sponsor.

4.2. Scientific Rationale for Study Design

The purpose of the sub study is to determine the PK and to assess the safety and tolerability of etrasimod clinical IR tablets 2 mg under fasted conditions in healthy adult participants in a hybrid DCT design. Since etrasimod has a long half-life of approximately 30 hours, requiring blood sampling up to 168 hours post-dose for PK characterization of its PK profile, standard crossover BA study designs can require relatively long CRU stay requirements and may impede participant recruitment and retention. Therefore, this hybrid DCT design sub study is designed to investigate the utility of self-assessment of PK, vitals and ECGs remotely by study participants in two fixed-sequence crossover study Periods, wherein Period 1 will include assessments by CRU staff up to Day 2 and a training session for participants. The participants will perform self-assessments on Days 3 to 8 (remote) of Period 1 and on Days -1 to 2 (at CRU) and 3 to 8 (remote) of Period 2. On Day 1 of each period, participants will receive a single dose of etrasimod IR tablet 2 mg at the CRU.

4.2.1. Rationale for ECG Measurements

In the heart, $S1P_1$ is expressed on atrial myocytes and is associated with the regulation of heart rate. $S1P_1$ agonism activates both G alpha i (Gi) and β-arrestin signaling pathways. β-arrestin activation leads to receptor internalization, while Gi coupled signaling activates GIRK channels that regulate potassium efflux and membrane potential. As a result, there is a transient, first dose associated, chronotropic (slowing of HR) and dromotropic (slowing of AV nodal conduction) effects associated with etrasimod (a class effect). For all Phase 1 studies, intensive ECG have been taken for the first 6-hours post first dose. For this study, this practice should be in place until the NDA is approved.

4.2.2. Rationale for PR and BP Monitoring

In addition to the transient, first dose associated, chronotropic effect associated with etrasimod, hypertension has been observed with S1P receptor modulators and AEs of hypertension have been reported. For all phase 1 studies, intensive BP and PR monitoring post dose has been undertaken and this will continue for this study.

4.2.3. Choice of Contraception/Barrier Requirements

Etrasimod is known to cause risk for severe manifestations of developmental toxicity in humans or suspected on the basis of the intended pharmacology. Therefore, the use of a

highly effective method of contraception is required for both female and male participants (see Appendix 4).

4.3. Justification for Dose

The dose of etrasimod 2 mg once daily has been shown to be efficacious and safe in moderate to severely active adult UC patients.

This study is designed to evaluate PK of etrasimod 2 mg clinical IR tablet formulation in healthy adult participants.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA and the investigator has reviewed the final safety data and determined that no additional evaluation is required.

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit or the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male and female participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at screening who are overtly healthy as determined by medical evaluation including a detailed medical history, full physical exam, which includes BP and pulse rate measurement, clinical laboratory tests, temperature, and 12-lead ECG.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

Other Inclusion Criteria:

2. BMI of 16 to 32 kg/m^2; and a total body weight > 50 kg (110 lb).

3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

4. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5. Capable of using wearable monitoring devices for the duration of this study, according to the requirements specified in the SoA.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, anaphylactic, ophthalmologic disorders (such as macular edema, uveitis, retinopathy), or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

    - Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure ≤6 months prior to study intervention

    - Second- or third-degree AV block, sick sinus syndrome without a functional pacemaker, or periods of asystole for >3 seconds without an implanted cardiac defibrillator

    - Recurrent symptomatic bradycardia or recurrent cardiogenic syncope

    - History of congenital long QT syndrome

    - Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior, laboratory abnormality or other conditions that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study

2. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

3. Known immunodeficiency disorder, including positive serology for HIV, or a first degree relative with a hereditary immunodeficiency.

4. Infection with hepatitis B or hepatitis C viruses according to protocol specific testing algorithm history.

    - For hepatitis B, all participants will undergo testing for HbsAg and HbcAb.
    - If HbsAg is positive, the participant must be excluded from participation in the study.
    - If HbsAg and HbcAb are both negative, the participant is eligible for study inclusion.
    - If HbsAg is negative and HbcAb is positive, HbsAb should be evaluated:
    - If HbsAb is negative, the participant must be excluded from participation in the study;
    - If HbsAb is positive, the participant is eligible for study inclusion.
    - For hepatitis C, all participants will undergo testing for HCVAb. Only participants who are HCVAb negative are eligible.

