Title Page

A PHASE 2/3, TWO-PART STUDY TO EVALUATE THE EFFICACY AND LONG-TERM SAFETY WITH ORAL ETRASIMOD, 2 MG, ONCE DAILY IN ADULT PARTICIPANTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS WITH A HISTORY OF PRIOR SYSTEMIC TREATMENT FAILURE

Study Intervention Number:	PF-07915503 (APD334)
Study Intervention Name:	Etrasimod
US IND Number:	142182
EudraCT/CTIS Number:	2022-003361-37
ClinicalTrials.gov ID:	NCT05732454
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5041005
Phase:	2/3
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
Brief Title: A Study of Etrasimod in Adults With Moderate-to-Severe Atopic Dermatitis, Who Have Tried Prior Systemic Treatments for Atopic Dermatitis	

Document History

Document	Version Date
Amendment 2	17 May 2023
Amendment 1	07 December 2022
Original protocol	13 October 2022

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

Protocol Amendment Summary of Changes Table

Amendment 2 (17 May 2023)

Overall Rationale for the Amendment: The main purposes for Protocol Amendment 2 are to address discontinuation of study intervention for participants with certain protocol-specified treatment-related AEs and update the approach to all-cause, i.e., irrespective of causality, and to update protocol statistical sections to reflect C5041005 as an estimation study rather than a superiority study. Protocol Amendment 2 includes previous administrative changes outlined in the Protocol Administrative Change Letter (PACL, Feb 2023).

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s).		
Discontinuation of study intervention irrespective of AE causality	Changes and/or clarification to the criteria for participant withdrawal	Section 1.3. Schedule of Activities, Section 7.1 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal, Section 7.1.1 Discontinuation after Part 1 DB (Week 16) due to a Clinically Significant Safety Concern, Section 7.1.3 ECG Changes, Section 8.4.8 Adverse Events of Special Interest, Section 10.10.2 Serious Infections Monitoring, Section 10.10.3.2 Study Treatment Discontinuation Related to Post Dose Cardiac Monitoring, Section 10.10.4 Pulmonary Function Monitoring, Section 10.10.5 Ophthalmic Symptom Monitoring

Description of Change	Brief Rationale	Section # and Name
Updated protocol statistical sections to reflect C5041005 as an estimation study rather than a superiority study.	Change of study design classification based on phase of development	Section 1.1 Synopsis, Section 3 Objectives, Endpoints, and Estimands, Section 9.1 Statistical Hypothesis
Sponsor may conduct earlier unblinded interim analysis	To inform internal decision making regarding the development program	Section 9.4 Interim Analysis
Changed Inclusion Criteria #4	Expanded criteria for what constitutes acceptable prior systemic therapy in Part 1	Section 1.1 Synopsis, Section 5.1 Inclusion Criteria
Non-substantial Modification(s)		
Contraception guidance regarding abstinence and pregnancy risk	To clarify the meaning of being truly abstinent and to provide instruction on ongoing inquiry about a change in pregnancy risk	Section 5.3.1 Contraception, Section 10.4 Appendix 4: Contraceptive and Barrier Guidance
The safety follow-up approach for participants with lymphocyte declines	Clarify instruction for the safety follow up to reflect local standard of care rather than a lab pre-specified cut-off value.	Section 10.10.1 Monitoring of Lymphocyte, Neutrophil, and White Blood Cell Counts
Expanded section to emphasize ECG values of potential concern at Screening and Day 1, and further detailed investigator responsibility and	For instruction to clarify the ECG values of concern predose and process of review and interpretation of ECGs, documentation of ECG data in the	Section 8.3.3. Electrocardiograms

Description of Change	Brief Rationale	Section # and Name
process of ECG evaluation	eCRF, use of local ECG machines in emergency situations.	
Emphasized investigator responsibility for participant continuation into the OLE at Week 16	Week 16 assessment for continuation into the OLE is based on investigator judgement (medical monitor may be consulted)	Section 1.1 Synopsis, Section 4.1 Overall Design, Section 7.1.1. Discontinuation after Part 1 DB (Week 16) due to a Clinically Significant Safety Concern
Removed the details of intercurrent events of the Estimands E1 and E2	Simplification of the estimand descriptions and leaving the details to Sections 9.1.1.1 and 9.1.1.2 for Estimands E1 and E2 as indicated respectively	Section 1.1 Synopsis and Section 3 – Objectives, Endpoints, and Estimands
Removed the detailed bullet of change from baseline in laboratory values for the listed parameters	These endpoints and analyses are already captured in previous bullet of "Incidence of clinically significant changes in clinical laboratory values, ECG measurements and vital signs" and this further consolidates the safety endpoints into one bullet and avoids repetition.	Section 1.1 Synopsis and Section 3 – Objectives, Endpoints, and Estimands
Correct that the baseline definitions for Part 1 OLE and Part 2 are different and clarified their definitions	Correction and clarification of the baseline definitions for Part 1 OLE and Part 2 Safety phase.	Section 1.1 Synopsis and Section 3 – Objectives, Endpoints, and Estimands

Description of Change	Brief Rationale	Section # and Name
Minor administrative changes/clarifications to the protocol	Better readability, consistency across the protocol, and improve compliance	Throughout
Pfizer protocol template updates (14 Apr 2023)		Section 1.1 Synopsis, Section 2.3 Benefit Risk Assessment, Section 4.2.3 Adjudication Committee, Section 5.3.1 Contraception, Section 6.1 Study Intervention(s) Administered, Section 6.1.1 Administration, Section 6.8 Treatment of Overdose, Section 7.1.8. Potential Cases of Acute Kidney Injury, Section 8.4.1 Time Period and Frequency for Collecting AE and SAE Information, Section 8.4.10 Medication Errors, Section 10.1.6 Dissemination of Clinical Study Data, Section 10.1.7 Data Quality Assurance, Section 10.1.9 Use of Medical Records, Section 10.6 Appendix 6: Kidney Safety Monitoring Guidelines, Section 10.13 Appendix 13: Protocol Amendment History
PACL 03 Feb 2023		
Correction of the Exploratory endpoint statement to align with the SoA	POEM is not collected at Week 4.	Section 1.1 Synopsis, Section 3 Objectives, Endpoints, and Estimands
Revised prohibited medication list based on internal Pfizer standards	The medication has to inhibit/induce 2 or more of the enzymes explicitly mentioned to be prohibited.	Section 6.9.2 Prior Treatments, Section 6.9.3, Prohibited During the Study, Appendix 10.8.1 Prohibited Concomitant Medications That May Result in DDI
Clarified pulmonary function testing requirements and provided exception circumstance	Ensures quality of data and address regional/geographic differences regarding the lab	Section 8.3.9 Pulmonary Function Test (and DLCO), Section 1.3 SoA for Part 1 and Part 2

Description of Change	Brief Rationale	Section # and Name
	certification availability.	
Expanded male contraception verbiage.	Requires males to use a male condom when having sexual intercourse with a pregnant or non-pregnant WOCBP	Section 10.4.1 Male Participant Reproductive Inclusion Criteria
Height is only assessed Day 1	Correction and alignment with SoA.	Section 8.3.1 Physical Examinations
Deleted Reference 34.	In accordance with changes to the prohibited medication text in Section 6.9.2	Section 11 References

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2/3, Two-Part Study to Evaluate the Efficacy and Long-term Safety with Oral Etrasimod, 2 mg, Once Daily in Adult Participants with Moderate-to-Severe Atopic Dermatitis with a History of Prior Systemic Treatment Failure

Brief Title: A Study of Etrasimod in Adults With Moderate-to-Severe Atopic Dermatitis, Who Have Tried Prior Systemic Treatments for Atopic Dermatitis.

Regulatory Agency Identification Number(s):

US IND Number:	142182
EudraCT/CTIS Number:	2022-003361-37
ClinicalTrials.gov ID:	NCT05732454
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5041005
Phase:	2/3

Rationale:

Etrasimod is a S1PRM and is being developed as an oral treatment for patients with moderate-to-severe AD. Part 1 of this study will evaluate efficacy of etrasimod therapy QD and long-term safety in participants with moderate-to-severe AD with a history of a prior systemic therapy failure. It will include a 16-week double-blind treatment period followed by an open-label extension treatment period. Part 2 of this study will evaluate the long-term safety of etrasimod therapy QD in participants with moderate-to-severe AD with a history of a prior systemic therapy failure. Enrollment into Part 2 will not begin until the IA data from Part 1 are reviewed, and determination made as to the favorable benefit/risk of etrasimod 2 mg in this new target population

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• Part 1 DB: To evaluate the efficacy of etrasimod, 2 mg, QD versus placebo in adult participants with moderate-to-severe AD and a history of a prior systemic therapy failure.	• Proportion of participants achieving IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction of ≥ 2 points from baseline at Week 16.	• Estimand E1: The difference in the proportions of the binary endpoint between etrasimod, 2 mg, QD and placebo in patients with moderate-to-severe AD and a history of a prior systemic therapy failure. More details of Estimand E1 are described in Section 9.1.1.1.
• Part 1 OLE and Part 2 (OL): To evaluate the long-term safety of oral etrasimod, 2 mg, QD in adult participants with moderate-to-severe AD and a history of a prior systemic therapy failure.	• Incidence and severity of treatment-emergent AEs, AEs leading to study treatment discontinuation, SAEs, and AESIs. • Incidence of clinically significant changes in clinical laboratory values, ECG measurements and vital signs.	• Not Applicable.
Secondary:	**Secondary:**	**Secondary:**
• Part 1 DB: To evaluate the efficacy of etrasimod, 2 mg, QD based on additional measures in adult participants with moderate-to-severe AD and a history of a prior systemic therapy failure.	• Proportion of participants achieving EASI-75 at Week 16. • Percent change from baseline in EASI at Week 16.	• Estimand E1 described above. • Estimand E2: The mean difference in percent change from baseline in EASI between etrasimod, 2 mg, QD and placebo in patients with moderate-to-severe AD and a history of a prior systemic therapy failure. More details of Estimand E2 are described in Section 9.1.1.2.
Exploratory:	**Exploratory:**	**Exploratory:**
• Part 1 DB: To evaluate the efficacy of etrasimod, 2 mg, QD based on additional measures in adult participants with moderate-to-severe AD and a history of a prior systemic therapy failure.	• Proportion of participants achieving IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction of ≥ 2 points from baseline at all timepoints except Week 16. • Proportion of participants achieving EASI-75 at all timepoints except Week 16.	• Estimand E1 described above, for all binary endpoints. • Estimand E2 described above, for all continuous endpoints.

Objectives	Endpoints	Estimands
	• Percent change from baseline in EASI at all timepoints except Week 16. • Proportion of participants achieving ≥ 4-point reduction in PP-NRS score from baseline at all timepoints. • Proportion of participants achieving ≥ 4-point reduction in Skin Pain NRS score from baseline at all timepoints. • Proportion of participants achieving EASI-90 at all timepoints. • Proportion of participants achieving ≥ 4-point reduction in POEM from baseline at Week 16.	
• Part 1 OLE and Part 2: To evaluate the long-term efficacy of oral etrasimod, 2 mg, QD in adult participants with moderate-to-severe AD and a history of a prior systemic therapy failure.	Baseline for Part 1 is the pre-dose Day 1 in Part 1. Baseline for Part 2 is the pre-dose Day 1 in the Part 2 OL Safety phase. • Proportion of participants achieving EASI-75 at all scheduled timepoints. • Proportion of participants achieving IGA of clear (0) or almost clear (1) (on a 5-point scale) at all scheduled timepoints. • Percent change from baseline in EASI at all scheduled timepoints. • Proportion of participants achieving ≥ 4-point reduction in PP-NRS score from baseline at all scheduled timepoints • Proportion of participants achieving ≥ 4-point reduction in Skin Pain NRS score from	• Not applicable.

Objectives	Endpoints	Estimands
	baseline at all scheduled timepoints. • Proportion of participants EASI-90 at all scheduled timepoints. • Change from baseline in POEM at all scheduled timepoints.	

Overall Design:

This is a 2-part study with Part 1 being randomized, DB, placebo controlled, with an OLE, to assess efficacy and safety of 2 mg etrasimod administered orally, QD in participants with refractory, moderate-to-severe AD, whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable (ie, participants with a history of a prior systemic treatment failure). The open-label Part 2 is to assess long-term safety of etrasimod 2 mg in participants with moderate-to-severe AD with a history of prior systemic therapy failure.

Part 1: Approximately 60 participants will be randomized (1:1 ratio) in a DB manner to receive etrasimod 2 mg or placebo orally, QD, for 16 weeks. Randomization will be stratified by disease severity as measured by IGA score (3 [moderate AD], 4 [severe AD]) at Baseline.

Following completion of the DB portion at Week 16, all participants remaining eligible with no clinically significant safety concerns as per investigator's judgement (investigator may seek medical monitor's consideration, if needed) at Week 16, will be given the option to continue in the OLE portion of Part 1, whereby they will receive etrasimod 2 mg QD for 52 weeks. The participants, investigators and sponsor study team will remain blinded to the treatments the participants received for the placebo-controlled period. Non responders, participants not achieving at least EASI-50, will be discontinued at Week 32 (ie, 16 weeks of treatment in the OLE period).

An interim analysis will be conducted after all Part 1 participants have completed their Week 16 visit. The IA will be performed by the Sponsor and data summaries will be shared with the study team. The participants and investigators will remain blinded to the treatments the participants received for the placebo-controlled period. The study team will review the data in the context of the overall benefit-risk profile of etrasimod for the treatment of moderate-to-severe AD with prior systemic failure. The data review will include but is not limited to, efficacy measures of IGA and EASI-75 response and safety parameters including the incidence and severity of AEs, AESIs, and clinically relevant changes in ECG, and vital signs, and laboratory values. The efficacy and safety data will be utilized to make a go/no-go decision for initiating Part 2 of the study, as well as for completing the 52-week treatment for the Part 1 participants in the OLE. Once the decision is made it will be promptly communicated to the sites.

Part 2: If the IA results in a decision to proceed to Part 2 of the study, approximately 340 additional participants will be enrolled to receive etrasimod 2 mg orally, once daily, for 52 weeks in an open-label manner in order to fulfill the safety database requirements. Enrollment into Part 2 will not begin until the IA data from Part 1 are reviewed, and determination made as to the favorable benefit/risk of etrasimod 2 mg QD in the new target population. Non-responders, ie, participants not achieving at least EASI-50 will be discontinued at Week 16, Part 2.

The participant population in both Part 1 and Part 2 will include at least 40% of participants with moderate AD (IGA score of 3) and at least 40% of participants with severe AD (IGA score of 4). The application of topical emollients/moisturizers (including those containing ceramide, hyaluronic acid, or urea) will be required at least once daily for at least 1 week prior to baseline (Day 1) and throughout the treatment period without change (ie, type, frequency, application). TCS and other medicated topical treatments for AD must be discontinued at least 1 week prior to baseline (Day 1) and are not permitted in the double-blind treatment period. Safety follow-up visits will occur at 2 and 4 weeks after the last dose of study treatment. Medicated and non-medicated rescue medications are not permitted during the Part 1 DB portion. For Part 1 OLE and Part 2 medicated and non-medicated topical treatments for AD will be permitted at the discretion of the investigator and in accordance with their usual practice.

Number of Participants:

Part 1: Approximately 60 participants will be randomized in the DB period. Participants who qualify based on acceptable safety and who complete the DB period will continue in the OLE.

Part 2: Approximately 340 participants will be enrolled in this OL part of the study.

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. Chronic AD (also known as atopic eczema) that was diagnosed at least 1 year prior to Screening and meets Hanifin and Rajka criteria at screening).[1]

2. Moderate-to-severe AD:

    a. IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 = moderate and 4 = severe) at screening and baseline (Day 1)

    b. BSA ≥10% of AD involvement at screening and baseline (Day 1)

    c. Eczema Area and Severity Index (EASI) ≥16 at screening and baseline (Day 1)

3. A participant who has failed a prior systemic therapy for AD, ie, refractory, moderate-to-severe AD that is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable (i.e., medical contraindications to systemic therapy prohibit use).

    a. Inadequate response to ≥ 2 weeks of cyclosporine, azathioprine, methotrexate, mycophenolate, biologic, JAK inhibitors, or systemic corticosteroid (CS; defined as pulse of systemic CS or ≥ 2 weeks of continuous oral CS), or when systemic therapy is inadvisable.

        - In Part 1, approximately 30% of participants are permitted with a failure of a prior systemic corticosteroid therapy without failing another systemic treatment for AD. For the remining participants, failure of a prior systemic corticosteroid therapy alone is not sufficient to meet the criterion of prior systemic failure, i.e., the participant must fail another systemic treatment for AD.

        -In Part 2, failure of systemic corticosteroids may qualify a participant for the study.

    b. Refractory is an insufficient clinical response defined as the inability to achieve and maintain remission or a low disease activity state of minimal or mild lesions only, within 1 year of screening, despite treatment with systemic therapy for a period sufficient to demonstrate efficacy as determined by the Investigator.

    c. Acceptable documentation for these criteria includes chart notes that record medication prescription and treatment outcome, or Investigator documentation

based on communication with the patient's treating physician. For study purposes, document failure of prior systemic drug(s) to adequately control AD in the CRF.

4. Willing to apply a topical emollient/moisturizer at least once daily for ≥1 week prior to baseline (Day 1) and willing to maintain consistent (ie, no change in type, frequency, or application) daily application over the course of the study.

Exclusion Criteria

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

1. Presence of potential confounding factors:

Skin conditions (eg, psoriasis, seborrheic dermatitis) that may interfere with evaluation of AD or assessment of treatment response as deemed by the Investigator.

Current significant active infection or requiring a treatment for infection that may interfere with the assessment of AD.

Study Arms and Duration:

Part 1 (DB period and OLE period):

- Etrasimod, 2 mg (tablet) QD for 16 weeks or Placebo (tablet) QD for 16 weeks; OLE period: Etrasimod, 2 mg (tablet) QD for 52 weeks.

- Up to 76 weeks duration: including up to 4 weeks for screening, 16-week DB treatment period, 52-week OLE treatment period, and a safety follow-up at 2 and 4 weeks after treatment completion.

Study Intervention(s)		
Intervention Name	etrasimod	Placebo (Part 1 DB period only)
Use	experimental	placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	tablet	tablet
Unit Dose Strength(s)	2 mg	Not applicable
Route of Administration	oral	oral
Study Arm(s)		
Arm Title	Etrasimod	Placebo (Part 1 DB period only)

Arm Description	Participants will receive etrasimod 2 mg QD	Participants will receive placebo QD

Part 2 (OL Safety period):

- Etrasimod, 2 mg (tablet) QD for 52 weeks.
- Up to 60 weeks duration: including up to 4 weeks for screening, 52-week OL treatment period, and a safety follow-up at 2 and 4 weeks after treatment completion.

Intervention Name	Etrasimod
Use	experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	Tablet
Unit Dose Strength(s)	2 mg
Route of Administration	Oral
Study Arm(s)	
Arm Title	Etrasimod
Arm Description	Participants will receive etrasimod 2 mg QD

Statistical Methods:

Approximately 60 participants will be randomized to etrasimod 2 mg or placebo in a ratio of 1:1 (30 participants per treatment group) in Part 1. This is an estimation study. The primary objective will be to estimate the proportion (95% CI) of participants achieving IGA response at Week 16 in each group and the difference (95% CI) in proportions between the two groups. With 30 participants per group, assuming the proportions of participants achieving IGA response at Week 16 are 9% and 39% for placebo and etrasimod 2 mg QD, respectively: (1) the half-width of the 2-sided 95% CI for the proportion of participants achieving IGA response at Week 16 will be ≤17.5% in each treatment group using normal approximation, (2) the half-width of the 2-sided 95% CI for the difference in proportions between etrasimod 2 mg QD and placebo will be 20.2% using normal approximation. The placebo response rate was estimated based on Phase 3 studies in literature (Simpson et al. 2016, Simpson et al. 2020, Silverberg et al. 2020). No adjustment for multiplicity will be made. In Part 2, approximately 340 participants are planned and intended as a supplementary safety database for the etrasimod 2 mg QD program. No formal sample size calculations were performed for Part 2 of the study.

The primary and secondary binary efficacy endpoints for Part 1 DB, placebo-controlled portion will be analyzed using the Cochran-Mantel-Haenszel method adjusted for the actual

randomization/stratification factor IGA score (3 [moderate AD], 4 [severe AD], based on clinical database) at Baseline using normal approximation for the difference in binomial proportions. For the primary endpoint, the IGA response rate difference between the etrasimod group and the placebo group in the proportion of participants achieving (ie, IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction of ≥ 2 points from baseline at Week 16) along with its 95% confidence interval will be reported.

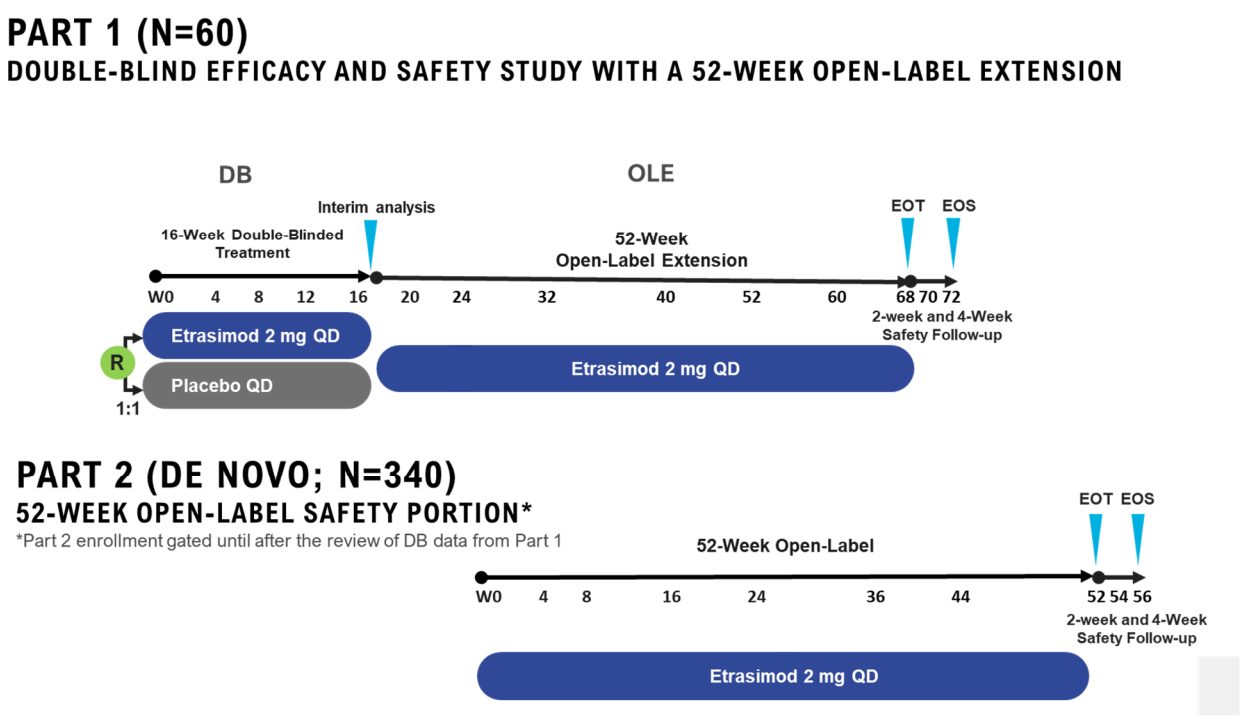
After all Part 1 participants complete the 16-week DB treatment period, an IA will be conducted. Study conduct will continue while the data are prepared and analyzed for the IA. Based on the IA results, the study may begin to enroll participants in Part 2, or the study may be terminated.

All safety analyses will be performed descriptively.

Ethical Considerations:

A clinically meaningful benefit and an acceptable safety profile for 2 mg etrasimod dose was demonstrated in the Phase 2b study (Arena study APD334-201) in adult participants with moderate-to-severe AD. The potential risks of treatment include those that were noted in Phase 2 and/or those based on the pharmacology of S1PRMs and include cardiovascular events (bradycardia, AV conduction delay, hypertension), macular edema, pulmonary events (airflow obstruction, decreased gas exchange), infections (severe infections, opportunistic infections, herpes simplex and herpes zoster), liver injury, posterior reversible encephalopathy syndrome and malignancies. The Phase 2b data in a limited sub-population of systemic failure indicated a similar efficacy of etrasimod 2 mg in participants with or without prior systemic failure. Appropriate risk evaluation and mitigation strategies (see Section 2.3.1 and Section 10.10) have been incorporated into this protocol. Overall, there is a favorable benefit-risk profile to support the continued development of etrasimod 2 mg in the treatment of adult participants with moderate-to-severe AD with a prior history of systemic failure.

1.2. Schema



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.

1.3.1. Part 1 (DB and OLE) Screening and Treatment Period

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Informed consent	X												• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Screen for inclusion/exclusion criteria	X	X											• See Section 5.1 and Section 5.2
Demographics	X												• See Section 8.1.1.1
Fitzpatrick Skin Type Assessment	X												See Section 8.1.1.1
Randomization		X											• At randomization, the participant enrollment number and study intervention are assigned.
Medical History and Physical Examination													
Medical history and AD history	X												• See Section 8.1.1.3
Complete Physical examination	X											X	• Physical examinations to be completed before administration of study intervention.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													• Symptom-directed (focused) examinations may be performed at the other study visits as described in Section 8.3.1.
Height		X											
Weight		X				X						X	• See Section 8.3.1 for additional information.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	• To be measured prior to any blood draws that occur within the same collection window. • See Section 8.3.2 for additional information. • Day 1 and Week 16 Vital signs will be collected pre-dose and at Hours 1, 2, 3, and 4 (± 15 minutes) post-dose as part of the first dose, in clinic cardiac monitoring procedure Section 8.3.2. • If the first reading is abnormal for any parameters, they may be repeated up to 2 times

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													during a visit (only applicable to first dose cardiac monitoring or cardiac monitoring during the treatment reinitiation following the defined periods of treatment interruption).
12-Lead ECG	X	X				X						X	• See Section 8.3.3 for additional information. • 12-lead ECGs (with participants in the supine position) will be performed prior to randomization, prior to dosing at Week 16 (prior to entering OLE) and at 4 (± 15 minutes) hours post-dose as part of the first dose, in-clinic cardiac monitoring procedure (Section 8.3.3). Pre-dose ECGs are to be collected prior to blood sample collection.
PML query		X	X	X	X	X	X	X	X	X	X	X	• See Section 10.11

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
PFT and DLCO	X											X	• Visit windows for post-screening assessments are ±10 days for performing PFT and DLCO (where locally available) are described in Section 8.3.9. Unscheduled visits should be performed, as clinically indicated, for participants reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the same day (refer to Section 10.10.4). • PFT and DLCO measurements will be performed at a pulmonary function laboratory or respiratory department per local regulations. Exceptional circumstances may apply; see Section 8.3.9. • Sites where DLCO is not available should consult the study medical monitor.
Ophthalmology exam	X											X	• Visit windows for post-screening assessments are ±10 days for performing ophthalmology exam as

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													described in Section 8.3.10. Unscheduled assessments should be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (Section 10.10.5).
C-SSRS	X												See Section 8.1.1.4 for additional information
Contraception check	X	X	X	X	X	X	X	X	X	X	X	X	See Section 5.3.1 and Section 10.4 for additional information.
Laboratory Assessments													• See Section 8.3.6 for additional information. • See Appendix 2 for a list of Clinical Laboratory tests to be done. • For laboratory collection volumes, see the laboratory manual.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Infectious Disease Serology	X					X						X	• Infectious diseases serology include HIV, HBV, HCV • See Exclusion Criteria for details. • See Section 8.3.7 for hepatitis testing details. • Week 16, Week 68, ET only for participants requiring HBV DNA repeat testing.
FSH	X												• FSH at Screening, only for females with no menses for ≥12 months to confirm postmenopausal status
TB Test and Chest imaging	X										X		• TB testing will be done via an IGRA (preferentially QFT-G In-Tube test, however other IGRAs are permitted) in all participants except those with a history of active, latent, or inadequately treated infection with TB.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													• If the result of the repeat test is indeterminate, participants may be screened using the Mantoux/PPD skin test with study medical monitor approval. If the Mantoux PPD tuberculin skin test is given, the participant must return between 48-72 hours post-injection for induration evaluation. • TB testing (IGRA and PPD, if needed) will be conducted at a certified local laboratory unless unavailable in which case the Central Lab will be used. • Chest images (posterior anterior and lateral views) are required for all participants. Chest image or other appropriate diagnostic image (ie CT or MRI) may be performed up to 12 weeks prior to Study Day 1. Official reading must be

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													located and available in the source documentation. • TB test and Chest Imaging at Week 52 only for participants in regions which are above a low risk for TB. • See Section 8.3.4 and Section 8.3.5
TB questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	• A TB questionnaire will be administered to all participants at Screening. The TB questionnaire will be administered at designated post-baseline visits only for participants residing in regions which are above a low risk for Tuberculosis (ie, >10/100,000 incidence, which will be determined based on WHO country level data). If TB is suspected at any time during the study, participants should be screened. • See Section 8.3.5 for details

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	• When dosing is administered during a visit, samples must be collected prior to dosing. • See Section 10.2 for details.
Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	• See Section 10.2 for details.
Urinalysis		X										X	• See Section 10.2 for details.
Coagulation		X										X	• See Section 10.2 for details.
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	• A serum pregnancy test for β-hCG will be performed on women of childbearing potential at Screening to determine eligibility. A urine pregnancy test (β hCG) will be performed at all other indicated visits unless a serum sample is required per investigator request. • On Day 1, a urine pregnancy test must be performed and result with a negative result prior to randomization. For visits that occur more than

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													4 weeks apart, participants must perform a home pregnancy test. Site personnel are expected to contact the participant every 4 weeks to confirm the home pregnancy test was taken, confirm participant continues to use contraception correctly, and document the pregnancy test results and contraception discussion in source. A home pregnancy test is required at W28, W36, W44, W48, W56, W60 and W64. If home pregnancy testing is not allowed per local regulations, pregnancy testing will be performed onsite during an unscheduled visit. Refer to Section 8.3.8 for additional guidance
TBNK panel cell counts	X	X				X			X			X	• When dosing is administered during a visit, TBNK samples must be collected prior to dosing.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Study Intervention and Other Treatments													See Section 6 for additional information.
Dispense study intervention		X	X	X	X	X	X	X	X	X	X		See Section 6.1 for additional information.
Study intervention administration at site		X				X							• The Week 16 visit is the first dose of open label treatment. Sites must contact participants 1-2 business days prior to the Week 16 visit to remind them not to take study intervention on the day of the Week 16 visit. • All PROs and AD clinical assessments should be completed prior to other clinical activities and investigative product administration. • Extended 4-hour visit on Day 1 and Week 16 due to cardiac monitoring (Section 10.10.3) and also required on the first day of treatment re-initiation

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													after a protocol-predefined treatment interruption (Section 7.1.7).
Study intervention accountability			X	X	X	X	X	X	X	X	X	X	• In the event a participant is not compliant with the assigned treatment regimen, the participant should be retrained on proper study treatment administration.
Prior/concomitant treatment(s)	X	X	X	X	X	X	X	X	X	X	X	X	See Section 6.9 for additional information
Confirm daily use of emollient/moisturizers	X	X	X	X	X	X	X	X	X	X	X	X	• Participants must apply topical emollient or moisturizer at least once daily for ≥1 week prior to Day 1 and continue daily application over the course of the study without change. On visit days during the study, participants should not apply any topical emollient or moisturizer until the study visit has been completed.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Assess treatment continuation criteria						X			X				• At Week 16, to continue into the OLE portion of the study, participants must remain eligible with no clinically significant safety concerns (see Section 7.1.1). • At Week 32, participants who do not meet the pre-specified continuation criteria (EASI-50) will be discontinued at Week 32 and will complete ET visit procedures. Refer to Section 7.1.5 of the protocol for details.
Assessments													See Section 8 for additional information.
Efficacy													See Section 8.2 for additional information.
EASI, IGA, BSA affected by AD	X	X	X	X	X	X	X	X	X	X	X	X	• All PROs and AD clinical assessments should be completed prior to other clinical activities and study intervention administration.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**DB Treatment Period**					**OLE Treatment Period**						**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 32**	**Week 40**	**Week 52**	**Week 68**	• Screening, and all visits during the 16 Week DB Treatment Period including Safety Follow up Visits MUST be conducted at the investigative study site. • Home health and/or telehealth visits may apply for certain extenuating circumstances only during the OLE Treatment period. See Section 8.1.2 and Section 8.1.3 • Due to first dose cardiac monitoring Day 1 and Week 16 visits should be conducted in the morning and not on a Friday or the day before a site-observed holiday. See Section 10.10.3. • In preparation for the Week 16 visit, site is to contact participant 1-2 business days prior to visit to remind them they will take study intervention at the site. See Section 6.5.
Study Day	**-28 to -1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**225**	**281**	**365**	**477**	• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	• All screening should be done ≤ 28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
PP-NRS, Skin Pain NRS		X	X	X	X	X	X	X	X	X	X	X	• All PROs and AD clinical assessments should be completed prior to other clinical activities and study intervention administration.
POEM		X				X			X			X	• All PROs and AD clinical assessments should be completed prior to other clinical activities and study intervention administration.
Safety													• See Section 8.3 for additional information.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	• See Section 8.4 for additional information.

1.3.2. Part 1 (DB and OLE) ET and Safety Follow-up

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**ET**	**Safety Follow-Up**		**Notes**
		Safety Follow-up 1 Week 70	**Safety Follow-up 2 Week 72**	• If a participant ends study treatment prior to Week 68 visit, the ET visit assessments should be performed within 1 week of the last dose of study treatment, unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). ET visit is only applicable to participants who end study treatment prior to EoT. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively, for participants who terminate treatment early or (for Part 1 only) who do not elect to participate in or are not eligible to continue in the OLE portion. • SFU 1 OLE visit may be a site or home health visit. SFU 1 DB visit (only for participants who do not continue to the Part 1 OLE) must occur on site due to the risk of unblinding based on WBC laboratory values.
Visit Window (±days)		**(±3)**	**(±3)**	
Complete Physical examination	X			• See Section 8.3.1 for additional information.
Weight	X			• See Section 8.3.1 for additional information.
Vital signs	X	X	X	• To be measured prior to any blood draws that occur within the same collection window. • See Section 8.3.2 for additional information.
12-Lead ECG	X		X	• See Section 8.3.3 for additional information. • ECG is only required at SFU 2 if there are abnormal, clinically significant results at Week 68 (EoT)/ET or if the Week 68 (EoT)/ET ECG is missing or if the participant does not continue to the OLE after completion of Week 16 DB visit and Week 16 results of the ECG are abnormal, clinically significant or missing (Section 8.3.9).
PML query	X	X	X	• See Section 10.11

Visit Identifier Abbreviations used in this table may be found in Appendix 12	ET	Safety Follow-Up		Notes
		Safety Follow-up 1 Week 70	**Safety Follow-up 2 Week 72**	• If a participant ends study treatment prior to Week 68 visit, the ET visit assessments should be performed within 1 week of the last dose of study treatment, unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). ET visit is only applicable to participants who end study treatment prior to EoT. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively, for participants who terminate treatment early or (for Part 1 only) who do not elect to participate in or are not eligible to continue in the OLE portion. • SFU 1 OLE visit may be a site or home health visit. SFU 1 DB visit (only for participants who do not continue to the Part 1 OLE) must occur on site due to the risk of unblinding based on WBC laboratory values.
Visit Window (±days)		**(±3)**	**(±3)**	
PFT and DLCO	X		X	• Visit windows for post-screening assessments are ±10 days for performing PFT and DLCO (where locally available) (Section 8.3.9). Unscheduled visit for clinical assessment and full PFT should be performed, as clinically indicated, for participants reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the same day (refer to Section 10.10.4). If PFT and DLCO were performed within 2 weeks of the ET Visit, repeat assessments are not required at the ET Visit. • PFT and DLCO measurements will be performed at a pulmonary function laboratory or respiratory department per local regulations. Exceptional circumstances may apply; see Section 8.3.9. • Sites where DLCO is not available should consult the study medical monitor. • Only required at SFU 2 if there are abnormal, clinically significant results at Week 68 (EoT)/ET or if the Week 68 (EoT)/ET PFT and DLCO is missing or if the participant does not continue to the OLE portion after completion of Week 16 DB visit and Week 16 results of PFT and DLCO are abnormal, clinically significant or missing (Section 8.3.9).

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**ET**	**Safety Follow-Up**		**Notes**
		Safety Follow-up 1 Week 70	**Safety Follow-up 2 Week 72**	• If a participant ends study treatment prior to Week 68 visit, the ET visit assessments should be performed within 1 week of the last dose of study treatment, unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). ET visit is only applicable to participants who end study treatment prior to EoT. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively, for participants who terminate treatment early or (for Part 1 only) who do not elect to participate in or are not eligible to continue in the OLE portion. • SFU 1 OLE visit may be a site or home health visit. SFU 1 DB visit (only for participants who do not continue to the Part 1 OLE) must occur on site due to the risk of unblinding based on WBC laboratory values.
Visit Window (±days)		**(±3)**	**(±3)**	
Ophthalmology exam	X		X	• Visit windows are ±10 days for performing ophthalmology exam as described in Section 8.3.10. Unscheduled assessments should be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (Section 10.10.5). If ophthalmoscopy and OCT were performed within 2 weeks of the ET Visit, repeat assessments are not required at the ET Visit. • Only required at SFU 2 if there are abnormal, clinically significant results at Week 68 (EoT)/ET or if the Week 68 (EoT)/ET ophthalmology exam is missing or if the participant does not continue to the OLE after completion of Week 16 DB visit and Week 16 results of the ophthalmology exam are abnormal, clinically significant or missing (Section 8.3.10).
Contraception check	X	X	X	• See Section 5.3.1 and Section 10.4 for additional information.
Laboratory Assessments				• See Section 8.3.6 for additional information. • See Appendix 2 for a list of Clinical Laboratory tests to be done. • For laboratory collection volumes, see the laboratory manual.
Infectious disease serology	X			• See Section 8.3.7 for hepatitis testing details. • Only for participants requiring HBV DNA repeat testing.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**ET**	**Safety Follow-Up**		**Notes**
		Safety Follow-up 1 Week 70	**Safety Follow-up 2 Week 72**	• If a participant ends study treatment prior to Week 68 visit, the ET visit assessments should be performed within 1 week of the last dose of study treatment, unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). ET visit is only applicable to participants who end study treatment prior to EoT. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively, for participants who terminate treatment early or (for Part 1 only) who do not elect to participate in or are not eligible to continue in the OLE portion. • SFU 1 OLE visit may be a site or home health visit. SFU 1 DB visit (only for participants who do not continue to the Part 1 OLE) must occur on site due to the risk of unblinding based on WBC laboratory values.
Visit Window (±days)		**(±3)**	**(±3)**	
TB questionnaire	X	X	X	• A TB questionnaire will be administered to all participants at screening. The TB questionnaire will be administered at designated post-baseline study visits only for participants in regions which are above a low risk for Tuberculosis (ie, >10/100,000 incidence, which will be determined based on WHO country level data),. If TB is suspected at any time during the study, participants should be screened. • See Section 8.3.5 for details
Hematology	X	X	X	See Section 10.2 for details
Blood chemistry	X	X	X	• Blood chemistry is only required at SFU2 if the results at SFU1 are abnormal, clinically significant or missing • See Section 10.2 for details
Urinalysis	X			See Section 10.2 for details
Coagulation	X			See Section 10.2 for details
Pregnancy test	X		X	• Refer to Section 8.3.8 for additional guidance.
TBNK panel cell counts	X		X	
Study Intervention and Other Treatments				See Section 6 for additional information.
Study intervention accountability	X			
Prior/concomitant treatment(s)	X	X	X	See Section 6.9 for additional information

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**ET**	**Safety Follow-Up**		**Notes**
		Safety Follow-up 1 Week 70	**Safety Follow-up 2 Week 72**	• If a participant ends study treatment prior to Week 68 visit, the ET visit assessments should be performed within 1 week of the last dose of study treatment, unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). ET visit is only applicable to participants who end study treatment prior to EoT. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively, for participants who terminate treatment early or (for Part 1 only) who do not elect to participate in or are not eligible to continue in the OLE portion. • SFU 1 OLE visit may be a site or home health visit. SFU 1 DB visit (only for participants who do not continue to the Part 1 OLE) must occur on site due to the risk of unblinding based on WBC laboratory values.
Visit Window (±days)		**(±3)**	**(±3)**	
Confirm daily use of emollient/moisturizers	X			• Participants must apply topical emollient or moisturizer at least once daily for ≥ 1 week prior to Day 1 and continue daily application over the course of the study without change. On visit days during the study, participants should not apply any topical emollient or moisturizer until the study visit has been completed.
Assessments				• See Section 8 for additional information.
Efficacy				• See Section 8.2 for additional information.
EASI, IGA, BSA affected by AD	X		X	
PP-NRS, Skin Pain NRS	X		X	• All PROs and AD clinical assessments should be completed prior to other clinical activities and investigative product administration
POEM	X			• All PROs and AD clinical assessments should be completed prior to other clinical activities and investigative product administration
Safety				• See Section 8.3 for additional information.
Serious and nonserious AE monitoring	X	X	X	• See Section 8.4 for additional information.