5. Participants with any of the following acute or chronic infections or infection history:

    - Any infection requiring treatment within 2 weeks prior to dosing.
    - Any infection requiring hospitalization or parenteral antimicrobial therapy within 60 days of the first dose of study intervention.
    - Any infection judged to be an opportunistic infection or clinically significant by the investigator, within the past 6 months of the first dose of study intervention.
    - Known active or history of recurrent bacterial, viral, fungal, mycobacterial or other infections.
    - History of recurrent (more than one episode of) localized dermatomal herpes zoster, or history of disseminated (single episode) herpes simplex or disseminated herpes zoster.
    - History of febrile illness within 5 days prior to the first dose of study intervention.

6. History of any lymphoproliferative disorder such as EBV related lymphoproliferative disorder, history of lymphoma, history of leukemia, or signs or symptoms suggestive of current lymphatic or lymphoid disease. Known present or a history of malignancy other than a successfully treated or excised nonmetastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

7. Evidence of untreated or inadequately treated active or latent Mycobacterium TB infection as evidenced by the following:

    - A positive QFT-G test performed within the 12 weeks prior to screening. If the laboratory reports the test as indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, a PPD test may be substituted for the QFT-G test only with approval from the Pfizer Medical Monitor on a case-by-case basis.
    - History of either untreated or inadequately treated latent or active TB infection.
    - If a participant has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a QFT-G test nor a PPD test need be obtained. Details of the previous course of therapy (eg, medication(s) used, dose, duration of therapy) should be documented in the source documentation.
    - A participant who is currently being treated for active or latent TB infection must be excluded from the study.

8. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening or Day -1, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - WBC <3500/mm^3 (<3.5 × 10^9 cells/L)
    - ANC <1500/mm^3 (<1.5 × 10^9 cells/L)
    - ALC <800/mm^3 (<0.8 × 10^9 cells/L)
    - Platelet count <100/mm^3 (<100 × 10^9 cells/L)
    - Hemoglobin <10 g/dL
    - AST **or** ALT level > ULN;
        - Total bilirubin level > ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;
        - Renal impairment as defined by an eGFR (units of mL/min/1.73m^2) of <60 mL/min(/1.73m^2). Based upon participant age at screening, eGFR will be calculated using the recommended CKD-EPI equation in Section 10.6.2 to determine eligibility (Screat-based formula)
        - In the opinion of the investigator or Pfizer (or designee), have any clinically significant laboratory abnormality that could affect interpretation of study data or the participant's participation in the study.

Prior/Concomitant Therapy:

9. Use of prescription or nonprescription drugs and dietary and herbal supplements within 5 half-lives plus 14 days prior to the first dose of study intervention. (Refer to Section 6.9 Prior and Concomitant Therapy for additional details).

Prior/Concurrent Clinical Study Experience:

10. Previous administration with an investigational product (drug or live or attenuated vaccine) within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

11. A positive urine drug test.

12. A positive pregnancy test.

13. Screening or Day 1 prerandomization vital signs (taken in the supine position) with a HR <50 bpm OR systolic BP <90 mm Hg or ≥140 mm Hg OR diastolic BP <50 mm Hg or ≥90 mm Hg. Abnormal vital signs should be confirmed by 2 repeat measurements. Abnormal results that are confirmed on a repeat assessment are considered exclusionary.

14. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

Other Exclusion Criteria:

15. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).

16. Use of tobacco/nicotine containing products in excess of 5 cigarettes/day.

17. WOCBP who are unwilling or unable to use an acceptable method of contraception as outlined in Section 10.4 during the intervention period and for at least 28 days after the last dose of study intervention.

18. History of severe allergic or anaphylactic reactions.

19. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

20. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the predose PK sample.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.
- An evening snack may be permitted.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.3. Caffeine, Alcohol, and Tobacco

Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.4. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;
- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

5.3.5. Vaccination(s)

Vaccination with live attenuated replication-competent vaccines is prohibited within the 4 weeks prior the first dose of study intervention, while receiving study intervention, and for 4 weeks after the last dose of study intervention. Similarly, current routine household contact with individuals who have been vaccinated with live attenuated, replication-competent vaccines should be avoided while receiving study intervention and for 4 weeks after the last dose of study intervention. Following vaccination with a live attenuated replication-competent vaccine, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted.