1.3.3. Part 2 (OL Safety)

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Informed consent	X												• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
Screen for inclusion/exclusion criteria	X	X											See Section 5.1 and Section 5.2
Demographics	X												• See Section 8.1.1.1.
Fitzpatrick Skin Type Assessment	X												• See Section 8.1.1.1.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Medical History and Physical Examination													
Medical history and AD history	X												See Section 8.1.1.3 for details
Complete Physical examination	X								X	X			• Physical examinations to be completed before administration of study intervention. • Symptom-directed (focused) examinations may be performed at the other study visits as described in Section 8.3.1
Height		X											
Weight		X							X	X			• See Section 8.3.1 for additional information.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	• To be collected prior to any blood draws that occur within the same collection window. • See Section 8.3.2 for additional information.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													• Day 1 Vital signs will be measured pre-dose and at Hours 1, 2, 3, and 4 (± 15 minutes) post-dose as part of the first dose, in clinic cardiac monitoring procedure (Section 8.3.2). • If the first reading is abnormal for any parameters, they may be repeated up to 2 times during a visit (only applicable to first dose cardiac monitoring or cardiac monitoring during the treatment reinitiation following the defined periods of treatment interruption).
12-Lead ECG	X	X			X				X	X		X	• See Section 8.3.3 for additional information. • 12-lead ECGs (with participants in the supine position) will be performed prior to dosing and 4 hours post dose (± 15 minutes) on Day 1 as part of the first dose, in-clinic cardiac monitoring

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													procedure (Section 10.10.3). Pre-dose ECGs are to be collected prior to blood sample collection. • ECG is only required at SFU 2 if there are abnormal, clinically significant results at Week 52 (EoT)/ET or if the Week 52 (EoT)/ET ECG is missing (Section 8.3.3).
PML query		X	X	X	X	X	X	X	X	X	X	X	• See Section 10.11
PFT and DLCO	X								X	X		X	• Visit windows for post-screening assessments are ±10 days for performing PFT and DLCO (where locally available) are described in Section 8.3.9. Unscheduled visit for clinical assessment and full PFT should be performed, as clinically indicated, for participants reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing), preferably on the

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													same day (refer to Section 10.10.4). If PFT and DLCO were performed within 2 weeks of the ET Visit, repeat assessments are not required at the ET Visit. • PFT and DLCO measurements will be performed at a pulmonary function laboratory or respiratory department per local regulations. Exceptional circumstances may apply; see Section 8.3.9. • Sites where DLCO is not available should consult the study medical monitor. • Only required at SFU 2 if there are abnormal clinically significant results at Week 52 or ET visit.
Ophthalmology exam	X								X	X		X	• Visit windows for post screening assessments are ±10 days for performing ophthalmology exam as

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													described in Section 8.3.10. Unscheduled ophthalmic examination may also be performed, as clinically indicated, as part of the study visit assessment due to complaints of decreased vision or identification of worsening visual acuity (Section 10.10.5). If ophthalmoscopy and OCT were performed within 2 weeks of the ET Visit, repeat assessments are not required at the ET Visit. • Only required at SFU 2 if there are abnormal clinically significant results at Week 52 or ET visit.
C-SSRS	X												See Section 8.1.1.4 for additional information
Contraception check	X	X	X	X	X	X	X	X	X	X	X	X	See Section 5.3.1 and Section 10.4 for additional information.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Laboratory Assessments													• See Section 8.3.6 for additional information. • See Appendix 2 for a list of Clinical Laboratory tests to be done. • For laboratory collection volumes, see the laboratory manual.
Infectious Disease Serology	X				X				X	X			• Infectious diseases serology include HIV HBV, HCV. • See Exclusion Criteria for details. • Week 16, Week 52 and ET only for participants requiring HBV DNA repeat testing . • See Section 8.3.7 for hepatitis testing details.
FSH	X												• FSH at Screening, only for females with no menses for ≥12 months to confirm postmenopausal status.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
TB test and chest imaging	X								X				• TB testing will be done via an IGRA (preferentially QFT-G In-Tube test, however other IGRAs are permitted) in all participants except those with a history of active, latent, or inadequately treated infection with TB. • If the result of the repeat test is indeterminate, participants may be screened using the Mantoux/PPD skin test with study medical monitor approval. If the Mantoux PPD tuberculin skin test is given, the participant must return between 48-72 hours post-injection for induration evaluation. • TB testing (IGRA and PPD, if needed) will be conducted at a certified local laboratory unless

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													unavailable in which case the Central Lab will be used. • Chest images (posterior, anterior and lateral views) are required for all participants. Chest images or other appropriate diagnostic image (ie CT or MRI) may be performed up to 12 weeks prior to Study Day 1. Official reading must be located and available in the source documentation. • TB test and Chest Imaging at Week 52 only for participants in regions which are above a low risk for TB. • See Section 8.3.4 and Section 8.3.5
TB questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	• A TB questionnaire will be administered to all participants at screening. The TB questionnaire

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													will be administered at designated post-baseline visits only for participants residing in regions which are above a low risk for Tuberculosis (ie, >10/100,000 incidence, which will be determined based on WHO country level data)If TB is suspected at any time during the study, participants should be screened. • See Section 8.3.5 for details
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	• When dosing is administered during a visit, samples must be collected prior to dosing. • See Section 10.2 for details
Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	• Blood chemistry is only required at SFU2 if the results at SFU1 are abnormal, clinically significant or missing.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													• See Section 10.2 for details
Urinalysis		X							X	X			See Section 10.2 for details
Coagulation		X							X	X			See Section 10.2 for details
Pregnancy test	X	X	X	X	X	X	X	X	X	X		X	• A serum pregnancy test for β-hCG will be performed on women of childbearing potential at Screening to determine eligibility. A urine pregnancy test (β hCG) will be performed at all other indicated visits unless a serum sample is required per investigator request. On Day 1, a urine pregnancy test must be performed and result with a negative result prior to dosing. For visits that occur more than 4 weeks apart, participants must perform a home pregnancy test. Site personnel are expected to contact the participant

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
													every 4 weeks to confirm the home pregnancy test was taken, confirm participant continues to use contraception correctly, and document the pregnancy test results and contraception discussion in source. A home pregnancy test is required at W12, W20, W28, W32, W40, W48. If home pregnancy testing is not allowed per local regulations, pregnancy testing will be performed onsite during an unscheduled visit. • See Section 8.3.8 for details
TBNK panel cell counts	X	X			X				X	X		X	• When dosing is administered during a visit, TBNK samples must be collected prior to dosing.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Study Intervention and Other Treatments													See Section 6 for additional information.
Dispense study intervention		X	X	X	X	X	X	X					See Section 6.1 for additional information.
Study intervention administration at site		X											• Extended 4-hour visit on Day 1 due to cardiac monitoring. May also required be on Day 2 (Section 10.10.3). • Also required on the first day of treatment re-initiation after a protocol-predefined treatment interruption (Section 7.1.7).
Study intervention accountability			X	X	X	X	X	X	X	X			• In the event a participant is not compliant with the assigned treatment regimen, the participant should be retrained on proper study treatment administration.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Prior/concomitant treatment(s)	X	X	X	X	X	X	X	X	X	X	X	X	See Section 6.9 for additional information
Confirm daily use of emollient/moisturizers		X	X	X	X	X	X	X	X	X			• Participants must apply topical emollient or moisturizer at least once daily for ≥1 week prior to Day 1 and continue daily application over the course of the study without change. On visit days during the study, participants should not apply any topical emollient or moisturizer until the study visit has been completed.
Assess treatment continuation criteria					X								• Participants who do not meet the pre-specified continuation criteria (EASI-50) will be discontinued at Week 16 and will complete ET visit procedures. Refer to Section 7.1.5 of the protocol for details.

Visit Identifier Abbreviations used in this table may be found in Appendix 12	**Screen**	**Treatment Period**								**ET**	**Safety Follow-up**		**Notes**
		Day 1	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 44**	**Week 52**		**1 Week 54**	**2 Week 56**	• If a participant ends study treatment prior to Week 52, the ET visit assessments should be performed within 1 week of the last dose of study treatment unless participant is discontinued due to the results of first dose cardiac monitoring when ET visit should occur within 3 calendar days (see Section 10.10.3). • Due to first dose cardiac monitoring, the Day 1 visit should be conducted in the morning and not on a Friday or the day before a site observed holiday. See Section 10.10.3. • The SFU 1 and SFU 2 Visits are to be conducted 2 and 4 weeks (± 3 days) after last dose of study treatment, respectively. • Home health and/or telehealth visits may apply for certain extenuating circumstances only. See Section 8.1.2 and Section 8.1.3.
Study Day	**-28 to -1**	**1**	**29**	**57**	**113**	**169**	**253**	**309**	**365**				• Day relative to start of study intervention (Day 1).
Visit Window (±days)	**NA**	**NA**	**(±5)**	**(±5)**	**(±5)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**		**(±3)**	**(±3)**	• All screening should be done ≤28 days before the first dose. • See Section 8.4.3 for follow-up AE and SAE assessments.
Assessments													• See Section 8 for additional information.
Efficacy													• See Section 8.2 for additional information.
EASI, IGA, BSA affected by AD	X	X	X	X	X	X	X	X	X	X		X	
PP-NRS, Skin pain NRS		X	X	X	X	X	X	X	X	X		X	• All PROs and AD clinical assessments should be completed prior to other clinical activities and investigative product administration.
POEM		X				X			X	X			• All PROs and AD clinical assessments should be completed prior to other clinical activities and investigative product administration
Safety													• See Section 8.3 for additional information.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	• See Section 8.4 for additional information.

2. INTRODUCTION

Etrasimod (also known as APD334) is a synthetic, next generation, selective modulator of $S1P_{1,4,5}$ in development as a once daily oral treatment for immune mediated inflammatory disorders.

$S1P_1$ is a cell surface expressed G protein coupled receptor shown to regulate lymphocyte egress from lymphoid tissues. Upon binding to $S1P_1$, synthetic receptor modulators, such as etrasimod, have been observed to act as functional antagonists by inducing sustained receptor internalization. Loss of cell surface expressed $S1P_1$ prevents cells from migrating along S1P gradients and results in lymphocyte retention within lymphoid tissue, thus lowering the amount of peripheral blood lymphocytes available for recruitment to sites of inflammation.[2] This reduction in infiltrating lymphocytes may result in decreases in the release of proinflammatory cytokines, signaling proteins known to mediate tissue inflammation.[3]

Modulation of the S1P/S1P receptor axis offers a potential therapeutic approach to the management of a variety of immune mediated disorders. Consistent with this hypothesis, S1P receptor modulators have been shown to be clinically beneficial in multiple T cell mediated diseases including, but not limited to, inflammatory bowel disease, multiple sclerosis, and plaque psoriasis. [2,4-7] Etrasimod may therefore provide therapeutic benefit to patients with AD.

Dendritic cells and T cells play critical roles in driving AD immunopathology. [8,9] In AD, skin resident dendritic cells readily engulf foreign antigens and allergens that have penetrated the perturbed dermal barrier, and traffic to the lymph nodes, where they activate and polarize naïve T cells.[10] Once activated, T cells exit lymphoid organs, migrate to the skin, and secrete inflammatory cytokines and chemokines. Activated T cells can directly drive skin inflammation, or recruit other immune cells, including eosinophils and mast cells, that further contribute to the inflammatory processes.

Trafficking of dendritic cells, T cells, and eosinophils have all been shown to be modulated in part by functional antagonism of $S1P_1$. In addition to the effect of reducing circulating lymphocytes described above, $S1P_1$ has been shown to modulate the trafficking of dendritic cells towards draining lymph nodes [11,12]and the egress of eosinophils from the bone marrow.[13] The role of $S1P_1$ functional antagonism in the immune cells implicated in AD pathogenesis, and therefore the potential to reduce skin inflammation, supports the development of etrasimod as a potential therapeutic for AD.

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

2.1. Study Rationale

Etrasimod is a S1PRM and is being developed as an oral treatment for patients with moderate-to-severe AD. Part 1 of this study will evaluate efficacy of etrasimod therapy QD and long-term safety in participants with moderate-to-severe AD with a history of a prior systemic therapy failure. Part 2 of this study will evaluate the long-term safety of etrasimod

therapy QD in participants with moderate-to-severe AD with a history of a prior systemic therapy failure.

2.2. Background

AD, also known as atopic eczema, is the most common chronic relapsing, inflammatory skin disease. [9,14] The lifetime prevalence of AD is 10 to 20% in developed nations with a 2- to 3-fold increase in prevalence during the past decades in industrialized countries.[15] AD is characterized by chronic cutaneous inflammation and perturbed epidermal-barrier function resulting in dry, red skin and intense itch. [8,14,16,17] Essential features for diagnosis of AD are pruritus, eczematous dermatitis, and a chronic or relapsing history of disease. [8,14] The pathogenesis of AD is thought to stem from the mutually reinforcing interaction between a disrupted epidermal barrier and an inappropriate immune response in the skin. [14,18] Epidermal barrier disruption facilitates allergen penetration, IgE sensitization, and bacterial colonization (particularly Staphylococcus aureus), all of which induce persistent type 2 helper T cell responses. Although an individual's predisposition to AD is not fully understood, it is likely determined by a combination of genetic, environmental, and immunologic factors. [19,20]

AD is a major cause of skin-related disability globally[21] with a substantial burden of disease on the patient.[22] Patients with AD are more likely to have other allergic or atopic conditions. In a 2016 study of 380 adults with moderate-to-severe AD, 51.3% had allergic rhinitis, 40.3% had asthma, 24.2% had allergic conjunctivitis, and 60.5% had other allergies.[23] Recent research also shows AD is associated with a significantly increased risk of anxiety and depression.[24] The disease burden of those with AD significantly impacts quality of life and patients report that their condition affects social and leisure activities (43.9%), work or studying (41.8%), and clothing choice (57.9%).[23] AD is difficult to treat due to its chronic, heterogeneous and relapsing-remitting nature, and it often requires the polypharmacy approach to effectively manage signs and symptoms long term.[25] The goals of treatment are to reduce AD signs (eg, lesions, erythema) and symptoms (pruritus and pain).

Currently, the available systemic treatments in the US and European countries include conventional immunosuppressants (eg, oral corticosteroid, cyclosporine, azathioprine, mycophenolate mofetil, methotrexate), biologics (eg, dupilumab) and JAK inhibitors (eg, baricitinib, abrocitinib and upadacitinib).[26-28] Overall, these systemic agents show varying degrees of efficacy and safety and there is no single systemic option that is widely accepted as standard of care for AD. Many of the currently available therapies for moderate-to-severe AD are limited to short-term or intermittent use due to inconvenience (phototherapy) or patient nonadherence due to factors including side effect intolerance. [29,30] In consideration of the current gaps in the AD treatment paradigm, there remains a significant unmet need for effective and safe treatments for AD.

2.3. Benefit/Risk Assessment

Etrasimod, an investigational, oral, and once daily S1P receptor modulator, offers an alternative treatment option for patients with moderate-to severe AD. The use of S1P receptor modulation for AD is supported by literature indicating association of S1P with a

variety of chronic itchy and inflammatory skin dermatoses including AD, allergic contact dermatitis, psoriasis, scleroderma as well as neuropathic pain.[31]

The safety and tolerability of etrasimod have been evaluated in Phase 1 studies with healthy adult participants at single doses up to 5 mg and repeat doses up to 4 mg once daily. Etrasimod 2 mg has been/is being evaluated in multiple indications including AD, AA, UC, CD and EoE.

Study APD334-201 was a Phase 2, multicenter, randomized, double-blinded, placebo-controlled study designed to assess the safety and efficacy of once daily etrasimod in participants with moderate-to-severe AD that could not be adequately controlled with topical medications. Participants were randomized 1:1:1 to etrasimod 1 mg, etrasimod 2 mg, or placebo taken orally once daily during a 12-week double-blind treatment period with a 4-week safety follow-up period following the last dose of study treatment. After the 4 week safety follow-up period, eligible participants could enter an OLE treatment period to receive etrasimod 2 mg once daily for 52 weeks. Compared with placebo, treatment with etrasimod 2 mg resulted in a greater percentage of participants achieving clear or almost clear skin per vIGA assessment at Week 12. The overall safety profile of etrasimod 2 mg was consistent with the safety demonstrated in healthy participants. The most common AEs for participants of >5% and greater than placebo were lymphocyte count decreased, UTI, nausea, constipation, back pain and dizziness. Maintenance of effect was observed in the 52-week OLE with no new clinically relevant safety signals. In the OLE, the most common AEs for >5% of participants were lymphocyte count decreased, headache, SARS-CoV-2 test positive and dermatitis atopic.

A clinically meaningful benefit and an acceptable safety profile for 2 mg etrasimod dose was demonstrated in the Phase 2b study (Arena study APD334-201) in adult participants with moderate-to-severe AD.

In conclusion, based on the overall exposure data to date, the safety profile of etrasimod 2 mg remains favorable and supports further development in participants with AD and the current Phase 2/3 study. The Phase 2/3 AD program is designed to exclude participants at high risk for S1P-related adverse events, proactively monitor and assess safety parameters, and includes predefined stopping criteria to manage patient safety as described in Section 7. The newly defined population for this study is adults with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable, for whom the benefit/risk ratio may be favorable based on the etrasimod MOA and totality of etrasimod 2 mg data.

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 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.	Limited long-term safety data of S1P receptor modulators is available in the AD population as there are no approved drugs in this class for dermatologic conditions. Adverse events associated with S1P receptor modulators are well characterized in the adult MS and UC population. AESIs associated with S1P receptor modulators (class labeling) include 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 decreased gas exchange), liver injury, malignancies, and PRES. The totality of clinical data up to date in several dermatological and non-dermatological inflammatory indications indicate that 2 mg etrasimod is well-tolerated with no clinically significant safety signals.	The proposed Phase 2/3 Study includes the following risk mitigation methods: • Exclusion criteria for participants with elevated risk factors for adverse events associated with S1P receptor modulators • Extensive safety monitoring measures for potential S1P receptor modulator drug reactions, including first dose reactions and active query for signs and symptoms of PML • Unscheduled assessments, as clinically indicated, for participants reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness or wheezing) and due to complaints of decreased vision or identification of worsening visual acuity • Clearly defined stopping criteria for clinical findings associated with S1P receptor modulators. • An E-DMC will be used throughout the study (Part 1 and Part 2) to review safety data.
S1P receptor modulator-specific lymphocyte level decreases.	Dose-dependent reductions in peripheral lymphocyte counts is an expected PD effect of etrasimod. A clinically significant reduction in peripheral lymphocyte count, especially CTCAE Grade 4, may increase the risk of infections in some participants. The PD effect (lymphocyte lowering) of etrasimod is reversible following treatment discontinuation. In Arena Study APD334-201 treatment with etrasimod resulted in a dose-dependent decrease in lymphocyte count and quick reversal (within 2 – 4	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. In the completed Phase 2 study APD334-201, including a 12-week DB treatment period and a 52-week OLE, there were no clinically relevant safety signals related to infections.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk.	Mitigation Strategy
	weeks) to normal levels following cessation of drug treatment, which is consistent with etrasimod clinical studies in other inflammatory conditions. Serial assessments of white blood cell count and differential will be performed in this study to assess the risk for serious and atypical infections.	Pre-defined stopping/drug interruption criteria are included in the design of this Study for CTCAE Grade 4 lymphopenia (ALC < 0.2×10^9 cells/L).
First dose cardiac effect.	The S1P receptor modulator 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 in several inflammatory indications indicate that 2 mg etrasimod is well-tolerated with modest HR reduction that is maximal on the first day of dosing without major clinically relevant cardiac safety events.	Participants with elevated cardiac risk factors will be excluded from participation in the study. 4-hour first dose cardiac monitoring is included in Part 1 (Day 1 and Week 16) and Part 2 (Day 1), including for participants with etrasimod re-initiation after a temporary interruption/re-initiation. 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 breast-feeding.	WONCBP or WOCBP status will be determined at screening. WOCBP who are pregnant, lactating, or breast-feeding 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 5.3.1 and Section 10.4 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. Pregnancy will be monitored monthly, including follow-up visit. Exposure during pregnancy and breastfeeding should be reported to Pfizer Safety. Participants who become pregnant will be permanently discontinued from study intervention.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk.	Mitigation Strategy
Potential risk of etrasimod on vaccine effect	Use of live attenuated vaccines while taking an S1P receptor modulator carries a theoretical risk of infection and should therefore be avoided during treatment and for a defined period of time after stopping treatment. Currently, there are no data on the effect of etrasimod treatment on vaccine efficacy and safety including severe acute respiratory system coronavirus 2 (SARs CoV 2) vaccines to protect against COVID-19.	Live attenuated vaccines are prohibited during study treatment, 6 weeks prior to baseline (Day 1) and for 4 weeks after the last dose of study treatment. It is recommended that participants receive a vaccination against COVID-19 to decrease the risk of contracting SARs-CoV-2.
Interactions with other medicinal products and other forms of interaction	Based on data from CYP-mediated clinical drug interaction studies, moderate increases in exposure of etrasimod were observed when multiple CYPs were inhibited (fluconazole) or decreased when multiple CYPs were induced (rifampin). Thus, the use of moderate or strong inhibitors or inducers that inhibit or induce at least 2 of the following is not recommended: cytochrome P450 CYP2C8, CYP2C9, and CYP3A4. Caution should be used during concomitant administration of immunomodulatory or immunosuppressive therapies with etrasimod due to the risk of additive immune effects during such therapy and in the weeks following administration.	To minimize potential DDI, drugs known to inhibit or induce the following cytochrome P450 enzymes, CYP2C8, CYP2C9, and CYP3A4 are prohibited within 4 weeks prior to baseline (Day 1): • Moderate to strong inducers/inhibitors of two or more of the CYP enzymes above (eg, fluconazole) To minimize the risk of additive immune effects during the study, mandatory washout periods for immune-modulating and immunosuppressive therapies will be implemented as described in Section 6.9.2.
Study Procedures		
Worsening of AD	Participants discontinuing their AD treatment during the washout period may experience the worsening of their AD symptoms. A worsening of AD may occur during the treatment period and follow-up period.	Participants may discontinue treatment or withdraw from the study at any time for any reason. Participants meeting withdrawal/discontinuation criteria (Section 7.2) may be able to use alternative treatments after withdrawal from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk.	Mitigation Strategy
		Participants will be assessed for safety at regular intervals throughout the study to identify and mitigate the risks the potential risks.
Other		
The COVID-19 pandemic/regional emergency situations may pose risks to study participation	Participants may be at increased safety risk by attending a clinic visit.	Use of telehealth and/or home health visits will be utilized in the study to minimize potential exposure of trial participants to emergency situations (Section 8.1.2 and Section 8.1.3).

2.3.2. Benefit Assessment

Oral administration of etrasimod is anticipated to provide a therapeutic benefit in the treatment of AD by targeting the signaling of cytokines in Th2 response through the reduction of dendritic cell trafficking to lymph nodes, sequestration of lymphocytes and reduction of levels of circulating T cells. In a Phase 2b clinical Study (Arena study APD334-201), efficacy for 2 mg etrasimod was shown in participants with moderate-to-severe AD with a history of a topical treatment failure. In the DB study portion statistically significant improvements were reported at Week 12 for the number of participants with vIGA of 0 or 1 and a 2-point improvement from baseline (29.8% vs 13.0% P=0<0.05), ≥4-point change in DLQI (69.8% vs 55.6% P<0.05) and ≥4-point change in POEM (56.7% vs 37.0% P<0.05). Further improvement and maintenance of response was observed in the 52-week OLE period of the study for the key endpoints of number of participants with vIGA of 0 or 1 and a 2-point improvement from baseline, EASI-75 and ≥4-point improvement in PP-NRS. Other S1P receptor modulators are being currently studied in other dermatological conditions including AD,[32] and an S1P receptor modulator ponesimod has demonstrated efficacy in the treatment of psoriasis.[33]

Similar clinical response was shown for etrasimod in participants with moderate-to-severe AD with a history of a prior systemic treatment failure vs without a history of a prior systemic treatment failure. Participants in this study, ie participants with moderate-to-severe AD with a history of a prior systemic therapy failure, may, therefore, receive a beneficial effect, in addition to regular intensive clinical trial assessment to support management of their AD.