Such vaccines include, but are not limited to: Flu Mist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever

vaccine, oral polio vaccine, MMR vaccine, vaccinia (smallpox) vaccine, and Zostavax® (zoster vaccine live).

Live attenuated vaccines that are known not to be replication-competent in humans are permitted. Such vaccines include but are not limited to the Modified Vaccinia Ankara Bavarian Nordic (Jynneos®, Imvamune®, Imvanex®) smallpox and monkeypox vaccine. By contrast, the ACAM2000 smallpox and monkeypox vaccine is prohibited because it is live and replicates in humans.

Vaccines (including COVID-19 vaccines) that are not live attenuated are permitted.

Individuals receiving immunosuppressive therapy may have a diminished response to vaccination.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to etrasimod.

6.1. Study Intervention(s) Administered

Study interventions will be administered orally and according to the conditions described in the SoA and Meals and Dietary Restrictions of this protocol.

Participants will receive a single dose of etrasimod on Day 1 of each period at the CRU.

Study Intervention(s)	
Intervention Name	Etrasimod clinical IR tablets, 2 mg Reference product
Type	drug
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	Coated tablets containing 2 mg etrasimod each
Unit Dose Strength(s)	2 mg/tablet
Dosage Level(s)	2 mg per Period
Route of Administration	Oral
Sourcing	Etrasimod provided centrally by the sponsor. See IPM for more information.
Packaging and Labeling	Study intervention will be provided in HDPE bottle. Each bottle will be labeled as required per country requirement.
SRSD	IB
Current/Former Name(s) or Alias(es)	Etrasimod/PF-07915503, APD334

Study Arm(s)		
Arm Title	Period 1	Period 2
Arm Description	Participants will receive a single dose of etrasimod 2 mg on Day 1 of each period. Participants will be assigned to a fixed crossover sequence to receive single-dose Treatments F and G in Periods 1 and 2, respectively. In each period, etrasimod 2 mg clinical IR tablet will be administered with 240 mL water under fasting conditions.	

Etrasimod will be supplied as clinical IR tablet to the CRU in bulk in HDPE bottles.

6.1.1. Administration

On Day 1 of each period, following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). Investigator site personnel will administer study intervention during each period.

Etrasimod clinical IR tablets will be administered with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the clinical IR tablets whole and will not manipulate or chew the study intervention prior to swallowing.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

Administration of study intervention(s) will be performed by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance.

Following administration of study intervention(s), participants will be observed for the complete period/study by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.1.2. Medical Devices

1. Medical devices (not manufactured by or for Pfizer) provided for use in this study are Tasso OnePlus, BioBeat and PCA500.

2. Instructions for medical device use are provided in the IPM.

3. All medical device deficiencies (including malfunction, use error, and inadequate labeling) for the above-listed medical devices shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.
3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.
4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined

and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.
6. Study interventions should be stored in their original containers and in accordance with the labels.
7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.
8. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's local/site procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.
9. Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IPM.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Etrasimod clinical IR tablets will be dispensed at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified pharmacist. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Dispensing will be performed in CRU by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of study interventions.

6.3. Assignment to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

When participants are dosed, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

A record of the number of clinical IR tablets and mini tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, will also be recorded in the CRF.

6.6. Dose Modification

Not applicable.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation.

6.8. Treatment of Overdose

For this study, any dose of etrasimod greater than 2 mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow-up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

5. Obtain a blood sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the study medical monitor as needed based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤2 g/day.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4). Postmenopausal hormonal therapy is allowed.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- Adverse event

- Pregnancy
- Withdrawal by participant

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Liver Injury

A participant who meets the criteria as described in Appendix 5 will be withdrawn from study intervention.

7.1.2. ECG Changes

Participants must permanently discontinue study intervention if suspected intolerance associated with first dose cardiac effects (Section 2.3.1).

If an ECG shows a new onset QTc interval above 500 ms during the treatment period, a repeat ECG is warranted. If this abnormal finding is confirmed, study intervention must be interrupted. Effective diagnostic and therapeutic strategies should be employed.

Reversible causes of prolonged QTc interval (eg, electrolyte abnormalities or hypomagnesemia), should be corrected as clinically indicated. When evaluating a participant with new onset QTc interval above 500 ms, referral to a cardiologist experienced in treating cardiac conduction disorders should be considered. Re-initiation of study treatment can only be considered after all of the following have occurred:

- The QTcF interval is <450 ms (males) or <470 ms (females),
- The QTc prolongation is considered by the investigator and confirmed by the cardiologist as not related to study treatment and likely caused by other factors,
- Individual risk-benefit is favorable (as determined by the investigator, in agreement with the cardiologist), and
- After discussion with the Medical Monitor.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection or acquired using wearable monitoring device must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Pregnancy

Pregnancy tests are conducted as per SoA and dosing of study intervention will occur only in the presence of a negative pregnancy test. If a participant is confirmed to be pregnant (See Section 8.3.6) during study, further dosing with study intervention will be discontinued immediately and permanently.

7.1.4. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up
- Lost to follow-up
- Death
- Study terminated by sponsor
- Adverse event

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may not need to be repeated, as appropriate.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 100 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Prior and Concomitant Therapy sections of the protocol.

8.1.1. Baseline Procedures

All procedures listed in the SoA must be conducted at this visit.

SoA must be conducted at the screening visit.

8.2. Efficacy Assessments

Efficacy parameters are not evaluated in this study.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant reported symptoms.

Complete physical examination must either be conducted at screening or upon admission on Day -1 only; targeted physical examination may be performed as appropriate at the investigator's discretion if there are findings during the previous examination, new/open adverse events.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Ophthalmologic examination, including fundoscopy, will be conducted by an ophthalmologist at baseline (Screening) and for clinical monitoring of any signs or symptoms throughout the trial, as needed.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

Vital signs (BP, PR and temperature) will be collected at times specified in the protocol SoA.

8.3.2.1. Blood Pressure and Pulse Rate

At screening, vital signs will be measured using standard methodology. Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

During periods 1 and 2, ambulatory BP and PR will be monitored using the BioBeat chest-monitor, a single-participant-use device and web-enabled management platform either (1) at the CRU by the CRU staff and/or by study participants or (2) remotely by the study participants, as specified in the protocol SoA. Investigational site staff and study participants will be provided training as well as the BioBeat user manual.

When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection. Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2.2. Temperature

Temperature will be measured orally. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.3.3. Electrocardiograms

Electrocardiograms (except at screening) will be obtained using the PCA 500 which is a wearable ECG monitor. The PCA500 provides 12-lead ECG monitoring and recording which is transmitted periodically at pre-specified time intervals. Investigational site and study participant training are supplemented by availability of the PCA500 user manual.

At screening, standard 12-lead ECGs will be collected to assess and quantify HR, PR, QT, QTcF, and QRS intervals. During Periods 1 and 2, ECGs will be collected using the PCA500 wearable monitoring device, at the times specified in the protocol SoA, either (1) at the CRU by the CRU staff or by the study participant or (2) remotely by the study participant.

All scheduled ECGs should be performed after the participant has rested quietly in a supine position or in the most recumbent position possible for at least 5 minutes.

The pre-etrasimod dose 12-lead ECGs will be done in triplicate. Triplicate 12-lead ECGs will be obtained approximately 5 minutes apart; the average of the triplicate ECG measurements collected pre-etrasimod dose on Day 1 of each period will serve as each participant's baseline QTcF value.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements from the current period. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QTcF value is ≥500 ms for any scheduled ECG for greater than four hours (or sooner, at the discretion of the investigator); or c) QTcF values get progressively longer. If any of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range. Please refer to Section 7.1.2 for guidance on QTcF changes management.

ECG values of potential clinical concern are listed in Appendix 7.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 5 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 6 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.3.5. COVID-19 Specific Assessments

Participants will be tested for COVID-19 infection by PCR according to local procedure.

8.3.6. Pregnancy Testing

A urine or serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to starting the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner on the days they are at the CRU and they will record the AEs on the CRF during remote participation in the study.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of

environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. 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 participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 9.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Sections 8.4.1 through 8.4.4 and Appendix 3 of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

Refer to Section 10.9.4 for instructions for documenting and reporting medical device deficiencies.