2.3.3. Overall Benefit/Risk Conclusion

A clinically meaningful benefit for 2 mg QD dose of etrasimod was demonstrated in the Phase 2b clinical Study (Arena Study APD334-201) in adult participants with moderate-to-severe AD. Compared with placebo, treatment with 2 mg QD dose of etrasimod resulted in a greater percentage of participants achieving clear or almost clear skin per vIGA assessment at Week 12. Maintenance of effect and continuous efficacy was observed in the 52-Week OLE with no new clinically relevant safety signals. The potential risks of treatment include those that were noted in Phase 2b and/or those based on the pharmacology of S1P receptor modulators and include cardiovascular events (bradycardia, AV conduction delay, hypertension), macular edema, pulmonary disorders (airflow obstruction, decreased gas exchange), infections (severe infections, opportunistic infections, herpes simplex and herpes zoster), liver injury (liver transaminase elevation, bilirubin elevation), PRES and malignancies. Considering the measures to minimize risk to study participants, the potential risks identified in association with 2 mg QD dose of etrasimod are justified by the anticipated benefits that may be afforded to participants with AD.

The Benefit/Risk balance of etrasimod is considered favorable and supported by:

- The favorable safety profile for etrasimod to date based on non-clinical studies and Arena clinical Study APD334-201 in AD.

- The totality of safety data for etrasimod to date including the long-term safety data based on an ongoing clinical study in AA (Arena Study APD334-205) with etrasimod 2 mg and 3 mg.

- The totality of safety and efficacy data from the Phase 3 UC Program.

- The expected efficacy of etrasimod for the treatment of AD based on pre-clinical and translational data generated with etrasimod and efficacy in Arena clinical Study APD334201

- The expected efficacy of etrasimod for the treatment of moderate-to-severe AD with a history of a prior systemic therapy failure based on the post hoc efficacy analysis of data from Arena clinical Study APD334-201

C5041005 study includes the appropriate safety monitoring and risk management measures including the exclusion of participants with increased risk, ongoing safety monitoring by the investigator and the sponsor during the study (e-DMC), and prespecified stopping criteria for participants with potential safety risks. In conclusion, Pfizer considers that the clinical experience to date with 2 mg QD dose of etrasimod support the continued development of etrasimod for the treatment of AD and the initiation of the Phase 2/3 Study C5041005. Additional background information on etrasimod can be found in the current version of the IB, especially the Summary of Data and Guidance for the Investigator (Section 6 of the Arena IB).

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 AD.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• Part 1 DB: To evaluate the efficacy of etrasimod, 2 mg, QD versus placebo in adult participants with moderate-to-severe AD and a history of a prior systemic therapy failure.	• Proportion of participants achieving IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction of ≥ 2 points from baseline at Week 16.	• Estimand E1 (binary endpoints): The difference in the proportions of the binary endpoint between etrasimod, 2 mg, QD and placebo in patients with moderate-to-severe AD and a history of a prior systemic therapy failure. More details of Estimand E1 are described in Section 9.1.1.1.
• Part 1 OLE and Part 2: To evaluate the long-term safety of oral etrasimod, 2 mg, QD in adult participants with	• Incidence and severity of treatment-emergent AEs, AEs leading to study treatment	• Not applicable.

Objectives	Endpoints	Estimands
moderate-to-severe AD and a history of a prior systemic therapy failure.	discontinuation, SAEs, and AESIs. • Incidence of clinically significant changes in clinical laboratory values, ECG measurements and vital signs.	
Secondary:	**Secondary:**	**Secondary:**
• Part 1 DB: To evaluate the efficacy of etrasimod, 2 mg, QD based on additional measures in adult participants with moderate-to-severe AD and a history of a prior systemic therapy failure.	• Proportion of participants achieving a EASI-75 at Week 16. • Percent change from baseline in EASI at Week 16.	• Estimand E1 described above. • Estimand E2: The mean difference in percent change from baseline in EASI between etrasimod, 2 mg, QD and placebo in patients with moderate-to-severe AD and a history of a prior systemic therapy failure. More details of Estimand E2 are described in Section 9.1.1.2.
Exploratory:	**Exploratory:**	**Exploratory:**
• Part 1 DB: To evaluate the efficacy of etrasimod, 2 mg, QD based on additional measures in adult participants with moderate-to-severe AD and a history of a prior systemic therapy failure.	• Proportion of participants achieving IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction of ≥ 2 points from baseline at all timepoints except Week 16. • Proportion of participants achieving a EASI-75 at all timepoints except Week 16. • Percent change from baseline in EASI at all timepoints except Week 16. • Proportion of participants achieving ≥ 4-point reduction in PP-NRS score from baseline at all timepoints. • Proportion of participants achieving ≥ 4-point reduction in Skin Pain NRS score from baseline at all timepoints.	• Estimand E1 described above, for all binary endpoints. • Estimand E2: described above, for all continuous endpoints.

Objectives	Endpoints	Estimands
	• Proportion of participants EASI-90 at all timepoints. • Proportion of participants achieving ≥ 4-point reduction in POEM from baseline at Week 16.	
• Part 1 OLE and Part 2: To evaluate the long-term efficacy of oral etrasimod, 2 mg, QD in adult participants with moderate-to-severe AD and a history of a prior systemic therapy failure.	Baseline for Part 1 is the pre-dose Day 1 in Part 1. Baseline for Part 2 is the pre-dose Day 1 in the Part 2 OL Safety phase. • Proportion of participants achieving EASI-75 at all scheduled timepoints. • Proportion of participants achieving IGA of clear (0) or almost clear (1) (on a 5-point scale) at all scheduled timepoints. • Percent change from baseline in EASI at all scheduled timepoints. • Proportion of participants achieving ≥ 4-point reduction in PP-NRS score from baseline at all scheduled timepoints. • Proportion of participants achieving ≥ 4-point reduction in Skin Pain NRS score from baseline at all scheduled timepoints. • Proportion of participants EASI-90 at all scheduled timepoints. • Change from baseline in POEM at all scheduled timepoints.	• Not applicable.

4. STUDY DESIGN

4.1. Overall Design

This is a two-part study with Part 1 being 16 week, randomized, DB, placebo controlled, with an OLE, to assess efficacy and safety of 2 mg etrasimod administered orally, QD in participants with refractory, moderate-to-severe AD, whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable (ie, participants with a history of a prior systemic treatment failure).

The open-label Part 2 is to assess long-term safety of etrasimod 2 mg QD in participants with moderate-to-severe AD with a history of prior systemic therapy failure.

Part 1: Approximately 60 participants with moderate-to-severe AD with a history of prior systemic treatment failure will be randomized (1:1 ratio) in a double-blind manner to receive etrasimod 2 mg QD or placebo orally, once daily, for 16 weeks. Randomization will be stratified by disease severity as measured by IGA score (3 [moderate AD], 4 [severe AD]) at baseline.

Following completion of the double-blind, placebo-controlled period, all participants with no clinically significant safety concerns as per investigator's judgement (investigator may seek medical monitor's consideration, if needed) at Week 16 will be given the option to continue in an OLE whereby they will receive etrasimod 2 mg (tablet) QD for 52 weeks. The participants, investigators and sponsor study team will remain blinded to the treatments the participants received for the placebo-controlled period. Non-responders, participants not achieving EASI-50, will be discontinued at Week 32 (ie, 16 weeks of treatment in the OLE period).

An interim analysis will be conducted after all Part 1 participants have completed the 16-week DB treatment period. The IA will be performed by the Sponsor and data summaries will be shared with the study team. The participants and investigators will remain blinded to the treatments the participants received for the placebo-controlled period. The study team will review the data in the context of the overall benefit-risk profile of etrasimod for the treatment of moderate-to-severe AD with prior systemic failure. The data review will include but is not limited to, efficacy measures of IGA and EASI-75 response and safety parameters including the incidence and severity of AEs, AESIs, and clinically relevant changes in ECG, and vital signs, and laboratory values. The efficacy and safety data will be utilized to make a go/no-go decision for initiating Part 2 of the study, as well as for completing the 52-week treatment for the Part 1 participants in the OLE. Once the decision is made it will be promptly communicated to the sites.

Part 2: If the IA results in a decision to proceed to Part 2 of the study, approximately 340 additional participants will be enrolled to receive etrasimod 2 mg orally, once daily, for 52 weeks in an open-label manner in order to fulfill the safety database requirements. Enrollment into Part 2 will not begin until the IA data from Part 1 are reviewed, and determination made as to the favorable benefit/risk of etrasimod 2 mg QD in this new target population. Non-responders, ie, participants not achieving at least EASI-50 will be discontinued at Week 16, Part 2.

The participant population in both Part 1 and Part 2 will include at least 40% of participants with moderate AD (IGA score of 3) and at least 40% of participants with severe AD (IGA score of 4). The application of topical emollients/moisturizers (including those containing ceramide, hyaluronic acid, or urea) will be required at least once daily for at least 1 week prior to baseline (Day 1) and throughout the treatment period without change (ie, type, frequency, application). TCS and other medicated topical treatments for AD must be discontinued at least 1 week prior to baseline (Day 1) and are not permitted in the

double-blind treatment period. Safety follow-up visits will occur at 2 and 4 weeks after the last dose of study treatment. Medicated and non-medicated rescue medications are not permitted during the Part 1 DB portion. For Part 1 OLE and Part 2 medicated and non-medicated topical treatments for AD will be permitted at the discretion of the investigator and in accordance with their usual practice.

4.2. Scientific Rationale for Study Design

This is a Phase 2/3 study designed to evaluate the efficacy and safety of etrasimod in participants 18 to 80 years of age with refractory, moderate-to-severe AD (IGA ≥3, EASI ≥16, BSA ≥10%) whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable, ie, participants with a history of a prior systemic treatment failure.

Part 1 will assess etrasimod 2 mg QD monotherapy compared to placebo. The choice of placebo as a control is appropriate for the objectives of this study as it will provide the most robust assessment of the efficacy and safety of etrasimod. The 16-week treatment duration for the DB portion was selected based on the Phase 2 Arena study APD334-201 to ensure that etrasimod could approach maximal efficacy while minimizing the time that a participant may be on placebo treatment.

The duration of study participation is up to 76 weeks, which includes a ≤ 4-week screening period, a 16-week DB treatment period, a 52-week OLE, and a 4-week follow-up period. The 2- and 4-week safety follow-up visits will provide off-treatment safety information for participants who terminate treatment early or who do not elect to participate in or are not eligible to continue to the OLE Part 1 portion. Participants with no clinically significant safety concerns as defined in Section 7.1.1 who complete the treatment period will have the option to continue to OLE study to further assess the 52-week, long term safety and efficacy of etrasimod 2 mg QD as a chronic therapy.

Efficacy will be primarily measured by evaluating changes in AD severity using IGA and EASI. To determine the potential efficacy of etrasimod, the primary endpoint will be the proportion of participants with an IGA score of 0 or 1 (on a 5-point scale) and a reduction of ≥ 2 points from baseline at Week 16.

Additionally, the study design includes the assessment of disease symptoms as secondary endpoints, ie, pruritus via PP-NRS and pain via Skin Pain NRS. Clinician-reported outcomes and broader quality of life measures will be collected to gather supportive information on participant perspectives on aspects of disease conditions and overall health status.

Part 2 will assess the long-term safety and efficacy of etrasimod 2 mg QD monotherapy. The duration of study participation is up to 60 weeks, which includes a ≤ 4-week screening period, a 52-week OL treatment period, and a 4-week follow-up period. Part 2 is intended as a supplementary safety database for the etrasimod 2 mg program.

4.2.1. Patient Input Into Design

No input was obtained specifically for this study, however input for other similar studies in moderate-to-severe AD has been obtained and incorporated into this protocol.

4.2.2. Diversity of Study Population

Reasonable attempts will be made to enroll participants that are representative of the patient population that will be treated with etrasimod in clinical practice after approval. The team will follow best practices for diverse study population enrollment and retention which include tactical diversity questioning in early site engagement and providing diversity materials to support the sites' patient engagements.

Decentralized elements of patient documentation, safety assessments, and testing will result in less burdensome procedures for patients and thus possibly enhancing enrollment for underrepresented populations.

4.2.3. Adjudication Committee

This protocol will use an independent endpoint adjudication committee to determine whether certain investigator-reported events meet the definition of disease-related safety endpoints, using predefined endpoint criteria. Further information about this endpoint adjudication committee is provided in a charter, including a description of the scope of the committee's responsibilities, the process and definitions to be utilized by the committee for adjudication, and communication plan including timelines.

Within the etrasimod program potential cases of PML will be adjudicated. The safety event adjudication committee will be blinded to treatment assignment in order to allow for unbiased assessments.

Events requiring review may be identified by the Pfizer study team or designee during the blinded review of participant data listings or monitors during routine monitoring of participants' study records. The Pfizer study team or designee will notify relevant investigators of any events identified. Investigators will be responsible for obtaining and submitting the documentation to be reviewed by the safety event adjudication committee.

Additional safety event adjudication committees may be established during the study to standardize additional safety event assessments. As described above, individual committee charters will provide specific descriptions of the scope of responsibilities and the processes and definitions used to assess specific safety events.

4.2.4. 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 (see Appendix 4).

4.3. Justification for Dose

The study investigates a dose regimen (2 mg, once daily) equivalent to the planned to be marketed dose regimen. The etrasimod 2 mg, once daily dose regimen has been selected based on the safety, efficacy, and PK data generated in Study APD3334-201 in participants with moderate-to-severe AD, which evaluated 2 doses of etrasimod (etrasimod 1 mg and 2 mg, once daily) versus placebo. Overall, the 2 mg etrasimod dose demonstrated higher efficacy than the 1 mg dose, in particular, 2 mg dose showed statistically significant improvement for the key endpoint of vIGA, whereas 1 mg etrasimod was non-significant. The etrasimod 2 mg dose selection was further supported by safety and PK data from Phase 2 and Phase 3 UC studies. The safety and efficacy data of the Phase 2 AD study (Study APD334-201) are summarized as follows:

- Etrasimod 2 mg demonstrated efficacy and superiority over placebo in the key clinical efficacy outcome measures including vIGA success as well as PRO measures, DLQI and POEM during the Double-Blind Treatment Period

- Etrasimod 2 mg showed continuous improvement and maintenance of response on the key efficacy measures of vIGA success, EASI-75, and pruritus improvement during the 52-week OLE Period of the study

- In post hoc analysis, the efficacy and safety profile of etrasimod 2 mg were not notably different for participants with prior systemic therapy failure as compared to participants without prior systemic therapy failure

- Treatment with etrasimod resulted in a dose-dependent decrease in lymphocyte count and quick reversal to normal levels following cessation of drug treatment

- Etrasimod 2 mg was generally safe and well-tolerated with no clinically relevant safety signals resulting from longer exposure (up to 52 consecutive weeks of treatment) in the moderate-to-severe AD population

In conclusion, the AD data to date show a clinical benefit in the absence of clinically significant safety signals and supports further evaluation of etrasimod 2 mg in this clinical trial.

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 for the last participant in the trial globally.

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. Participants aged 18 (or the minimum age of consent in accordance with local regulations) to 80 years of age at screening.

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

Disease Characteristics:

2. Chronic AD (also known as atopic eczema) that was diagnosed at least 1 year prior to Screening and meets Hanifin and Rajka criteria at screening.[1]

3. Moderate-to-severe AD:

   a) IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 = moderate and 4 = severe) at screening and baseline (Day 1).

   b) BSA ≥10% of AD involvement at screening and baseline (Day 1).

   c) EASI ≥16 at screening and baseline (Day 1).

4. A participant who has failed a prior systemic therapy for AD, ie refractory, moderate-to-severe AD that is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable (i.e., medical contraindications to systemic therapy prohibit use).

   a. Inadequate response to ≥ 2 weeks of cyclosporine, azathioprine, methotrexate, mycophenolate, biologic, JAK inhibitors, or systemic corticosteroid (CS; defined as pulse of systemic CS or ≥ 2 weeks of continuous oral CS), or when systemic therapy is inadvisable.

      - In Part 1, approximately 30% of participants are permitted with a failure of a prior systemic corticosteroid therapy without failing another systemic treatment

for AD. For the remining participants in Part 1, failure of a prior systemic corticosteroid therapy alone is not sufficient to meet the criterion for prior systemic failure, i.e., the participant must fail another systemic treatment for AD.

- In Part 2, failure of systemic corticosteroids may qualify a participant for the study.

b. Refractory is an insufficient clinical response, defined as the inability to achieve and maintain remission or a low disease activity state of minimal or mild lesions only, within 1 year of screening, despite treatment with systemic therapy for a period sufficient to demonstrate efficacy as determined by the Investigator.

c. Acceptable documentation for these criteria includes chart notes that record medication prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician. For study purposes, document failure of prior systemic drug(s) to adequately control AD in the CRF.

5. Willing to apply a topical emollient/moisturizer at least once daily for ≥1 week prior to baseline (Day 1) and willing to maintain consistent daily application over the course of the study

5.2. Exclusion Criteria

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

Medical Conditions:

1. Presence of confounding factors:

- Skin conditions (eg, psoriasis, seborrheic dermatitis) that may interfere with evaluation of AD or assessment of treatment response as deemed by the investigator.

- Current significant active infection or requiring a treatment for infection that may interfere with the assessment of AD.

2. Hypersensitivity to etrasimod or any of the excipients.

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

- Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS);

- "Yes" answer to any of the suicidal behavior items of the C-SSRS in the past 5 years;

- Participants who answer "Yes" on items 4 or 5 of the C-SSRS or suicidal behavior may still be included in the study if a mental health professional judges the potential benefits of the participant inclusion outweigh the risk (see Section 8.1.1.4).

- Have undergone significant trauma or major surgery within 4 weeks prior to Day 1.

4. Active or past history of macular edema, any type of retinopathy (including diabetic) or uveitis.

5. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised nonmetastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.

Prior/Concomitant Therapy:

6. Current use of any prohibited concomitant medication(s) or participants unwilling/unable to use required concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

Prior/Concurrent Clinical Study Experience:

7. Prior treatment with etrasimod or prior participation in an etrasimod clinical study.

Diagnostic Assessments:

8. Renal impairment as defined by an eGFR of <30 mL/min/1.73m^2 confirmed by 1 repeat measurement at screening. Based upon participant age at screening, eGFR or eCrCl is calculated using the recommended formulas in Section 10.6.2.1 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events.

   For eligibility assessment based upon estimated renal function, the higher of the screening and baseline eGFR values may be used.

9. Hepatic dysfunction defined as:

   - Total bilirubin ≥1.5 × ULN (except for Gilbert's syndrome)

   - AST ≥2 × ULN

   - ALT ≥2 × ULN

10. Hematologic abnormalities defined as:

    - WBC <3500/mm^3 (<3.5 x 10^9 cells/L)

    - ANC <1200/mm^3 (<1.2 x 10^9 cells/L)

- ALC <1000/mm^3 (<1.0 x 10^9 cells/L)

11. Have any of the following conditions or risk factors related to infection or immune function:

    - Participants with active, uncontrolled bacterial, fungal, or viral infection, including (but not limited to) COVID-19/SARS-CoV-2, HBV, HCV, and HIV or AIDS related illness. Comments regarding specific circumstances follow.

        - Hepatitis B: This criterion excludes participants with a positive HBsAg (ie, either acute or chronic active hepatitis). Participants who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. For more details, refer to Section 8.3.7.

        - Hepatitis C: Positive HCV Ab is indicative of infection but may not necessarily render a potential candidate ineligible, depending on clinical circumstances. If exposure to HCV is recent, HCV Ab may not have yet turned positive. In these circumstances test for HCV RNA. If HCV RNA is detected the patient is not eligible. Refer to CDC website for further details (https://www.cdc.gov/hepatitis/hbv/pdfs/SerologicChartv8.pdf).

        - COVID-19/SARS-CoV-2: While SARS-CoV-2 testing is not mandated for entry into this study, testing should follow local clinical practice standards. If a participant has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV-2, the participant is excluded until a negative antigen test and resolution of symptoms if applicable.

    - History of organ transplant (except corneal transplant).

    - History of an opportunistic infection (eg, cryptococcal meningitis, PML).

    - History (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

    - Have evidence of active or latent or inadequately treated infection with TB as defined by the following:

        - A positive QFT-G In-Tube test (preferred) performed at or within the 12 weeks prior to Day 1. NOTE: The QFT-G (or an alternative IGRA) for screening may be repeated once if the investigator deems this to be necessary. If the result of the repeat test is indeterminate, participants may be screened using the Mantoux/PPD skin test with study medical monitor approval.

- Chest radiograph (or chest computed tomography scan, or magnetic resonance imaging [MRI], if available) taken at screening with changes suggestive of active TB infection as determined by a qualified radiologist. A chest image or other appropriate imaging is required, unless previously performed and documented within 12 weeks prior to Study Day 1.

- A 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 (eg, 9 months of isoniazid in a locale where rates of primary multi-drug TB resistance are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a QFT-G test, nor a Mantoux/PPD tuberculin skin test is needed, but a chest imaging is required if not performed within 12 weeks prior to Day 1. To be considered eligible for the study, chest imaging must be negative for active tuberculosis infection as determined by a qualified radiologist. Documentation of adequate treatment for TB and negative chest imaging results must be obtained prior to Day 1. If the current incidence rates of multi-drug resistant TB infection in the locale are unavailable, an adequate treatment regimen should be defined as the regimen recommended by the health ministry or expert panel in the locale;

- It is recommended that participants with a history of BCG vaccination be tested with the QFT-G test since the Mantoux/PPD tuberculin skin test may be positive due to vaccination. See Section 8.3.5 for requirements for Mantoux/PPD tuberculin skin testing.

- A participant who is currently being treated for active TB infection is to be excluded.

12. FEV1 or FVC < 70% of predicted values at screening.

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

    a. Myocardial infarction, unstable angina, stroke/transient ischemic attack, decompensated heart failure requiring hospitalization or Class III/IV heart failure within 8 weeks prior to Screening

    b. History of second degree or third-degree atrioventricular block, sick sinus syndrome or periods of asystole for > 3 seconds without a functional pacemaker

    c. History of recurrent symptomatic bradycardia or recurrent cardiogenic syncope

    d. Screening or Day 1 predose vital signs (taken in the sitting position) with a HR < 50 bpm OR systolic blood pressure (BP) < 90 mm Hg OR diastolic BP < 55 mm Hg. Abnormal vital signs should be confirmed by 1 repeat measurement.