8.4.9.2. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

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.**

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide approximately 1.5 mL of plasma, will be collected for measurement of plasma concentrations of etrasimod as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of etrasimod. Samples collected for analyses of etrasimod plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for protein binding, metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

Genetic analyses will not be performed on these PK samples.

Samples collected for measurement of plasma concentrations of etrasimod will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol deviation. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

Additional blood samples of approximately 0.5 mL using a micro sampling device (Tasso) will be collected, to provide approximately 0.25 mL serum into appropriately labeled tubes for measurement of etrasimod at selected timepoints as specified in the SoA.

The “Tasso device” is an integrated capillary blood collection device. Blood samples from capillary blood vessels, collected using the Tasso device, should be timed as close as possible to the collection of etrasimod blood samples. The Tasso device should be attached to the upper arm. Details for collection and handling of the samples will be provided in the laboratory manual.

The blood samples collected using venous sampling will be used for internal exploratory purposes for comparing the etrasimod concentrations between venous and capillary blood.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

Retained Research Samples for Genetics are not collected in this study.

8.7. Biomarkers

Biomarker assessments are not included in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

No statistical hypothesis will be tested in this study.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Safety Analysis Set	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Concentration Set	All participants who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported.

Participant Analysis Set	Description
PK Parameter Set	All participants who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported.

9.3. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.3.2. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE (Appendix 3). Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.3. Pharmacokinetic Analyses

Plasma PK parameters of etrasimod will be derived (as data permit) from the concentration-time data using standard noncompartmental methods as outlined in the Table 2 below. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 2. Plasma Etrasimod PK Parameters Definitions

Parameter	Definition	Method of Determination
AUC_{inf}	Area under the concentration-time curve from time zero extrapolated to infinity	$AUC_{last} + (C_{last}*/k_{el})$,

Table 2. Plasma Etrasimod PK Parameters Definitions

Parameter	Definition	Method of Determination
		where C_{last}* is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method.
$AUC_{24\ hr}$	Area under the plasma concentration-time profile from time zero to 24 hr	Linear/Log trapezoidal method.
$AUC_{24hr\text{-}last}$	Area under the plasma concentration-time profile from time 24 hr to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method.
C_{max}	Maximum observed concentration	Observed directly from data

PK parameters will be summarized descriptively by treatment, in accordance with Pfizer data standards. Plasma concentrations will be listed and summarized descriptively by nominal PK sampling time and treatment. Individual participant and median profiles of the plasma concentration-time data will be plotted by treatment using actual and nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales.

Natural log transformed AUC_{24hr}, $AUC_{24hr\text{-}last}$, AUC_{inf}, AUC_{last}, and C_{max} will be analyzed using a mixed effect model with treatment as fixed effect and participant within the sequence as a random effect. Treatment F (etrasimod 2 mg, DCT Tasso PK micro samples taken by CRU staff and participants) will be the Reference treatment while Treatment G (etrasimod 2 mg, DCT Tasso PK micro samples taken by participants only) will be the Test treatment.

Additionally, natural log transformed AUC_{24hr}, $AUC_{24hr\text{-}last}$, AUC_{inf}, AUC_{last}, and C_{max} will be analyzed using a mixed effect model with treatment as a fixed effect. Treatment A (etrasimod 2 mg, Main study, venous PK samples) will be the Reference treatment while Treatment F (etrasimod 2 mg, DCT Tasso PK micro samples taken by CRU staff and participants) and Treatment G (etrasimod 2 mg, DCT Tasso PK micro samples taken by participants only) will be the Test treatments.

9.3.4. Micro Sampling and Venous Sampling

Etrasimod concentrations at the predose and 2- and 4-hour postdose sampling time points from paired samples obtained via micro sampling and venous sampling will be compared. Individual participant differences and % differences of concentrations by PK sampling time, will be listed and summarized descriptively.

9.4. Interim Analyses

No formal interim analysis will be conducted for this study.

9.5. Sample Size Determination

A sample size of 8 participants will provide adequate precision to estimate the rBA of etrasimod across studies. These estimates are based on the assumption that standard deviations are 0.281 and 0.305 for $lnAUC_{inf}$ and lnC_{max}, respectively, as obtained from studies APD334-007 and APD334-114.

The width of 90% confidence interval for different estimated effects, with 80% coverage probability, is presented in the Table 3.

Table 3. Expected Width of 90% Confidence Interval for Different Possible Estimated Effects and Parameters of Interest

Parameter	Estimated Effect (100*Test/Reference)	90% CI		CI Width
AUC	85%	64.13%	112.67%	48.54%
	90%	67.90%	119.29%	51.39%
	95%	71.67%	125.92%	54.25%
	100%	75.44%	132.55%	57.10%
	105%	79.22%	139.17%	59.96%
	110%	82.99%	145.80%	62.81%
	115%	86.76%	152.43%	65.67%
C_{max}	85%	62.60%	115.41%	52.81%
	90%	66.29%	122.2%	55.91%
	95%	69.97%	128.99%	59.02%
	100%	73.65%	135.78%	62.13%
	105%	77.33%	142.56%	65.23%
	110%	81.02%	149.35%	68.34%
	115%	84.70%	156.14%	71.44%

Participants who withdraw from the study or whose study data are determined to be non-analyzable may be replaced at the discretion of the investigator upon consultation with the sponsor.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 participants.

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 participants.

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.

10.1.1.1. 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 intervention, 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 participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

10.1.3.1. Electronic Consent

Participants may be able to experience the informed consent process by electronic means (eConsent). The eConsent process includes an electronic presentation of the informed consent document (eICD), clinical trial educational components (as applicable), and electronic signatures (if allowed by local regulations). The use of eConsent does not replace or alter the ICD content or informed consent process as described above. The eConsent process complies with applicable regulations and sponsor policies to ensure reliability and data privacy.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes a source document and its origin can be found in the Source Document Locator, which is maintained by the Pfizer CRU.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the Pfizer CRU.

The investigator must maintain accurate documentation (source record) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;

- Inadequate recruitment of participants by the investigator;

- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. 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 CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, and (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant 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 participant.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests (Table 4) will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 4. Protocol Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	Urea/BUN and creatinine Cystatin C[a] eGFR, eCrCl[b] Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[c]	• Pregnancy test (β-Hcg)[f] • Urine drug screening[e] **At screening:** • FSH[d] • HbsAg[g] • HbcAb[g] • HCVAb[g] • HIV • QuantiFERON- TB Gold Test[h]

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1.1).
b. Screening and Baseline eGFR or eCrCl is measured with Screat-based formula. Age-specific kidney function calculation (see Section 10.6.2) is recommended to assess presence or absence of post-baseline change in kidney function.
c. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
d. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT only.
e. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study-specific).
f. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. See SoA for collection times.
g. If HbsAg is negative and HbcAb is positive, HbsAb should be evaluated.
h. Complete at screening. Previous testing for QuantiFERON TB Gold Test will be accepted if completed within 12 weeks prior to screening. Otherwise, the testing should be completed at screening and results available prior to Day 1.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety

samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs using the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2)

nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study nonparticipant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated SAE) is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have 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, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.
- The investigator may change their opinion of causality in light of follow-up 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.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eg, eSAE or PSSA).
- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is one of the methods to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom when having sexual intercourse with a pregnant or non-pregnant WOCBP.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she (a) is not pregnant or breastfeeding; (b) agrees to not donate eggs (ova, oocytes) for the purpose of reproduction for at least 28 days after the last dose of study intervention; and (c) at least 1 of the following conditions applies:

- Is not a WOCBP (see definition in Section 10.4.3).

  OR

- Is a WOCBP who agrees to use a highly effective contraceptive method (failure rate of <1% per year) with low user dependency during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  OR

- Is a WOCBP and agrees to use a highly effective (failure rate of <1% per year) user-dependent method of contraception during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time

needed to eliminate any reproductive safety risk of the study intervention(s). In addition to her use of the highly effective method above, she agrees to concurrently use an effective barrier method. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for reviewing the woman's medical history, menstrual history, and recent sexual activity in order to decrease the risk of enrolling a woman with an early, undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea or oligomenorrhea) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
     - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
     - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods

if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner.