Abnormal results that are confirmed on a repeat assessment are considered exclusionary.

e. Screening or Day 1 predose electrocardiogram (ECG) with PR interval ≥ 200 ms or QTcF ≥ 450 ms in males or ≥ 470 ms in females

f. Start, stop, change dosage of any Class I to IV anti-arrhythmic drugs within 1 week before Day 1

Other Exclusion Criteria:

14. 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

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 the 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. The investigator or designee should inquire of both WOCBP and male participants if a change in the risk of becoming pregnant or getting someone pregnant has occurred.

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 be truly abstinent as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

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. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT

publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once at the Investigator's discretion.

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 and placebo.

6.1. Study Intervention(s) Administered

Study Intervention(s)		
Intervention Name	etrasimod	placebo (Part 1 DB period only)
Type	drug	drug
Use	experimental	placebo
Dose Formulation	tablet	tablet
Unit Dose Strength(s)	2 mg	Not applicable
Dosage Level(s)	one tablet once daily	one tablet once daily
Route of Administration	oral	oral
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.
Packaging and Labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.
SRSD	IB	Not applicable
Current/Former Name or Alias	APD334, PF-07915503	Not applicable

Study Arm(s)		
Arm Title	Etrasimod	Placebo (Part 1 DB period only)
Arm Description	Participants will receive etrasimod 2 mg QD	Participants will receive placebo QD

Study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments, including temperature monitoring data, and the chain of custody of study intervention must be kept in the participant's source documents/medical records.

6.1.1. Administration

Participants will self-administer one tablet of study treatment each day by mouth (with water either with or without food) at approximately the same time each day, preferably in the morning. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing.

- Participants will be observed for at least 4 hours following administration of study intervention on Study Day 1 of Part 1 and Part 2, Week 16 of Part 1, and whenever participants interrupt study intervention for ≥ 2 consecutive days within the first week of treatment or Week 16 of Part 1, or for ≥ 7 consecutive days after the first week of treatment (excluding Week 16 of Part 1 where missing 2 doses applies) (See Section 10.10.3). Observation will be performed 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.

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

In the event a participant is not compliant with the assigned treatment regimen, the participant should be retrained on proper study treatment administration. Participants should be instructed to contact the Investigator if they miss 2 or more consecutive doses within the first week of treatment or Week 16 of Part 1, or if they miss 7 or more consecutive doses after the first week of treatment (excluding Week 16 of Part 1 where missing 2 doses applies). Participants must contact the Investigator to discuss treatment reinitiation if consecutive days of study treatment are missed as described in Section 7.1.7.

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 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. Site staff will instruct participants on the proper storage requirements for take home study intervention.

6. Study interventions should be stored in their original containers.

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. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. **Returned study intervention must not be redispensed to the participants.**

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. 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.

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

A qualified staff member will dispense the study intervention using unique container numbers via an IRT system in the bottles provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant should be instructed to maintain the product in the bottle throughout the course of dosing and return the bottle to the site at the next study visit.

6.3. Assignment to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a

confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Study intervention will be dispensed at the study visits summarized in the SoA.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.4. Blinding

This is a double-blind study with OLE (Part 1) and OL study (Part 2).

6.4.1. Blinding of Participants

In Part 1, participants will be blinded to their DB treatment assignment for the entire portion of Part 1, i.e., participants will remain blinded to their DB treatment assignment until the completion of Part 1 DB and OLE periods of the study.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will remain blinded during the OLE to participants' assigned study intervention received in the DB portion until the completion of Part 1 DB and OLE periods of the study.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4.3. Blinding of the Sponsor

Sponsor staff will be blinded to participants' assigned study intervention during the DB treatment period in Part 1 of the study, until all applicable participants had completed their Week 16 visit. The Sponsor study team will be unblinded to treatment assignment for the first 16 weeks of Part 1 (DB period) once treatment assignments are released for the IA.

6.4.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF/DCT.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit through a combination of the accounting of unused study intervention returned by the participant at the study visits and discussion (direct questioning) with the participant which will be documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of 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.

Part 1: The Week 16 visit is the first dose of open label (etrasimod) treatment. Sites must contact participants 1-2 business days prior to the Week 16 visit to remind them not to take study intervention on the day of the Week 16 visit. Should the participant come to the site having already taken study intervention, all Week 16 procedures will be completed, except for administering open label treatment and first-dose cardiac monitoring procedures for which an unplanned visit is required as soon as possible (within 3 days). The unplanned visit should be scheduled in the morning and not on a Friday or day before a site-observed holiday. The participant will continue taking blinded study intervention up to 1 day prior to the unplanned visit. Again, sites must contact the participants 1-2 business days prior to the unplanned visit to remind them not to take study intervention the day of the visit. The unplanned visit will be the start of the OLE period. See Section 10.10.3 for details of first-dose cardiac monitoring procedures.

The following non-compliance cases will be considered **medication errors** and will be discussed with the sponsor for possible withdrawal from the study:

1. Participants interrupting study intervention for ≥ 2 consecutive days within the first week of treatment or Week 16 of Part 1, or for ≥ 7 consecutive days after the first week of treatment (excluding Week 16 of Part 1 where missing 2 doses applies).

   NOTE The first-dose cardiac monitoring outlined in Section 10.10.3 must be performed any time a participant reinitiates study treatment following dose interruptions as described above and the participant must take the next dose of study treatment at the study site.

2. Participants who have an overall compliance of <80% or >120% between visits.

3. Participants who have taken >5 mg meeting the definition of overdose (see Section 6.8).

4. When participants take the Week 16 dose prior to the visit it will be considered a medication error (wrong drug administered).

Any deviation from protocol specified dosing should be recorded as a protocol deviation and the investigator or designee is to counsel the participant, legally acceptable representative/ legal guardian (if applicable) and ensure steps are taken to improve compliance. In addition, if the compliance deviation reaches the thresholds defined above it should also be recorded as a medication error (see Section 8.4.10).

Note: temporary interruption to dosing per investigator judgement, as described in Section 10.10, will not be considered a protocol deviation or medication error.

6.6. Dose Modification

Dose modification is not permitted in this study.

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. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

The following scenarios are considered overdose:

- Consuming >3 mg on Day 1, on Week 16 visit day in Part 1, or on a day of treatment re-initiation after protocol defined treatment interruptions.
- Consuming >5 mg any day after Day 1 or starting a day after Week 16 visit in Part 1 except on a day of treatment re-initiation, as specified above.

There is no specific treatment recommended for an overdose but to provide supportive care if clinically indicated. AV conduction delays and bradycardia were observed on Day 1 in several participants who received 5 mg etrasimod in Phase 1 single-ascending dose Study (Arena Study APD334-001); this dose was not used in subsequent clinical studies. Etrasimod has not been evaluated for drug abuse or dependence. Participants with suspected overdose will be counseled on correct dosing and administration of study treatment.

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.

Decisions regarding dose interruptions or permanent discontinuation 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

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine that a participant receives and all procedures that are performed during the screening period and during the study through the safety reporting period must be recorded in the eCRF along with:

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

The study medical monitor should be contacted if there are any questions regarding concomitant therapy.

6.9.1. Required Concomitant Therapy

Participants are required to apply topical emollients/moisturizers (including those containing ceramide, hyaluronic acid, or urea) at least once daily for at least 1 week prior to baseline (Day 1) and throughout the study without change (ie, type, frequency, application). All topical emollients/moisturizers are generally permitted, except for new prescription emollients/moisturizers or emollients/moisturizers containing additives (including ceramide, hyaluronic acid, or urea) during the study. On visit days during the study, participants should not apply any topical emollient or moisturizer until the study visit has been completed.

6.9.2. Prior Treatments

Table 1. Prohibited Medication or Procedure Washout Periods Prior to Day 1

Time Frame	Therapies
Any time prior to Randomization	S1P receptor modulators (eg, fingolimod, siponimod, ozanimod), α4β1 integrin receptor antagonist (eg, natalizumab)
Within 24 weeks	Anti-CD20 antibodies (eg, rituximab, ocrelizumab), anti CD52 antibodies (eg, alemtuzumab), other cell depleting therapies (eg, bone marrow transplantation, total body irradiation)
Within 8 weeks (or 5 half-lives if shorter)	Any biologic treatment other than already listed, eg, anti-IL4/13 antibodies (eg, dupilumab), anti-IL13 antibodies (eg, tralokinumab, lebrikizumab), anti-IL-17 antibodies (eg, secukinumab), anti-IL-12/23 antibodies (eg, ustekinumab), anti-IL-31 antibodies (eg, nemolizumab), anti-IL-23 antibodies (eg, risankizumab)
Within 6 weeks	Live-attenuated replication-competent vaccines are prohibited
Within 4 weeks (or 5 half-lives if shorter)	Any investigational therapy other than the study treatment, unless therapy belongs to a drug category described above which requires a longer washout period, in which case the longer washout period should be used.

Table 1. Prohibited Medication or Procedure Washout Periods Prior to Day 1

Time Frame	Therapies
Within 4 weeks	Any other systemic treatment intended for AD (eg, azathioprine, methotrexate, cyclosporine, mycophenolate, PDE-4 inhibitors, and systemic glucocorticoids) Note: corticosteroid intranasal sprays and/or corticosteroid inhalers are allowed for participants with stable asthma. Ophthalmic and ear drop corticosteroids are also allowed.
	Topical and systemic JAK inhibitors (eg, baricitinib, abrocitinib, upadacitinib, ruxolitinib, delgocitinib, tofacitinib)
	Any IV medications taken in response to serious infection that required hospitalization or treatment
	Moderate or strong inhibitors or inducers that inhibit or induce at least 2 of the following: cytochrome P450 (CYP)2C8, CYP2C9, and CYP3A4 (e.g., fluconazole, rifampin, enzalutamide)
	Phototherapy for AD or artificial tanning (beds, booths, or lamps), including psoralen and ultraviolet A, ultraviolet B, tanning booth, and excimer laser
Within 1 week	Topical treatments that could affect AD disease and/or evaluation of AD (eg, crisaborole, corticosteroids, calcineurin inhibitors [eg, tacrolimus, pimecrolimus], tars, antibiotic creams, topical antihistamines).
	Sedating, systemic antihistamines (eg, diphenhydramine, hydroxyzine, promethazine) (non-sedating systemic antihistamines are allowed)

6.9.3. Prohibited During the Study

In the event of an emergency, any needed medications may be prescribed without prior approval, but the study medical monitor must be notified of the use of any prohibited medications immediately.

Prohibited Medications Not Requiring Interruption or Discontinuation of Study Treatment

- The following therapies are prohibited during the study until completion of study treatment. Participants receiving any of the following must discontinue such use immediately without interruption or discontinuation of study treatment:

- Low-to-moderate potency TCS (Class VII-IV), calcineurin inhibitors (eg, tacrolimus and pimecrolimus), or crisaborole or high potency TCS (Class III-I) administered for <7 consecutive days. TCS classes (VII-IV) are based on WHO classification of topical corticosteroids[34,35]). See CRF guidelines.

- Topical antihistamines, tars, topical anesthetics, or antibiotic creams

- Sedating, systemic antihistamines (eg, diphenhydramine, hydroxyzine, promethazine) (nonsedating systemic antihistamines are allowed)

- Initiation of any new (ie, during the screening and treatment period) emollients/moisturizers containing additives such as ceramide, hyaluronic acid, urea, antipruritic or antiseptic agents during the screening and treatment period (patients may continue using stable doses of such emollients/moisturizers if initiated before the screening visit)

Prohibited Medications Requiring Permanent Discontinuation of Study Treatment

Use of the following therapies during the study until completion of study treatment will require permanent discontinuation of study treatment and withdrawal from the study except when specified otherwise below:

- High- to ultra-high potency TCS (Class III-I) administered for ≥7 consecutive days. TCS Classes III-I are based on WHO classification of topical corticosteroids[34,35]. See CRF guidelines.

- Systemic corticosteroids (intranasal sprays, corticosteroid inhalers, ophthalmic and ear drop corticosteroids are allowed) (requires permanent discontinuation of study treatment but participants are not required to withdraw from the study).

- S1P receptor modulators (eg, fingolimod, ozanimod).

- α4β1 integrin receptor antagonist (eg, natalizumab).

- Anti-CD20 antibodies (eg, rituximab, ocrelizumab), anti-CD52 antibodies (eg, alemtuzumab), other cell depleting therapies (eg, bone marrow transplantation, total body irradiation).

- Systemic immunosuppressive/immunomodulating drugs (eg, cyclosporine, azathioprine, methotrexate), including topical or oral JAK inhibitors (requires permanent discontinuation of study treatment but participants are not required to withdraw from the study).

- Any biologic treatment, anti-IL4/13 antibodies (eg, dupilumab), anti-IL13 antibodies (eg, tralokinumab, lebrikizumab), anti-IL17A antibodies (eg, secukinumab), anti-IL12/23 antibodies (eg, ustekinumab), anti-IL31 antibodies (eg, nemolizumab), anti-IL23 antibodies (eg, risankizumab) requires permanent discontinuation of study treatment, but participants are not required to withdraw from the study.

- Any IV medications taken in response to serious infection that required hospitalization or treatment.

- Moderate/strong inhibitors or inducers that inhibit or induce at least 2 of the following: cytochrome P450 (CYP)2C8, CYP2C9, and CYP3A4 (e.g., fluconazole, rifampin, enzalutamide, Section 10.8.1).

- Live-attenuated replication-competent vaccines starting 6 weeks prior to baseline (Day 1), during study treatment and for 4 weeks after the last dose of study treatment.

- Start, stop, or change in dosage of any anti-arrhythmic drugs (Class I to IV) within 1 week before or after treatment initiation or reinitiation following dose interruption of a duration requiring in-clinic cardiac monitoring (Section 6.1.1).

- Any investigational drug other than the study treatment.

Participants who complete the treatment period no longer need to abstain from the medications that were prohibited during the treatment periods, unless noted otherwise (eg, live attenuated vaccines for 4 weeks after the last dose of study treatment).

For prohibited concomitant procedures:

- Participants may not undergo phototherapy for AD or artificial tanning (beds, booths, or lamps), including psoralen and ultraviolet A, ultraviolet B, tanning booth, and excimer laser.

- Participants should not take bleach baths.

- Participants should not undergo cell depleting therapies (eg, bone marrow transplantation, total body irradiation).

- Participants should not undergo major elective surgery while on study treatment.

- Participants may not donate blood during the study and for 30 days after the last dose of study treatment.

- Participants may not donate sperm, or oocytes during the study and for 28 days after the last dose of study treatment.

6.9.4. Rescue Medicine

Medicated and non-medicated rescue medications are not permitted during the Part 1 DB portion. For Part 1 OLE and Part 2 medicated and non-medicated topical treatments for AD will be permitted at the discretion of the investigator and in accordance with their usual practice.

6.9.5. Permitted During the Study

Vaccinations are permitted as clinically indicated except for live-attenuated replication-competent vaccines. At this time, there are no data on the effect of etrasimod treatment on vaccine efficacy and safety including severe acute respiratory system

coronavirus 2 (SARs-CoV-2) vaccines to protect against COVID-19. It is recommended that participants receive a vaccination against COVID-19 to decrease the risk of contracting SARs-CoV-2.

The American Academy of Dermatology has published recommendations that advise patients on immunomodulating drugs to be vaccinated as "The CDC does not consider COVID-19 vaccine to be contraindicated in persons taking biologic or traditional immunosuppressive medications, hedgehog pathway inhibitors, and PD-1 inhibitors".

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

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4) and should be captured on the Concomitant Medication log/eCRF.

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 events noted below (participants with AEs listed below, irrespective of causality, will be discontinued from the study intervention) NOTE: Sub bullets below are examples and are not intended to be an all-inclusive list.
    - Second episode of confirmed Grade 4 lymphopenia in the same participant (Protocol Sections 10.10.1, 10.10.2)
    - Repeated episode of a serious infection for the same participant (Protocol Section 10.10.2)
    - Diagnosis of PML (Protocol Section 10.11)
    - Diagnosis of PRES (Protocol Section 8.4.8)
    - ECG changes (Protocol Section 7.1.3)
    - Suspected intolerance associated with first dose cardiac effects (Protocol Section 10.10.3.2)
    - Malignancy (Protocol Section 8.4.8)
    - HBV DNA above LLQ (Protocol Section 8.3.7)
    - Active, latent, or inadequately treated TB infection (Protocol Section 8.3.5)

  - Clinically significant respiratory AE and or a decline in confirmed PFT values (FEV1 and/or FVC below 50% of the predicted values; Protocol Section 10.10.4)
  - Confirmed macular edema (Protocol Section 10.10.5)
  - Drug-induced liver injury confirmed cases after all results of reasonable investigations have been received as per Protocol Section 10.5, and alternative etiology have been excluded (Protocol Section 10.10.5)
  - Clinically significant safety concern as per investigator's judgement at Week 16 (Protocol Section 7.1.1)
- Death
- Lost to follow up
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by participant
- Lack of Efficacy

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, further study follow-up, and/or future collection of additional information.

7.1.1. Discontinuation after Part 1 DB (Week 16) due to a Clinically Significant Safety Concern

Per investigator's judgement, participants must permanently discontinue study intervention at the Part 1 Week 16 visit if they experienced an AE and/or SAE during the DB study portion that was a clinically significant safety concern for study continuation which may or may not have resulted in study treatment interruption. The investigator may seek medical monitor's consideration, if needed, to determine participant continuation.

7.1.2. Liver Injury

Participants must permanently discontinue study intervention if drug-induced liver injury (Section 10.5).

7.1.3. ECG Changes

Participants must permanently discontinue study intervention if suspected intolerance associated with first dose cardiac effects (Section 10.10.3.2).

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 (refer to Section 10.10.3) 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 intervention 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 Sponsor Medical Monitor.

If, after re-initiation, the QTc interval is again prolonged above 500 ms, then study intervention must be permanently discontinued.

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 must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4. Pregnancy

Female participants who have missed a menstrual period, suspect a pregnancy, or who show an indeterminate or positive result on the urine test may not progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory). Study intervention should be interrupted immediately until pregnancy status is confirmed. See Section 7.1.7 for details.

In the case of a confirmed positive pregnancy, the participant will be permanently withdrawn from administration of study intervention but may remain in the study until completion of the 4 week follow-up period. See Section 8.4.1 for details.

7.1.5. Lack of Efficacy

Lack of efficacy will result in permanent discontinuation of study intervention only for the reason below:

- Participants who do not meet EASI-50 criteria at Week 32 in Part 1 (Week 16 of OLE) or at Week 16 of Part 2. In the case of lack of efficacy, the participant will be permanently withdrawn from administration of study intervention, complete Early Termination procedures, and then complete the 2- week (SFU 1) and 4-week (SFU 2) follow-up visits.

7.1.6. 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 (Section 7.1.7).

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

7.1.7. Temporary Discontinuation

Dose interruptions are defined as the following consecutive days of missed study treatment:

- ≥2 consecutive days within the first week of treatment or during Week 16 of Part 1, or
- ≥7 consecutive days after the first week of treatment (excluding Week 16 of Part 1 where missing 2 doses applies)

If the Investigator deems it necessary to withhold study treatment due to an adverse event, temporary withholding is permitted for up to 6 days (after the first week of treatment) without obtaining prior approval from the study medical monitor. Planned dose interruptions during the first week of treatment requires consultation with the study medical monitor. If study treatment interruption ≥ 7 days is required for a medical reason at any time in the study, the Investigator must contact the study medical monitor for further instruction as soon as this is anticipated. **Any time a participant reinitiates study treatment following protocol-defined dose interruptions, the first dose cardiac monitoring outlined in Section 10.10.3 must be performed and the participant must take the next dose of study treatment at the study site.**

Doses not taken due to an adverse event per investigator's request do not constitute protocol deviations or medication errors and should not be considered dosing errors but should be noted in the dosing log with the reason for reduced drug consumption clearly described.

7.1.8. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCL require expedited evaluation to differentiate AKI

from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

AKI may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

Follow-Up Assessments

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results.

Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals.

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR, eCrCl and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 6.

Assessments of urine albumin-to-creatinine ratio or urine volume may also be performed as appropriate.

Differentiating Acute Kidney Injury from DICI

A confirmed Screat increase is defined as:
(i) ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR
(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows.

Adult Participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	
Albuminuria or proteinuria	Confirmed albuminuria increase (see Appendix 6 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either (i) new-onset or worsening albuminuria or proteinuria are detected or (ii) urine volume (if measured) is <0.5 mL/kg/h for 6 consecutive hours.

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

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 include the following:

- Adverse event
- Death
- Lost to follow up
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by participant
- Lack of efficacy
- Other

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 attend 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 followup, 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 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.

Chest imaging conducted as part of the participant's routine clinical management (and obtained (within 12 weeks of Day 1) before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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.

Laboratory results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel.

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 165 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.

8.1.1. Baseline Procedures

8.1.1.1. Demography and Other Participant Characteristics

Demographics including year of birth, sex at birth, Hispanic ethnicity, and race as described by the participant will be collected at screening. As part of baseline characteristics, a skin type assessment will be done at the Screening visit using the Fitzpatrick Skin Type assessment. This assessment classifies a person's skin type by their response to sun exposure (ie, burning or tanning).

8.1.1.2. Prior and Ongoing Therapies

Any use of S1P receptor modulators (eg, fingolimod, siponimod, ozanimod), α4β1 integrin receptor antagonist (eg, natalizumab), or vaccines for COVID-19 at any time prior to enrollment must be recorded. All AD therapy attempts, both systemic and topical, within 1 year prior to screening will be recorded. Use of any other medication or therapy listed in

Table 1 within 24 weeks of screening will be recorded to confirm last known dose/treatment meets washout requirements. All other medications and procedures conducted within 30 days prior to screening will be recorded at screening. For prior AD therapies, documentation should include history of inadequate response to and/or intolerance to prior treatment. Updates to medications or procedures prior to dosing at the Day 1 visit should be made as needed.