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral + barrier*
   - Injectable + barrier*

   * Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

      - Male or female condom with or without spermicide;
      - Cervical cap, diaphragm, or sponge with spermicide;
      - A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

8. Sexual Abstinence

9. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

10.5. Appendix 5: 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 participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants 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 participant's individual baseline values and underlying conditions. Participants 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:

- Participants 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 participants 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 participant 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, ALT, and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), 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, total bile acids, 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.

10.6. Appendix 6: Kidney Safety: Monitoring Guidelines

10.6.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Obtaining Screening or Baseline Scys and postbaseline reflex Scys (if confirmed Screat increase ≥0.3 mg/dL) makes it feasible to distinguish AKI from DICI. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated:

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat only-based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat only-based equation (see Table 10.6.2.1.) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat only-based eGFR and combined Screat plus Scys eGFR).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.6.2. Age-Specific Kidney Function Calculation Recommendations

10.6.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

eGFR (mL/min/1.73m²)[13]

2021 CKD-EPI Screat Only	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	N/A	$eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	N/A	$eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤ 0.9	N/A	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	N/A	$eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Screat-Scys Combined	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ≤ 0.7	if ≤ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤ 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ≤ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if ≤ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤ 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ≤ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.6.3. Kidney Function Calculation Tool

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age-appropriate formulae (see Section 10.6.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) – 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.6.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria for adult participants.

KDIGO criteria grade (G)	**Study Population**	**G1**	**G2**	**G3**	**G4**	**G5**
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	Adult participants eGFR (mL/min/1.73m²)	≥90	≥60 to 89	30 to 59	15 to 29	<15

KDIGO albuminuria (A) criteria	**A1**	**A2**	**A3**
Albumin-to-creatinine ratio (ACR)	<30 mg/g OR <3 mg/mmol	30 to 300 mg/g OR 3 to 30 mg/mmol	>300 mg/g OR >30 mg/mmol

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 ms.
• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30-second duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The major events of potential clinical concern listed above are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what is to be reported as AEs/SAEs.

10.8. Appendix 8: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with etrasimod for the period of time at least equal to the required washout period listed in the table, and throughout the conduct of the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs), if the overall benefit:risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Drug Category	Drugs	Required Washout Period Requirement
Dual Moderate CYP2C9 and Moderate to Strong CYP3A4 Inhibitors	fluconazole	2 weeks or 5 half-lives whichever is longer
Moderate to Strong Inducers of CYP2C8 CYP2C9 CYP3A4	enzalutamide rifampicin	5 half-lives plus 14 days For example, carbamazepine: The average half-life of carbamazepine after repeat dosing is on average 15 hours, so the washout period is calculated as the sum of 5 half-lives (approximately 3 days) and an additional 14 days for a total of 17 days.

Investigators should consult the SRSD for active comparator for information regarding medication that is prohibited for concomitant use.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

10.9. Appendix 9: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6 for the list of sponsor medical devices).

10.9.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.9.2. Definition of SAE, SADE, and USADE

SAE Definition:
• An SAE is defined in Appendix 3 (Section 10.3.2).
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition
• A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is an SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.9.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.9.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and will also capture the required information on the Medical Device Complaint Form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint Form. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms.

Requirements for recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3).

- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in their assessment.
- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have 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, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change their opinion of causality in light of follow-up 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.

Follow-Up of Medical Device Deficiency
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint Form. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the CT SAE Report Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

10.9.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.4).

10.9.6. Reporting of SADEs

SADE Reporting to Pfizer Safety
Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.10. Appendix 10: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
AA	alopecia areata
Abs	absolute
ACR	albumin-to-creatinine ratio
AD	atopic dermatitis
ADE	adverse device effect
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the plasma concentration-time curve over the last 24 h dosing interval
AUC_{inf}	Area under the concentration-time curve from time zero extrapolated to infinity
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})
AV	atrioventricular
AxMP	auxiliary medicinal product
BA	bioavailability
BBS	Biospecimen Banking System
β-Hcg	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{last}	the last quantifiable concentration
CL/F	apparent clearance
C_{max}	maximum observed concentration
CNS	cardiopulmonary nervous system
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019

Abbreviation	Term
CRF	case report form
CRO	Contract Research Organization
CRU	clinical research unit
CSR	Clinical Study Report
C_{trough}	predose trough concentration
CT	clinical trial
CTMS	Clinical Trial Management System
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DCT	data collection tool/decentralized clinical trial
DDI	drug-drug interaction
DHT	digital health technology
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
EBV	Epstein-Barr virus
EC_{50}	half maximal effective concentration
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EoE	eosinophilic esophagitis
eSAE	electronic serious adverse event
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FPFV	first participant first visit
FSH	follicle-stimulating hormone
F/U	follow-up
G1 to G5	Grade (KDIGO eGFR category standardization)
GCP	Good Clinical Practice
GIRK	G-protein-gated inwardly rectifying potassium
GGT	gamma-glutamyl transferase
HbcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody

Abbreviation	Term
HDPE	high-density polyethylene
hERG	human ether-a-go-go gene
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IR	immediate release
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
MDR	medical device regulation
MMR	Measles, Mumps, Rubella
MQI	medically qualified individual
MS	multiple sclerosis
NDA	New Drug Application
NIMP	noninvestigational medicinal product
PCR	polymerase chain reaction
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetic(s)
PPD	purified protein derivative
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QFT-G	QuantiFERON-TB Gold
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative

Abbreviation	Term
Rac	accumulation ratio
rBA	relative bioavailability
RBC	red blood cell
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
Screat	serum creatinine
Scys	serum cystatin C
S1P	sphingosine 1-phosphate
$S1P_1$	S1P receptor 1
$S1P_{1,4,5}$	S1P receptors 1, 4, and 5
SDEI	sponsor-designated event of interest
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal half-life
TB	tuberculosis
T bili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
USADE	unanticipated serious adverse device effect
UTI	urinary tract infection
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

1 FDA. Decentralized clinical trials for drugs, biological products, and devices. May 2023. Available from: Decentralized Clinical Trials for Drugs, Biological Products, and Devices | FDA. Accessed: 09 Aug 2023.

2 EMA. Recommendation paper on decentralised elements in clinical trials. Version 01, 13 Dec 2022. Available from: mp_decentralised-elements_clinical-trials_rec_en.pdf (europa.eu). Accessed: 09 Aug 2023.

3 FDA. Guidance for industry: enhancing the diversity of clinical trial populations - eligibility criteria, enrollment practices, and trial designs. November 2020. Available from: Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry | FDA. Accessed: 09 Aug 2023.

4 Ivanova-Nikolova TT, Nikolov EN, Hansen C, et al. Muscarinic K+ channel in the heart. Modal regulation by G protein beta gamma subunits. J Gen Physiol. 1998;112(2):199-210.

5 Camm J, Hla T, Bakshi R, Brinkmann V. Cardiac and vascular effects of fingolimod: mechanistic basis and clinical implications. Am Heart J. 2014;168(5):632-44.

6 Sykes DA, Riddy DM, Stamp C, et al. Investigating the molecular mechanisms through which FTY720-P causes persistent $S1P_1$ receptor internalization. Br J Pharmacol. 2014;171(21):4797-807.

7 Taylor S, Gray JR, Willis R, et al. The utility of pharmacokinetic-pharmacodynamic modeling in the discovery and optimization of selective $S1P_1$ agonists. Xenobiotica. 2012;42(7):671-86.

8 GILENYA® (fingolimod) United States Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022527s031lbl.pdf. Accessed: 05 Feb 2023.

9 Mayzent® (siponimod) United States Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/209884s015lbl.pdf. Accessed: 05 Feb 2023.

10 Zeposia® (ozanimod) United States Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209899s005lbl.pdf. Accessed: 05 Feb 2023.

[11] Ponvory™ (ponesimod) United States Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213498s001lbl.pdf. Accessed: 05 Feb 2023.

[12] Cartier A, Hla T. Sphingosine 1-phosphate: Lipid signaling in pathology and therapy. Science. 366(6463):eaar5551.

[13] Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-49.

Document Approval Record

Document Name:	C5041050 (C5041034 Sub Study) Protocol Amendment 2_06 Nov 2023_Clean
Document Title:	C5041050 (C5041034 Sub Study) Protocol Amendment 2_06 Nov 2023_Clean

Signed By:	Date(GMT)	Signing Capacity
PPD	06-Nov-2023 14:59:51	Final Approval
PPD	07-Nov-2023 16:37:54	Final Approval