8.1.1.3. Medical History/AD History

A complete medical history of each participant will be collected and documented during screening to determine participant eligibility. The history should include illnesses, hospitalizations, procedures, and participation in other investigational drug studies.

The diagnosis of AD by Hanifin and Rajka criteria[1], and the duration of AD will be recorded.

8.1.1.4. Suicidal Ideation and Behavior Risk Screening

Any psychiatric condition including recent (within the past year) or active suicidal ideation/behavior that, in the investigator's judgement, may increase the risk of study participation and make the participant inappropriate for the study.

The C-SSRS is a validated tool for investigative staff to use to evaluate suicidal ideation and behavior.[36] At the screening visit, if there are "yes" answers on items 4 or 5 in the past year, or if there is a "yes" answer to any of the suicidal behavior items of the C-SSRS in the past 5 years, the participant will not be included in the study as deemed by the investigator unless a mental health professional judges the potential benefits of the participant's inclusion outweigh the risks, and this is documented in the source. Trained site staff is to administer the C-SSRS to all participants at screening and immediately score to assess the participant's eligibility based on the answers.

For participants meeting screening exclusionary results on the C-SSRS, the participant should be referred for follow up with a mental health professional practice.

8.1.2. Telehealth Visits

The following visits may be conducted via Telehealth only due to pandemic/regional emergency situations:

- In Part 1 **OLE only** due to the risk of unblinding: Visits 7, 9 (Week 24, 40) and SFU1 but not SFU1 after DB portion (if applicable)
- In Part 2: Visits 3, 5, 7 (Weeks 8, 24, 44) and SFU1

In the event that in-clinic study visit cannot be conducted, every effort should be made to follow up on safety of study participants at scheduled visits per the SoA or unscheduled visits.

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication

technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- The substitution of the in-clinic visit by a telehealth visit for efficacy assessments can increase data variability and require changes to the planned SAP, therefore Clinician Reported Outcomes (IGA, EASI) should not to be performed at a telehealth visit.
- Unless clinically urgent, blood work collection for WBC and TBNK are not permitted at a local laboratory during the Part 1 DB portion due to risk of unblinding; however, blood work may be collected at a certified local laboratory if permitted by local regulations during Part 1 OLE and during Part 2.

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

8.1.3. Home Health Visits

The following visits may be conducted via Home Health only due to pandemic/regional emergency situations and only by site investigators who are qualified raters:

- In Part 1 **OLE only** due to the risk of unblinding: Visits 7, 9 (Week 24, 40) and SFU1 but not SFU1 after DB portion (if applicable)
- In Part 2: Visits 3, 5, 7 (Weeks 8, 24, 44) and SFU1

Home health visits will be only conducted by site investigators who are qualified raters.

In the event that in-clinic study visit cannot be conducted, every effort should be made to follow up on safety of study participants at scheduled visits per the SoA or unscheduled visits.

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

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.
- Unless clinically urgent, blood work collection for WBC and TBNK are not permitted at a local laboratory during the Part 1 DB portion due to risk of unblinding; however, blood work may be collected at a certified local laboratory if permitted by local regulations during Part 1 OLE and during Part 2.
- Clinical laboratory assessments vital signs, ECGs, physical examination.

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

8.2. Efficacy Assessments

Clinician Reported Outcomes include IGA, EASI, and BSA assessments and will be conducted only if a qualified rater is available. Rater qualifications are defined in Section 8.2.1. Patient Reported Outcomes (PROs) include PP-NRS, Skin Pain NRS, and POEM.

8.2.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Rater Qualification Plan provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. The rater must become certified to perform selected study assessments before they can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written documentation will be provided by the site for each rater's certification. In return, each site will be provided written documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

Clinical evaluations of atopic dermatitis will be performed by an experienced and qualified dermatologist (board certified or equivalent) or an experienced and qualified nondermatology physician. Alternatively, an experienced and qualified medical professional with experience in the conduct of dermatology clinical trials may be permitted to perform the clinical evaluations of atopic dermatitis when designated by the primary site Investigator. The evaluator must receive and document protocol specific and applicable efficacy assessment scales training prior to performing these evaluations. To ensure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual participant throughout the study whenever possible; a backup experienced and qualified, protocol trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation.

8.2.2. Clinical Assessments

All PROs and AD clinical assessments should be completed prior to other clinical activities and study intervention administration. Results of clinical assessment of AD should not be shared with the participant until they have completed their PROs.

8.2.2.1. IGA

The Investigator's Global Assessment of atopic dermatitis is scored on a 5-point scale (0-4), reflecting a global consideration of the erythema, induration and scaling. The clinical evaluator of atopic dermatitis will perform an assessment of the overall severity of atopic dermatitis and assign an IGA score and category as described in Table 2. The assessment will be a static evaluation without regard to the score at a previous visit.

The IGA will be performed at time points specified in the Schedule of Assessments SoA.

Table 2. IGA of Atopic Dermatitis Score

Score	Category	Description
0	Clear	Atopic dermatitis is cleared, except for any residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation).
1	Almost Clear	Overall, the atopic dermatitis is not entirely cleared and remaining lesions are light pink (not including post inflammatory hyperpigmentation) and/or; have barely palpable hard thickened skin and/or papules and/or; have barely perceptible lichenification; excoriation and oozing/crusting are absent.
2	Mild	Overall, the atopic dermatitis consists of lesions that are light red; with slight, but definite hard thickened skin and/or papules; with slight, but definite linear or picked scratch marks or penetrating surface injury; with slight, but definite thickened skin, fine skin markings, and lichenoid scale; oozing/crusting is absent.

Table 2. IGA of Atopic Dermatitis Score

Score	Category	Description
3	Moderate	Overall, the atopic dermatitis consists of lesions that are red; with easily palpable moderate hard thickened skin and/or papules; with moderate linear or picked scratch marks or penetrating surface injury; with moderate thickened skin, coarse skin markings, and coarse lichenoid scale; with slight oozing/crusting.
4	Severe	Overall, the atopic dermatitis consists of lesions that are deep, dark red; with severe hard thickened skin and/or papules; with severe linear or picked scratch marks or penetrating surface injury; with severe thickened skin with very coarse skin markings and lichenoid scale; with moderate-to-severe oozing/crusting.

8.2.2.2. EASI

The EASI quantifies the severity of a participant's atopic dermatitis based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring by the atopic dermatitis clinical evaluator of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.

Lesion Severity by Clinical Signs: The basic characteristics of atopic dermatitis lesions-erythema, induration/papulation, excoriation, and lichenification-provide a means for assessing the severity of lesions. Assessment of these four main clinical signs is performed separately for four body regions: head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks). Average erythema, induration/papulation, excoriation, and lichenification are scored for each body region according to a 4-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Morphologic descriptors for each clinical sign severity score are shown in Table 3.

Table 3. Clinical Sign Severity Scoring Criteria for EASI

Score		Description
Erythema (E)		
0	Absent	None; may have residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation).
1	Mild	Light pink to light red
2	Moderate	Red
3	Severe	Deep, dark red
Induration/Papulation (I)		
0	Absent	None
1	Mild	Barely palpable to slight, but definite hard thickened skin and/or papules
2	Moderate	Easily palpable moderate hard thickened skin and/or papules
3	Severe	Severe hard thickened skin and/or papules

Table 3. Clinical Sign Severity Scoring Criteria for EASI

Score		Description
Excoriation (Ex)		
0	Absent	None
1	Mild	Slight, but definite linear or picked scratch marks or penetrating surface injury
2	Moderate	Moderate linear or picked scratch marks or penetrating surface injury
3	Severe	Severe linear or picked scratch marks or penetrating surface injury
Lichenification (L)		
0	Absent	None
1	Mild	Barely perceptible to slight, but definite thickened skin, fine skin markings, and lichenoid scale
2	Moderate	Moderate thickened skin, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale

Percent BSA with Atopic Dermatitis: The number of handprints of skin afflicted with atopic dermatitis in a body region can be used to determine the extent (%) to which a body region is involved with atopic dermatitis (Table 4). When measuring, the handprint unit refers to the size of each individual participant's hand with fingers in a closed position.

Table 4. Handprint Determination of BSA

Body Region	Total Number of Handprints in Body Region*	Surface Area of Body Region Equivalent of One Handprint*
Head and Neck	10	10%
Upper Limbs	20	5%
Trunk (including axillae and groin/genitals)	30	3.33%
Lower Limbs (including buttocks)	40	2.5%

*Handprint refers to the hand size of each individual participant.

The extent (%) to which each of the four body regions is involved with atopic dermatitis is categorized to a numerical Area Score using a non-linear scaling method according to the following BSA scoring criteria (Table 5).

Table 5. Eczema Area and Severity Index Score Criteria

Percent BSA with Atopic Dermatitis in a Body Region	Area Score
0%	0
>0 - <10%	1
10 - <30%	2
30 - <50%	3
50 - <70%	4
70 - <90%	5
90 - 100%	6

Body Region Weighting: Each body region is weighted according to its approximate percentage of the whole body (Table 6).

Table 6. EASI Body Region Weighting

Body Region	Body Region Weighting
Head and Neck	0.1
Upper Limbs	0.2
Trunk (including axillae and groin/genitals)	0.3
Lower Limbs (including buttocks)	0.4

In each body region, the sum of the Clinical Signs Severity Scores for erythema, induration/papulation, excoriation, and lichenification is multiplied by the Area Score and by the Body Region Weighting to provide a body region value, which is then summed across all four body regions resulting in an EASI score as described in Equation 3.

Equation 3: $EASI = 0.1Ah(Eh+Ih+Exh+Lh) + 0.2Au(Eu+Iu+Exu+Lu) + 0.3At(Et+It+Ext+Lt) + 0.4Al(El+Il+Exl+Ll)$

A = Area Score; E = erythema; I = induration/papulation; Ex = excoriation; L = lichenification; h = head and neck; u = upper limbs; t = trunk; l = lower limbs

The EASI score can vary in increments of 0.1 and range from 0.0 to 72.0, with higher scores representing greater severity of atopic dermatitis.

8.2.2.3. Atopic Dermatitis BSA Involvement

BSA affected by AD will be determined by the participant's handprint method, where the full hand of the participant (ie, the participant's fully extended palm, fingers and thumb together in a closed position) represents approximately 1% of total BSA. The BSA AD involvement ranges from 0 to 100%, with higher values representing greater severity of AD. The BSA is performed separately for 4 regions of the body: Region 1 – head and neck; Region 2 – trunk (including genital area); Region 3 – upper limbs; and Region 4 – lower limbs (including buttocks) (Table 4). BSA Efficacy will be derived from the sum of the BSA in handprints across 4 body regions assessed as part of the EASI assessment.

The BSA assessment will be performed at timepoints specified in the SoA.

8.2.3. PROs

All PROs and AD clinical assessments should be completed prior to other clinical activities and investigative product administration. Results of clinical assessment of AD should not be shared with the participant until they have completed their PROs. The PROs should be checked for completeness by the study site staff before proceeding with other steps of the clinical visit procedures.

8.2.3.1. PP-NRS

The PP-NRS is a single-item measuring a 0 (no itch) to 10 (worst itch imaginable) NRS rating scale to assess itch at the worst moment during the previous 24 hours. Participants will complete the PP-NRS at study visits specified in the SoA.

8.2.3.2. Skin Pain NRS

The Skin Pain NRS is a single-item score using a 0 (no skin pain) to 10 (worst skin pain imaginable) NRS rating scale to assess the skin pain at its worst over the previous 24 hours. Participants will complete the Skin Pain NRS at study visits specified in the SoA.

8.2.3.3. POEM

The POEM is a 7-item measure used for monitoring symptom severity of atopic eczema. [37,38] To address severity, the POEM measures 7 aspects of the experiences of participants with eczema including skin itch, sleep disturbance, skin bleeding, weeping/oozing of the skin, cracked skin, flaking skin, and skin dryness/roughness. Participants are asked to answer based on the number of days they experienced each on a 5-point scale (0: No days, 1: 1 to 2 days, 2: 3 to 4 days, 3: 5 to 6 days, and 4: everyday) over the past week based on recall. The scores from the 7 questions are accumulated to provide an overall POEM score with a range of 0 to 28. An overall POEM score is as follows: 0 to 2 = ‘clear/almost clear’; 3 to 7 = ‘mild’; 8 to 16 = ‘moderate’; 17 to 24 = ‘severe’; and 25 to 28 = ‘very severe’ atopic eczema.

The POEM will be assessed at timepoints specified in the SoA.

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, assessments of the general inspection, head/ears/eyes/nose/throat examination, neck and thyroid, lymph nodes, cardiac examination, auscultation of lungs, skin, abdominal examination (liver, spleen, and lower abdomen), neurological assessment, musculoskeletal assessment to include lower extremity edema evaluation systems. Height (at Day 1 only) and weight will also be measured and recorded.

Symptom-directed (focused) physical examinations may be performed at the Investigator's discretion at any time during the study and should include, at a minimum, a physical examination that assesses any new signs or symptoms. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data 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

Resting vital signs measurements will be made in the seated position and include pulse rate, blood pressure, body temperature, and respiratory rate. Pulse rate will be collected as part of vital signs and heart rate will be collected as part of the ECG. Vital signs will be measured prior to any blood draws that occur within the same collection window. Vital signs will be collected at timepoints specified in the SoA. See Section 10.10.3.1.2 for first dose cardiac monitoring details. If the first reading is abnormal for any parameters, they may be repeated up to 2 times during a visit (only applicable to first dose cardiac monitoring or cardiac monitoring during the treatment reinitiation following the defined periods of treatment interruption).

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.

8.3.2.1. Blood Pressure and Pulse Rate

BP and PR measurements will be assessed in the seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP and PR measurements should be preceded by at least 5 minutes of rest with the participant in a sitting position, in a quiet setting without distractions.

Vital signs will be taken before blood collection for laboratory tests and consist of a single measurement of PR and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute apart). The average of the 3 BP readings will be recorded on the CRF. See Section 10.10.3 for first dose cardiac monitoring details.

8.3.2.2. Temperature and Respiratory Rate

Temperature, and respiratory rate, will be assessed.

Temperature and respiratory rate findings collected during the study will be considered source record and will not be required to be reported, unless they meet the definition of AE or SAE (see Section 8.2.2).

8.3.3. Electrocardiograms

Every attempt should be made to ensure the participant ECG readings are obtained using the same machine throughout the study. ECGs recordings will be transferred to and interpreted by a central reader. Parameters to be provided on the confirmed read for each safety ECG are HR and the following intervals: RR, PR, QRS, QT, QTc, and QTcF.

ECG values of potential concern and are **exclusionary at Screening and Day 1 predose** are noted below. A complete review of conditions or treatments that may affect cardiovascular function are seen in Protocol Section 5.2 Exclusion Criterion #13.

- Screening or Day 1 predose ECG with PR interval ≥ 200 ms or QTcF ≥ 450 ms in males or ≥ 470 ms in females are exclusionary.

ECG values of potential concern for all other visits are listed in Protocol Sections 7.1.3 and 10.7.

Use ECG machine provided to the site; local ECG machine can be used only if provided ECG machine is not functional. Qualified study site personnel must order, receive, and review results.

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position. If a meal or snack is scheduled at the same time as an ECG, the ECG measurement must be performed prior to the meal or snack.

ECGs will be interpreted by a central reader. Clinically significant or exclusionary ECG findings at the screening visit will result in screen failure. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Day 1 ECG may potentially be AEs (Section 10.3) and should be evaluated further, as clinically warranted.

The Investigator will be responsible for review and interpretation of ECGs on site and assessing whether the ECG is normal, abnormal clinically insignificant, or abnormal clinically significant. Abnormal clinically significant findings will be documented in the eCRF. All ECGs performed should be available for collection upon request.

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 7.1.3. ECG Changes for guidance on QTcF changes management.

Specific guidance on cardiac monitoring including ECG assessment following the first dose is provided in Section 10.10.3

ECGs will be performed at timepoints specified in the Schedule of Assessments SoA and if clinically indicated at any time during the treatment period at the Investigator's discretion

8.3.3.1. Alternative Facilities for Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative certified facility to have the ECGs performed. Use of alternative facilities for ECGs is not permitted on Day 1 (and Day 2, if applicable), Week 16 of Part 1 (and a day after, if extended cardiac monitoring is applicable), or for cardiac monitoring during treatment re-initiation after protocol pre-defined treatment interruptions (see Section 7.1.6). Qualified study site personnel must order, receive, and review results.

8.3.4. Chest Imaging

Chest X-ray or other appropriate diagnostic image (ie, computerized tomography or magnetic resonance imaging) to aid in TB status determination may be performed up to 12 weeks prior to Day 1. Chest images (posterior/anterior and lateral views) are required of all participants. Official reading must be located and available in the source documentation. Having a negative chest image alone does not rule out latent TB, and is thus not sufficient to qualify for the study. Likewise, having a negative chest image but a positive IGRA or PPD/Mantoux does not qualify the participants to participate in the study.

8.3.5. Tuberculosis Testing

At the time of screening, all participants will undergo TB testing unless performed within 12 weeks of Day 1. QFT-G in-Tube Test is the preferred testing method, however an alternative IGRA is permitted if QFT-G in-Tube is not available. The IGRA may be repeated once if the investigator deems this to be necessary.

TB testing (IGRA and PPD, if needed) will be conducted at a certified local laboratory unless unavailable in which case the Central Lab will be used.

If the results of IGRA (eg, QFT-G In-Tube test) cannot be determined by the reference laboratory to be either positive or negative, then participants may retest with the IGRA or be screened using the PPD Tuberculin Skin Test (Mantoux method) with approval of the study medical monitor. Participants must have the PPD test administered and evaluated by a health care professional 48 to 72 hours later in order to be eligible for the study, unless performed

and documented within the last 3 months. The test should be performed according to local standards with induration of <5 mm required for inclusion.

In addition to TB testing as specified in this clinical protocol, a chest image will be performed to aid in TB status determination. Following one year of total exposure to study intervention since the last TB test, all participants will undergo tuberculosis re-testing (including chest imaging) in regions which are above a low risk for Tuberculosis (ie, >10/100,000 incidence; as determined based on WHO country level data at the site below **https://worldhealthorg.shinyapps.io/**/tb_profiles/?_inputs_&entity_type="country"&lan="EN"&iso2="AF").

QFT-G In-Tube is an in vitro diagnostic test using a peptide cocktail simulating ESAT6, CFP10 and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon gamma by ELISA is used to identify in vitro responses to these peptide antigens that are associated with Mycobacterium tuberculosis infection. QFT-G Gold In-Tube is an indirect test for M. tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

A blood sample (approximately 3 mL) will be collected at screening for IGRA testing (eg, QFT-G InTube test) at a certified local laboratory.

During Screening, a TB questionnaire will be completed by the Investigator for all participants.

TB questionnaire will be completed at designated post-baseline study visits (per protocol schedule of assessments) for participants with suspected TB during the study and for participants who reside in regions which are above a low risk for TB (ie, >10/100,000 incidence) as identified by WHO.

TB questionnaire findings collected during the study will be considered source record and will not be required to be reported, unless they meet the definition of an AE or SAE.

8.3.6. 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 Section 10.5 for suggested actions and follow-up assessments in the event of potential DILI.

See Section 10.6 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

For laboratory collection volumes, see the laboratory manual.

8.3.6.1. Alternative Facilities for Clinical Safety Laboratory Assessment

During Part 1 DB portion, all attempts should be made to collect bloodwork at the study site in order to use Central Lab analysis and maintain the blinding. If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a certified local laboratory if permitted by local regulations in Part 1 OLE and Part 2. The local laboratory may be a standalone institution or within a hospital. Unless clinically urgent, blood work collection for WBC and TBNK are not permitted at a local laboratory during the Part 1 DB portion (including the SFU for participants who do not continue to Part 1 OLE) due to risk of unblinding; however, blood work may be collected at a certified local laboratory if permitted by local regulations during Part 1 OLE and during Part 2. If there is a question or safety concern, contact the unblinded independent medical monitor for guidance. Refer to Section 10.10.1.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

8.3.7. Hepatitis Testing

Hepatitis B testing: HB surface antigen (HBsAg), HB core antibody (HBcAb), HB surface antibody (HBsAb).

Interpretation of Hepatitis B Testing Results:

- HBsAg negative and HBcAb negative: Participant is eligible for the study;
- HBsAg positive and HBcAb negative: Participant is excluded from study participation;

- HBsAg negative and HBcAb positive and HBsAb positive: Participant is eligible for study if HBV DNA is negative or below LLQ;
    - Participants who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Participants who have HBV DNA at or above the LLQ will be excluded. Participants who are HBV DNA negative or below LLQ may enroll but will have HBV DNA testing repeated at Weeks 16, 68 or ET in Part 1 and Week 16, Week 52 or ET in Part 2.
- HBsAg negative and HBcAb positive and HBsAb negative: participant is excluded from study participation.

A single positive HBV DNA test result above the LLQ for a participant requires immediate and permanent discontinuation from treatment, and the study medical monitor (or designee) must be notified. The participant must be scheduled for an End of Treatment visit/Early Termination visit, enters the end of treatment follow up period, and must be scheduled for an End of Study visit. No further scheduled HBV DNA tests will be required for a participant once a result above the LLQ is established for that participant during any study in the program.

Hepatitis C testing: Hepatitis C Antibody (HCV Ab), Hepatitis C Viral RNA (HCV RNA for confirmation of positive HCV Ab result).

Interpretation of Hepatitis C Testing Results:

- HCV Ab positive and HCV RNA positive: participant is excluded from study participation.

8.3.8. Pregnancy Testing

A 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 the participant's receiving 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.

For visits that occur more than 4 weeks apart, participants must perform a home pregnancy test. Site personnel are expected to contact the participant every 4 weeks to confirm the home pregnancy test was taken, confirm participant continues to use contraception correctly, and document the pregnancy test results and contraception discussion in source. If home

pregnancy testing is not allowed per local regulations, pregnancy testing will be performed onsite during an unscheduled visit.

8.3.8.1. At-Home Pregnancy Testing

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

8.3.9. Pulmonary Function Test (and DLCO)

Pulmonary function testing will include FEV1 and FVC measurements. In addition, DLCO measurements will be performed, where locally available. Pulmonary function testing will be performed in a pulmonary function laboratory or respiratory department per local regulations. In exceptional cases, pulmonary function will be performed at the clinical trial site or qualified physician's office by a qualified pulmonary technician/professional and results interpreted by a pulmonologist or other qualified physician, as per local standard practice. This exception requires Sponsor's approval.

Because carbon monoxide binds readily to hemoglobin, the diffusion capacity needs to be corrected for hemoglobin in order to reflect an altered lung gas transport rather than altered hemoglobin. All DLCO values will be corrected for hemoglobin concentration (ie, hemoglobin adjusted diffusion capacity). PFTs and DLCO assessments must be completed during the Screening Period (ie, prior to randomization). The window to perform PFTs and DLCO is ±10 days for all post-screening visits. Sites where DLCO is not available should consult the study medical monitor. PFTs and DLCO will be conducted in a manner consistent with the American Thoracic Society/European Respiratory Society guidelines for standardization of spirometry and single breath determination of carbon monoxide uptake in the lung.[39-41] Spirometers must be compliant with ATS/ERS guidelines for the standardization of spirometry, including calibration and record keeping. Records must be available to confirm compliance.

Participants who demonstrate a ≥ 20% decline in PFT values (FEV_1 and/or FVC) from baseline after enrollment should have the PFT repeated for confirmation. Any issues with participant effort or compliance with the test procedure should be explicitly recorded. This information is important to determine whether PFT abnormalities may be the result of poor effort or compliance with test procedure. Smoking status (including e cigarettes) will be collected and recorded in the source record each time a PFT assessment is conducted.

Participants reporting any respiratory symptoms (eg, dyspnea, shortness of breath, chest tightness, or wheezing) should be seen at an unscheduled visit for clinical assessment and full PFT assessment, preferably on the same day.

Additional guidance on clinical monitoring of pulmonary function is provided in Section 10.10.4.

PFTs will be performed at timepoints specified in the SoA.

8.3.10. Ophthalmology Exam

A complete ophthalmoscopy and OCT assessment will be performed at timepoints specified in the SoA and all clinically significant ophthalmic findings should be recorded in eCRF. Ophthalmoscopy and OCT assessment must be completed during the screening period (ie, prior to randomization) and the window is ± 10 days for all post-screening visits.

The OCT machine used should preferably not be changed during the study to allow for comparison of center point thickness measurements within each participant across timepoints.

The ophthalmologist/optometrist (where permitted) will be provided with a study referral letter explaining the reason for the referral along with information about the study, the investigational drug, and the ophthalmic clinical data to be collected for the study.

Eye examination performed by an ophthalmologist will include:

- Ophthalmologic history
- Best corrected visual acuity measurement (autorefraction, using Snellen chart internationally)
- Ophthalmoscopy
- Intraocular pressure
- May include contact lens biomicroscopy to examine the macula and optic disc
- A dilated fundus exam should be performed in all participants at the Screening Visit and as needed at subsequent visits in participants with significant abnormalities identified on the screening exam. Participants should be advised to wear sunglasses after pupil dilation and arrange for a driver to transport them after the exam
- Retinal photographs (only if evidence of clinically significant abnormalities)
- OCT for the measurement of center point thickness (recorded in microns)
- FA (at the discretion of the ophthalmologist) if there is a suspicion of macular edema by ophthalmoscopy and increased center point thickness by OCT.

In the event that restrictions imposed by governments or regional health authorities, or safety recommendations issued by professional societies limit the capacity to perform OCT (eg, COVID 19 or similar public emergency situations), the 28-day screening period may be extended on a case-by-case basis to accommodate reasonable delays in OCT. The study medical monitor should be consulted on each case.

When ophthalmoscopy with OCT cannot be performed, exclusion criterion 4 may be modified as shown by the following text to identify and exclude participants with potential macular edema at Screening: “History of macular edema or retinopathy or symptoms of blurry or wavy central vision, report colors appearing washed out or different, or have difficulty reading ≤ 6 months prior to baseline (when Screening ophthalmoscopy with OCT cannot be performed due to COVID 19 pandemic/regional emergency situations).”

Under the scenario above, the missed ophthalmoscopy with OCT exam must be performed no later than 10 days after restrictions are lifted and the ophthalmology consultant’s office is opened for nonurgent ophthalmic evaluations.

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

Additional guidance on clinical monitoring of ophthalmic symptoms is provided in Section 10.10.5.

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/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

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 4 weeks 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 concluded study participation, 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/legally authorized representative 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, inhalation, or skin contact.

- A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, 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 on the CT SAE Report Form and an 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 pregnancy completion or termination.
- 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, inhalation, 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

Based on the mechanism of action of etrasimod and prior experience with etrasimod and other agents acting via a similar mechanism, certain AESIs have been identified as they may be associated with exposure to etrasimod. In addition to appropriate reporting of these events as an adverse event or SAE, supplementary detailed information may be collected, and close monitoring may be required.

Cardiovascular AESIs associated with S1P receptor modulators, such as etrasimod, include HR reduction and/or transient atrioventricular conduction delays after the initial dose. For participants who experience a cardiovascular symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, and/or syncope) at any time during the first-dose cardiac monitoring, the Investigator should determine whether or not this event is associated with a HR reduction or clinically relevant change in 12 lead ECG.

Cardiac monitoring is described in Section 10.10.3.

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

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. They require close monitoring and are assessed as close to real time as possible, and they are promptly reported to the study monitor even if the event is not considered an SAE according to the criteria in Section 10.3.2. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form or via PSSA.

AESI for etrasimod are:

- Cardiovascular events (eg, bradycardia, AV conduction delay and hypertension),
- Macular edema* (Section 10.10.5),
- Pulmonary events (airflow obstruction or decreased gas exchange; Section 10.10.4),
- Infections (severe infections, opportunistic infections, Herpes simplex and Herpes zoster, PML*; Section 10.10.2 and Section 10.11),
- Liver injury (liver transaminase elevation and bilirubin elevation; Section 10.5),
- PRES*,
- Malignancies*

* A diagnosis of this event requires permanent discontinuation of study intervention. See Section 7.1 for additional AEs requiring discontinuation.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

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.
- Refer to Section 6.5 for examples of medication error related to compliance with study intervention.

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 AE(s), serious and nonserious, 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 or via PSSA **only when associated with an SAE.**

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

Genetic analyses will not be collected in this study.

8.7. Biomarkers

Biomarkers are not evaluated 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 will also be reflected in a protocol amendment. Data from Part 1 and Part 2 of the study will not be pooled.

9.1. Statistical Hypothesis

Part 1 of this study is an estimation study with the objective to estimate the IGA response rates of the treatment groups (Etrasimod 2 mg QD and Placebo) as well as the IGA response rate difference between the treatment groups at Week 16. There are no statistical hypotheses in this study. The sample size calculation considers only the precision of the estimation of IGA response rates and the treatment difference in response rate (Section 9.5).

9.1.1. Estimands

9.1.1.1. Primary Estimand

The primary estimand (E1) is defined by the following attributes:

1. Treatment condition: received study intervention of etrasimod 2 mg QD or placebo.

2. Population: Participants with moderate-to-severe AD as defined by the inclusion and exclusion criteria.

3. Variables: Proportion of participants achieving IGA score of clear (0) or almost clear (1) and a reduction from baseline of ≥2 points at Week 16. A participant who experiences an intercurrent event of initiation of prohibited medications or discontinuation of study treatment due to any reason (whichever is earlier), will be considered an IGA non-responder (ie, treatment failure) at Week 16.

4. Intercurrent Events:

   A) Initiation of prohibited medications – a participant who receives prohibited medication post-randomization prior to the Week 16 visit will be considered an IGA non-responder (ie, treatment failure) at Week 16.

   B) Discontinuation of study intervention due to any reason prior to the Week 16 visit – a participant who discontinues study intervention due to any reason will be considered an IGA non-responder (ie, treatment failure) at Week 16.

5. Population level summary: The difference in IGA response rates at Week 16 between etrasimod 2 mg QD and placebo.

Estimand E1 will be similarly applied to the binary secondary endpoint (ie, EASI-75 at Week 16) as well as the binary exploratory endpoints (eg, ≥4-point reduction from baseline in PP-NRS score at Week 16) with the endpoint substituted appropriately.

9.1.1.2. Secondary Estimands

Estimand (E2) strategy is defined for a continuous secondary endpoint at a visit (eg, percent change from baseline in EASI score at Week 16). The secondary estimand (E2) for continuous endpoints is defined by the following attributes:

1. Treatment condition: received study intervention of etrasimod 2 mg QD or placebo.

2. Population: Participants with moderate-to-severe AD as defined by inclusion and exclusion criteria.

3. Variables: Percent change from baseline in EASI total score at Week 16. If a participant in the etrasimod 2 mg QD group experiences the intercurrent event of initiation of prohibited medications or discontinuation of study treatment due to any reason (whichever is earlier), the endpoint data after the intercurrent event will be treated as missing and then imputed via multiple imputations as if they are in placebo group (ie, no treatment benefit).

4. Intercurrent events:

   A) Initiation of prohibited medications – a participant who receives prohibited medications post-randomization prior to Week 16, the endpoint data after the intercurrent event will be treated as missing and then imputed via multiple imputation as if they are in placebo group (ie, no treatment benefit).

   B) Discontinuation of study intervention due to any reason prior to the Week 16 visit - a participant who discontinues study treatment due to any reason, the endpoint data after the intercurrent event will be treated as missing and then imputed via multiple imputation as if they are in placebo group (ie, no treatment benefit).

5. Population-level summary: The mean difference in percent change from baseline in EASI score at Week 16 between etrasimod 2 mg QD and placebo.

Estimand E2 will also be applied to percent change from baseline in EASI score at visits prior to Week 16.

9.1.2. Multiplicity Adjustment

No multiplicity adjustment will be made in the study.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Full analysis set	All participants randomly assigned to study intervention, irrespective of whether they received any dose of study intervention. Participants will be analyzed in the treatment groups as they are randomized.
Safety analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe 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. General Considerations

The efficacy and safety data will be summarized by treatment group in Part 1. The Part 2 will be summarized separately. The efficacy endpoints will be summarized using descriptive statistics: the number and percent of participants for response-type endpoints, and with the number of participants, mean, standard deviation, median, minimum, and maximum for continuous endpoints.

9.3.2. Primary Endpoint Analysis

A landmark analysis of the IGA response endpoint at Week 16, defined in Section 9.1.1.1, will be performed in the FAS (among participants with baseline IGA ≥2) using the Cochran-Mantel-Haenszel method adjusted for the actual randomization/stratification factor IGA score (3 [moderate AD], 4 [severe AD] based on clinical database) at Baseline using normal approximation for the difference in binomial proportions. The IGA response rate difference between the etrasimod group and the placebo group in the proportion of participants achieving (ie, IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction of ≥ 2 points from baseline at Week 16) along with its 95% confidence interval will be reported. Estimand E1 defined in Section 9.1.1.1 will be used. Any missing values after accounting for the intercurrent events will be considered as an IGA non-responder (ie, treatment failure).

9.3.3. Secondary Endpoint Analysis

Binary secondary endpoints will be analyzed similarly to the primary endpoint.

A landmark analysis of continuous endpoints including percent change from baseline in EASI at Week 16, defined in Section 9.1.1.2. will be performed by the Jump-to-Control

(JTC) method. An MMRM that includes fixed effects of treatment group, visit, treatment group-by-visit interaction, actual randomization/stratification factor (baseline IGA of 3 or 4 based on clinical database), actual-stratification-factor-by-visit interaction, EASI baseline value, and EASI-baseline-value-by-visit interaction will be used to analyze the endpoint's data across all visits after accounting for intercurrent events as the imputation model. MMRM parameters will be estimated using Bayesian framework. Multiple imputation will be performed from multivariate conditional Normal distribution constructed from the sampled posterior parameter values. Participants in the etrasimod group with missing data at a visit will be imputed using mean estimated for the placebo group for the same visit (ie, JTC implementation). This will result in multiple imputed datasets for this visit. An ANCOVA model will include treatment group, EASI baseline value and actual randomization/stratification factor (IGA of 3 or 4 based on clinical database) as covariates and it will be applied to the multiple complete imputed datasets. Results of the multiple ANCOVA analyses will be combined using Rubin's rules (Rubin 1987) to generate the combined LSM (SE) for each treatment group and LSM treatment difference estimate and its SE, 95% CI, and 2-sided p-value for the visit of interest. The EASI baseline value will be obtained on Day 1 or prior in the double-blind phase. Estimand E2 defined in Section 9.1.1.2 will be used.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Exploratory endpoints will be analyzed descriptively. Any additional analyses will be described in the SAP.

9.3.5. Safety Analyses

The safety data will be summarized in accordance with CDISC and Pfizer Standards (CaPS). All safety analyses will be performed on the safety population. Safety endpoints include Incidence of treatment emergent AEs and SAEs, clinically significant changes in laboratory tests and ECG. All safety analyses will be performed descriptively.

9.3.5.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment group and time.

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment group and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment group:

Safety QTcF Assessment

Degree of Prolongation	Mild (ms)	Moderate (ms)	Severe (ms)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

9.4. Interim Analyses

An interim analysis will be conducted to assess efficacy and safety after all Part 1 participants complete the 16-week DB treatment period. The interim analysis results will be used for decisions regarding stopping for futility and internal program development. Study conduct, including Part 1 participant continuation in OLE, will continue while the data are prepared and analyzed for the IA. The Part 2 enrollment will not be triggered until after the IA shows an acceptable safety and efficacy of etrasimod 2 mg QD in the target population. Based on the IA results, the study may continue to enroll participants, or the study may be early terminated. Details on the IA will be provided in the SAP. The IA will be conducted by the Sponsor (refer to Section 4.1). Prior to this formal Part 1 DB IA, Sponsor may perform earlier unblinded interim analyses to inform internal decision-making regarding the development program. These earlier interim analyses will be conducted and reviewed by a limited number of team members independent of the study team. Details on these earlier unblinded interim analyses will be described in an unblinding operational plan.

9.5. Sample Size Determination

Part 1: Approximately 60 participants will be randomized to etrasimod 2 mg QD or placebo in a ratio of 1:1 (30 participants per treatment group). This is an estimation study. The primary objective will be to estimate the proportion (95% CI) of participants achieving IGA response at Week 16 in each treatment group and the difference (95% CI) in proportions between the two groups.

With 30 participants per group, assuming the proportions of participants achieving IGA response at Week 16 are 9% and 39% for placebo and etrasimod 2 mg QD, respectively:

- the half-width of the 2-sided 95% CI for the proportion of participants achieving IGA response at Week 16 will be $\leqslant$ 17.5% in each treatment group using normal approximation.
- the half-width of the 2-sided 95% CI for the difference in proportions between etrasimod 2 mg QD and placebo will be 20.2% using normal approximation.

The placebo response rate was estimated based on Phase 3 studies in literature.[42-44]

No adjustment for multiplicity will be made.

Part 2: Approximately 340 participants are planned in order to fulfill the safety database requirements. No formal sample size calculations are performed.

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 or their legally authorized representative and answer all questions regarding the study. The participant or their legally authorized representative 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 or their legally authorized representative (if allowed by local regulations) 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 or their legally authorized representative 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 or their legally authorized representative 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 or their legally authorized representative.

The participant or their legally authorized representative 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 or their legally authorized representative 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 or their legally authorized representative 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 or their legally authorized representative (if allowed by local regulations).

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

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 standard operating procedures 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 use an E-DMC. The E-DMC is independent of the study team and includes only external members. The E-DMC charter describes the role of the E-DMC in more detail.

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities and investigators, as appropriate.

Members of the E-DMC and an independent statistician responsible for interacting with the E-DMC will have access to unblinded study data. The E-DMC recommendations to the study team will be communicated in a blinded fashion (ie, treatment assignment for individual participants will not be shared). To ensure the scientific integrity of the study, members of the E-DMC will not be directly involved in the ongoing management of the study.

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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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 source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

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

The investigator must maintain accurate documentation (source data) 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

In certain situations, sponsor review of redacted copies of participant medical records for certain cases may be performed, 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, participant 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 supporting study documentation.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study 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, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the 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. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests 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 7. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other	Reflex Tests
CBC with differentials[a] Hemoglobin Hematocrit RBC count Platelet count WBC count: Full differential including % Total neutrophils (Abs and %) Eosinophils (Abs and %) Monocytes (Abs and %) Basophils (Abs and %) Lymphocytes (Abs and %) TBNK Panel[a] Total T-Cells (CD3+), B cells (CD3-CD19+), NK cells (CD3-CD16+CD56+), CD4+ Tcells (CD3+CD4+) and CD8+ Tcells (CD3+CD8+) count (Abs and %) Coagulation Panel aPTT INR PT	Urea and creatinine, Cystatin C (at baseline) Sodium Potassium AST, ALT Total bilirubin Alkaline phosphatase Albumin Total protein GFR[b]	Local dipstick: Protein (qual) Blood (qual) Nitrites Leukocyte esterase Laboratory: Microscopy and culture[c]	At screening: • FSH[d] • Pregnancy test (β-hCG)[e] • TB[f] • HBsAg (if equivocal, reflex to HBV DNA quantification) • HBcAb[g] • HBsAb[g] • HCVAb (if positive, reflex to HCV RNA quantification) • HIV serology	**Required Tests:** For suspected DILI: AST/ALT T bili, direct and indirect bili Total bile acids, GGT Total protein, albumin CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative) For suspected DICI/DIKI: Creatinine (Scr) Cystatin C (Scys) eGFR (Scr only and combined Scr+Scys) Spot (dipstick) UACR

a. Site staff, including Investigators, will be blinded to the WBC count, WBC differential (percentage and absolute number), and TBNK panel cell counts; results will be assessed by an unblinded Independent medical monitor who will notify Investigators when participants experience events of Grade 4 lymphopenia (ALC < 0.2 × 109 cells/L) and will direct Investigators on specific actions to take. Refer to Section 10.10.1

Table 7. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other	Reflex Tests

b. GFR will be calculated with the CKD-EPI algorithm.
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.
e. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine βhCG for female participants of childbearing potential.
f. In addition to a chest imaging (ie, CT or MI), TB screening will be done via an IGRA (QFT-G In-Tube test (preferred)) in all participants except those with a history of active, latent, or inadequately treated infection with TB. If the result of the repeat test is indeterminate, participants may be screened using the Mantoux/PPD skin test with study medical monitor approval. If a participant has previously received an adequate course of therapy for either latent (eg, 9 months of isoniazid in a locale where rates of primary multi-drug TB resistance are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection, neither a QFT-G test, nor a Mantoux/PPD tuberculin skin test is needed, but a chest imaging is required if not performed within 12 weeks prior to Day 1. If the current incidence rates of multi-drug resistant TB infection in the locale are unavailable, an adequate treatment regimen should be defined as the regimen recommended by the health ministry or expert panel in the locale. Tuberculosis testing is required at Week 52 in Part 1 and Part 2 of the study for all participants in regions which are above a low-risk for tuberculosis (ie, >10/100,000 incidence) which will be determined based on World Health Organization (WHO) country-level data, and a negative test result for TB will be required for ongoing eligibility for study participation.
g. Reflex testing for HBV DNA only if HBsAg negative, HBcAb positive and HBsAb positive at screening. Participants who are HBsAg negative, HBsAb negative and HBcAb positive are excluded from the study (Section 8.3.7)

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.

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 nonpathogenic

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 or via PSSA 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/PSSA 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/PSSA for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form/PSSA 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 or 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 AE or SAE)is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form or via PSSA.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form or via PSSA, 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 or via PSSA.

- 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/PSSA 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 preferred methods to transmit this information to Pfizer Safety.
- Facsimile transmission of the CT SAE Report Form is the back-up method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours.
- 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

At time points indicated in the SoA, the investigator or designee should inquire of both WOCBP and male participants if a change in the risk of becoming pregnant or getting someone pregnant has occurred, and they will inform the participant of the need to use highly effective contraception consistently and correctly. Refer to details in Section 5.3.1.

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 truly 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 in adolescents or athletes) 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 of age 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

   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. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception for female participants. Male condom and female condom should not be used together (due to risk of failure with friction).

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

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

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

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]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Screat increase. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated.

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

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

Inker LA et al. N Engl J Med. 2021;385:1737-49.[45]

10.6.3. Kidney Function Calculation Tools

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 KDIGO criteria.

KDIGO criteria	**Study Population**	**G1**	**G2**	**G3**	**G4**	**G5**
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	Adult participants eGFR (mL/min/1.73m^2)	≥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) or 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 seconds' 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.
• 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 periods of asystole ≥3.0 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 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 seconds' 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 enumerated list of major events of potential clinical concern 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 to be reported as AEs/SAEs.

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

10.8.1. Prohibited Concomitant Medications That May Result in DDI

Moderate or strong inhibitors or inducers that inhibit or induce at least 2 of the following are prohibited: Cytochrome P450 (CYP)2C8, CYP2C9, and CYP3A4. Examples include fluconazole, rifampin, and enzalutamide.

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).

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: Country-Specific Requirements

This appendix is only applicable to Part 2.

10.9.1. France

Contrat Unique

1. GCP Training

   Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

   No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

   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 ICH GCP that the investigator becomes aware of.

4. Termination Rights

   Pfizer retains the right to discontinue development of etrasimod at any time.

10.10. Appendix 10: Safety Monitoring Guidance

This study will utilize 2 medical monitors:

The unblinded independent medical monitor

- is a clinician independent from and not a member of the study team
- monitors unblinded WBCs and TBNK values while remaining blinded to study treatment
- will notify investigators when participant has Grade 4 lymphopenia (ALC < 0.2 × 109 cells/L) and will direct investigators on specific actions to take (outlined in Protocol Section 10.10.1)
- will notify investigators when there is at least 1 measurement of ANC < 1.0×10^9 cells/L or WBC count > 20×10^9 cells/L (outlined in Protocol Section 10.10.1)

The blinded study medical monitor:

- is a Pfizer clinician and a blinded member of the C5041005 study team
- should be contacted for questions on the protocol, eligibility (including roll-over to the OLE) and continuation criteria based on EASI-50
- Should be contacted if participant does not meet discharge criteria after 4 hours of cardiac monitoring (outlined in Protocol Section 10.10.3)
- Should be contacted when referenced as the "study medical monitor" in the protocol, in cases of overdose, protocol predefined study intervention interruption and re initiation, suspected cases of PML (outlined in Protocol Section 10.11), and for all other safety concerns.

Temporary Interruption to Dosing

Dose interruptions are defined as the following consecutive days of missed study treatment:

- ≥2 consecutive days within the first week of treatment and Week 16 of Part 1, or
- ≥7 consecutive days after the first week of treatment (excluding Week 16 of Part 1 where missing 2 doses applies)

If the Investigator deems it necessary to withhold study treatment due to an adverse event, temporary withholding is permitted for up to 6 days (after the first week of treatment) without obtaining prior approval from the study medical monitor. Planned dose interruptions during the first week of treatment requires consultation with the study medical monitor. If study treatment interruption ≥ 7 days is required for a medical reason at any time in the study, the Investigator must contact the study medical monitor for further instruction as soon as this is anticipated.

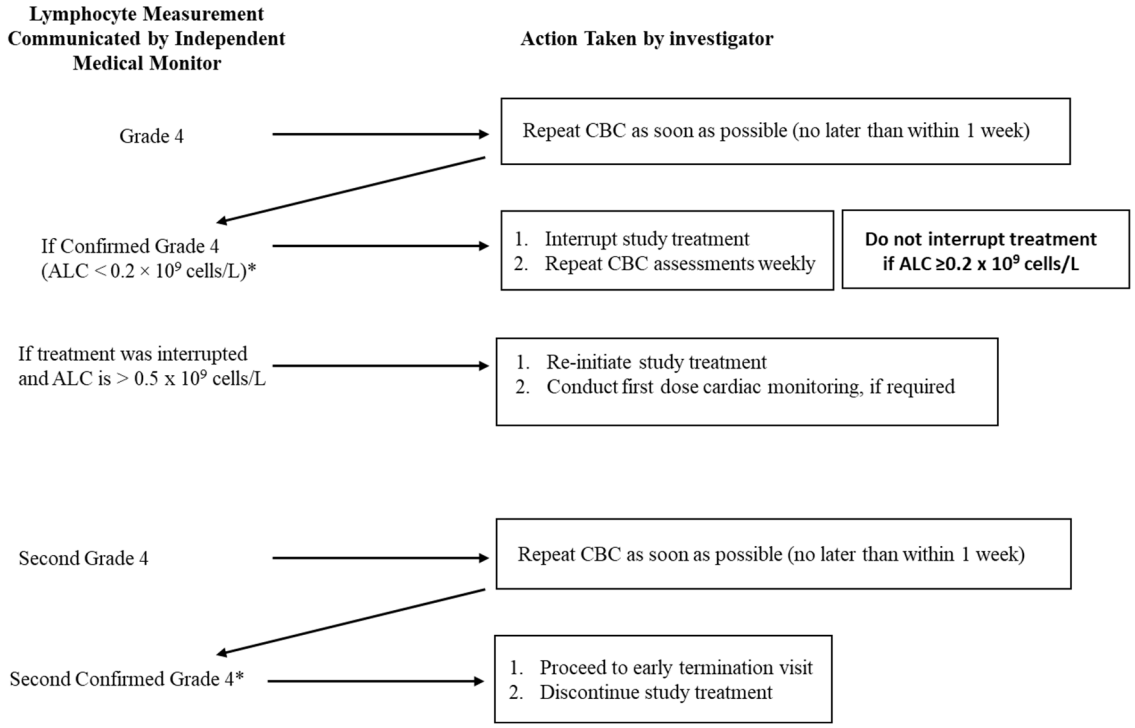
Any time a participant reinitiates study treatment following protocol-defined dose interruption, the first dose cardiac monitoring outlined in Section 10.10.3 must be performed and the participant must take the next dose of study treatment at the study site.

Doses not taken due to an adverse event per investigator's request do not constitute protocol deviations or medication errors and should not be considered dosing errors but should be noted in the dosing log with the reason for reduced drug consumption clearly described.

10.10.1. Monitoring Of Lymphocyte, Neutrophil, and White Blood Cell Counts

Etrasimod prevents lymphocyte egress from lymphoid tissues, resulting in a reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. Site staff, including Investigators, will be blinded to the WBC count, WBC differential (percentage and absolute number) and TBNK panel cell counts. WBC count, WBC differential, and TBNK panel results will be assessed by the unblinded independent medical monitor who is not involved in any other aspects of study conduct or data analysis and who is blinded to study treatment. The unblinded independent medical monitor will notify Investigators when participants experience events of Grade 4 lymphopenia (ALC $< 0.2 \times 10^9$ cells/L) and will direct Investigators on specific actions to take as described in Figure 1. Participants must permanently discontinue study treatment in the event of sustained Grade 4 lymphopenia, defined as a second confirmed Grade 4 measurement with treatment rechallenge after study treatment interruption.

Figure 1: Management of Grade 4 Lymphopenia Events



*If repeat assessment does not confirm Grade 4 lymphopenia, continue study treatment. **If study intervention has been interrupted ≥2 consecutive days during Week 1 or Week 16 of Part 1 or ≥7 consecutive days after Week 1 (excluding Week 16 of part 1 where 2 doses applies), First Dose Cardiac Monitoring must be conducted when study intervention is re-initiated (see Section 10.10.3).**

In addition, the unblinded independent medical monitor will notify Investigators when there is at least 1 measurement of ANC < 1.0×10^9 cells/L or WBC count > 20×10^9 cells/L. Blinded values may be released to treating physicians and Investigators as deemed medically necessary to monitor the risk of infection and/or aid in diagnostic workup as clinically indicated, and/or as a tool to assess the effectiveness of therapeutic interventions for an infection. Investigators will repeat CBC with differentials weekly until ANC > 1.0×10^9 cells/L or the increased WBC count trends downward (on 2 separate days), respectively.

Participants with an ongoing AE of decreased lymphocyte count or infection at the 4-Week Follow Up Visit should return for CBC with differential according to local standard of care (captured as subsequent Follow-Up Visit or unscheduled visit).

10.10.2. Serious Infections Monitoring

Low lymphocyte counts observed with the use of other S1P receptor modulators in patients with multiple sclerosis have been associated with serious and atypical infections. [4,5,46] Investigators should remain vigilant in monitoring for signs and symptoms of serious and atypical infections during the study and after discontinuation of study treatment. Serious infection monitoring (refer to definition for Serious Adverse Events in Section 10.3.2) requires a temporary interruption of study intervention. Study intervention cannot be restarted until the serious infection has resolved per investigator judgement (investigator may discuss restarting study intervention with the medical monitor, if needed). If the participant cannot be restarted on study intervention, then the participant must be permanently discontinued.

Participants will be queried for signs and symptoms of PML. If a participant exhibits signs and symptoms suspicious for PML, study treatment must be interrupted and cannot be restarted until diagnostic evaluation is completed and PML has been excluded. The study medical monitor should be informed of any suspected cases of PML. Refer to Section 10.11 for signs and symptoms of PML and a PML case evaluation algorithm. In the evaluation and management of treatment emergent infections, the Investigator may consult with infectious disease or relevant experts, as needed.

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

10.10.3. First-Dose Cardiac Monitoring

Cardiac monitoring following treatment initiation applies to the first dose administered in the Treatment Period (Day 1). Day 1 predose (ie, Baseline) vital signs (resting HR, BP, body temperature, and respiratory rate) will be used as the baseline measurements. The lowest predose HR measurement (by vital signs) will be used for comparison to the postdose measurement. It should be noted that in this section heart rate refers to pulse rate. Pulse rate will be collected as part of vital signs and heart rate will be collected as part of the ECG.

Cardiac monitoring is required at the Day 1 (first blinded dose) of Part 1 and Part 2 and Week 16 (first open label etrasimod dose) of Part 1 and will also be necessary to reinitiate study treatment if consecutive days of study treatment are missed as described in Section 7.1.7. These visits for cardiac monitoring should be conducted in the morning and not on a Friday or the day before a site-observed holiday. In the following sections describing first-dose cardiac monitoring, Day 1 refers to the first day of treatment in the Treatment Period, but the same procedures will also be used at the Week 16 visit in Part 1 (first open label dose) and the first day of treatment re-initiation following the defined periods of treatment interruption noted above. Day 2 refers to the subsequent dosing day.

10.10.3.1. Cardiac Monitoring Schedule After First Dose

After the first dose of study treatment on Day 1 of Part 1 and Part 2, participants will be observed up to 8 hours. Cardiac monitoring on the first 4 hours (0H, 1H, 2H, 3H and 4H) is required for all participants. The second 4 hours (5H, 6H, 7H, and 8H) are **not** required and will only be performed for participants who do **not** meet discharge criteria at hour 4 of cardiac monitoring. The in-clinic cardiac monitoring on Day 1 will include assessments at the timepoints specified in Table 8. These criteria will also be used at the Part 1 Week 16 visit, the first day of treatment re-initiation following the defined periods of treatment interruption, and for Day 1 Part 2 of the study.

Participants who do not meet discharge criteria at 4 hours postdose on Day 1 will require extended cardiac monitoring on Day 1 (Table 8) and on Day 2, as described in Section 10.10.3.1.2.

For participants who experience a cardiovascular symptomatic event (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, and/or syncope) at any time during the first 4-hours postdose (ie, on Day 1), the Investigator should determine whether or not this event is associated with a HR reduction or clinically relevant change in 12-lead ECG. Participants who experience a symptomatic event associated with HR reduction or clinically relevant 12-lead ECG should be discontinued from study treatment if they meet the criteria described in Section 10.10.3.2. Participants who experience a symptomatic event that is not associated with HR reduction or clinically relevant 12-lead ECG may be discharged on Day 1 at Hour 4 postdose (at the Investigator's discretion and provided they meet the discharge criteria (Section 10.10.3.1.1), but must return to the clinic on Day 2 for extended cardiac monitoring as described in Section 10.10.3.2.

Table 8. Procedures to be Performed During the First-Dose Cardiac Monitoring Period

Procedure	Predose	Hours 1, 2, and 3 Postdose[a]	Hour 4 Postdose[a]	Day 1 Extended Cardiac Monitoring[b]
Blood pressure and HR derived from vital signs (seated position)	X[e]	X[c]	X[c]	X[c]
12-lead ECG (supine position)[d]	X	–	X	X
Assess discharge criteria	–	–	X	X

a Measurements may be taken within ± 15 minutes of the scheduled time. Record time of assessment.
b Only for participants not meeting discharge criteria (Section 10.10.3.1.1) at Hour 4. Assessments should be repeated hourly (± 15 minutes of the scheduled time) until the participant meets the discharge criteria; the blinded study medical monitor should be contacted if the participant does not meet the discharge criteria after 4 hours of extended cardiac monitoring on Day 1. Record time of assessment.
c If the participant has a vital sign HR of < 50 bpm or if cardiovascular symptoms develop (eg, chest pain, dizziness, palpitations, and/or syncope associated with reduction of HR), conduct 12-lead ECGs as clinically indicated. Include body temperature and respiratory rate.
d Additional 12-lead ECGs may be conducted as clinically indicated.
e Include body temperature and respiratory rate.

10.10.3.1.1. Discharge Criteria After First-Dose Cardiac Monitoring

These criteria will also be used on Day 1 Part 1, at the Week 16 visit of Part 1, first day of treatment re-initiation following the defined periods of treatment interruption, and for Day 1 Part 2 of the study.

Participants will be released from the clinical site after dosing (but no sooner than 4 hours postdose) when they fulfill the following **discharge criteria**:

1. Vital sign HR ≥ 50 bpm

- If vital sign HR < 50 bpm, then the decrease from baseline must be < 10 bpm

- If participant is meeting the protocol pre-specified discharge criteria at Hour 4, **the participant can only be discharged if the lowest HR recorded is not at Hour 4**. If Hour 4 HR has the lowest value, the participant needs to be further monitored following extended cardiac monitoring on Day 1 procedures until it is confirmed the HR is on the upward trend before participant is discharged from the site. The full 4 hours of extended cardiac monitoring is not required to establish the upward trend, and participant is not required to return for additional cardiac monitoring on Day 2.

2. No evidence from ECG of second-degree AV block or higher

3. No participant-reported cardiac symptoms (eg, chest pain, dizziness, palpitations, lightheadedness, shortness of breath, or syncope)

For participants not meeting discharge criteria on Day 1:

- The blinded study medical monitor should be contacted if the participant does not meet the discharge criteria after 4 hours of extended cardiac monitoring on Day 1 (after 8 hour post dose).
- PI and the blinded study medical monitor should come to agreement on how to proceed and if it is appropriate to discharge the participant.
- Participants should have written instructions on when to return to the clinic on Day 2 and a 24-hour contact phone number to call in the event of any new or worsened cardiovascular symptoms.

Additional cardiac-monitoring data collected post Hour 4 needs to be captured on the CRFs.

Medically qualified personnel as per local clinical practice standards, experienced in interpreting ECGs may perform local ECG reads. If the machine-read is normal, not clinically significant, and the participant meets all other protocol pre-specified discharge criteria, the medically qualified site personnel can choose to discharge the participant based on the local ECG read. **If, however, there is any clinical uncertainty, the site should wait for the interpretation by the Central reader prior to discharging the participant.**

10.10.3.1.2. Cardiac Monitoring on Day 2 for Participants Not Meeting Discharge Criteria on Day 1 (and Week 16 + 1 day in Part 1)

Table 9 describes extended cardiac monitoring on Day 2 for participants not meeting discharge criteria at 4 hours on Day 1 (Section 10.10.3.1.1) or for participants who experienced a cardiovascular symptomatic event associated with HR reduction or clinically relevant 12-lead ECG during the 4-hour monitoring period on Day 1.

Table 9. Procedures to be Performed for Extended Cardiac Monitoring on Day 2

Procedure	Predose	Hours 1, 2, 3 Postdose[a]	Hour 4 Postdose[a]
Blood pressure and HR derived from vital signs (seated position)	X[b]	X[c]	X[c]
12-lead ECG (supine position)[d]	X	–	X
Assess discharge criteria	–	–	X

a Measurements may be taken within ± 15 minutes of the scheduled time. Record time of assessment.
b Include body temperature and respiratory rate.
c If the participant has a vital sign HR of < 50 bpm or if cardiovascular symptoms develop (eg, chest pain, dizziness, palpitations, and/or syncope associated with reduction of HR), the participant should continue to be closely monitored, including 12-lead ECGs as clinically indicated, until the Hour 4 discharge assessment. Include body temperature and respiratory rate.
d Additional ECGs may be performed as clinically indicated.

10.10.3.2. Study Treatment Discontinuation Related to Postdose Cardiac Monitoring

Study treatment discontinuation specific to postdose cardiac monitoring will occur in the following scenarios:

- Suspected intolerance associated with first dose cardiac effects – Symptomatic cardiovascular events associated with first dose cardiac monitoring (e.g., chest pain, dizziness, palpitations, lightheadedness, shortness of breath, and/or syncope) associated with HR reduction or associated with clinically relevant 12-lead ECG changes at any time during the cardiac monitoring period on Day 1 or the extended cardiac monitoring on Day 2, if extended cardiac monitoring is applicable; participants with such AEs, irrespective of causality will be discontinued from the study intervention.

- Participants who have not met the discharge criteria by 4 hours postdose during the extended cardiac monitoring on Day 2 will be discontinued from the study treatment.

Participants who discontinue treatment due to first dose cardiac monitoring should return to site within 3 calendar days for ET visit that includes an ECG (in accordance with the SoA). The study medical monitor should be contacted before discontinuing a participant from study treatment.

10.10.4. Pulmonary Function Monitoring

Based on changes in pulmonary function observed with the use of S1P receptor modulators for relapsing multiple sclerosis[4,5], pulmonary function will be assessed in this study.

Participants experiencing clinically significant dyspnea or other respiratory AEs, may need to have additional PFT testing as clinically indicated. Severity of respiratory AEs should be categorized using the CTCAE scale. Investigators should consider interruption of study treatment when there is a clinically significant respiratory AE that leads to limitations in self-care activities of daily living and is associated with PFT decrease. Participants experiencing a confirmed decline in PFT values (FEV1 and/or FVC) below 50% of the predicted values must be discontinued from study treatment and scheduled for a follow-up visit. The decision to interrupt study treatment should be discussed with the blinded Pfizer medical monitor. Participants should be promptly referred to a pulmonologist for further evaluation and treatment. The pulmonologist should be provided with a standard referral letter explaining the reason for the referral along with information about the investigational drug. Clinically significant respiratory AEs should be followed until there is stability, improvement, or resolution.

Reinitiation of study treatment can only be considered if the respiratory AE has improved, stabilized, and/or resolved; the individual risk benefit is favorable (as determined by the Investigator, in agreement with the pulmonologist); and after discussion with the blinded Pfizer medical monitor. The investigator is to ensure first dose cardiac monitoring (Section 10.10.3) is implemented upon drug reinitiation if consecutive days of study treatment are missed as described in Section 7.1.7.

Information regarding the collection of PFTs is provided in Section 8.3.9. PFTs will be performed at timepoints specified in the SoA.

10.10.5. Ophthalmic Symptom Monitoring

Participants experiencing unexpected ophthalmic symptoms, including blurred vision, decreased visual acuity, or other clinically significant ocular AEs, without a known/suspected etiology may need to have repeat ophthalmoscopy and OCT testing performed.

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

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

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

If there is evidence of confirmed macular edema, then study treatment should be permanently discontinued, and the participant should be monitored closely with the appropriate diagnostic and clinical work-up.

These participants must be followed up monthly with ophthalmologic evaluations until such time as resolution is confirmed or no further improvement is expected by the ophthalmologist (based on a follow-up period of no less than 3 months).

These evaluations will include repeat best-corrected visual acuity, fundus examination, and OCT. FA may also be performed at the discretion of the ophthalmologist/optometrist (where permitted). If the participant does not show definite signs of improvement on examination by specialist testing (eg, OCT, FA) 6 to 8 weeks after interruption of study treatment, then therapy for macular edema in conjunction with an ophthalmologist/optometrist (where permitted) experienced in the management of this condition should be initiated.

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

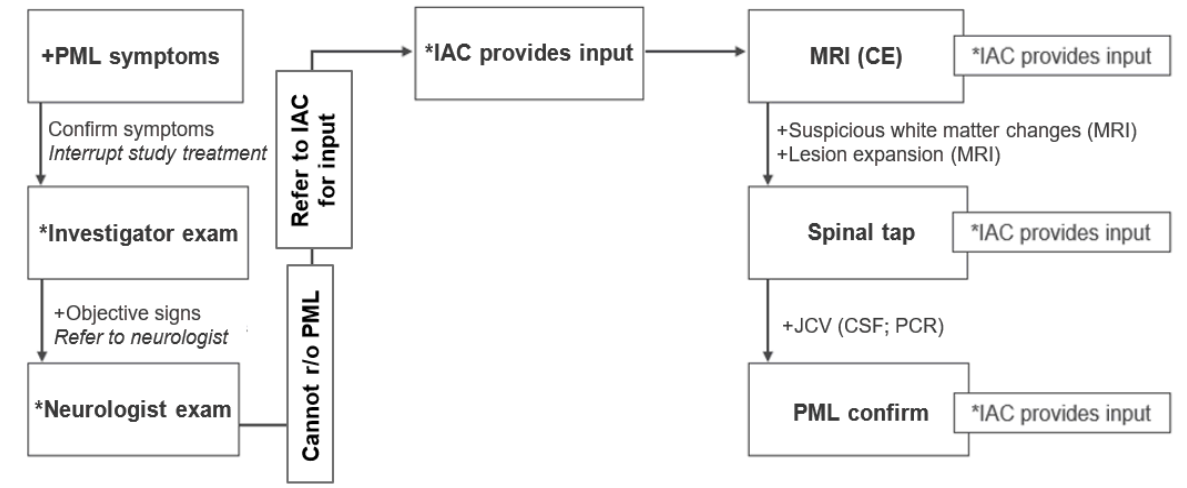
Information regarding ophthalmoscopy and OCT is provided in Section 8.3.10. Ophthalmoscopy and OCT will be performed at timepoints specified in the SoA.

10.11. Appendix 11: Guidance for the Assessment of Potential Progressive Multifocal Leukoencephalopathy

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

All suspected cases of PML will be adjudicated by an independent adjudication committee (refer to Section 4.2.3). The study medical monitor should be informed of any suspected cases of PML and, if needed, will facilitate Investigator/local neurologist consultation with PML medical experts on the independent adjudication committee.

Progressive Multifocal Leukoencephalopathy Case Evaluation Algorithm



*Note: Study treatment administration may resume, and no further evaluation is needed if the Investigator assessment reveals no objective signs of PML, the local neurologist confirms that the participant does not have PML, or the IAC's review of the evidence concludes that PML is ruled out.

10.12. Appendix 12: Abbreviations

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

Abbreviation	Term
Abs	absolute
AA	alopecia areata
AD	atopic dermatitis
ADL	activity/activities of daily living
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATS	American Thoracic Society
AV	atrioventricular
AxMP	auxiliary medicinal product
BCG	Bacillus Calmette-Guérin
β-hCG	β-human chorionic gonadotropin
BP	blood pressure
bpm	beats per minute
BSA	body surface area
CaPS	CDISC and Pfizer Standards
CBC	complete blood count
CD	cluster of differentiation
CD4	CD4 T lymphocytes
CDC	Centers for Disease Control
CDISC	Clinical Data Interchange Standards Consortium
CE	contrast-enhanced
CFP10	10-kDa culture filtrate protein
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
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization

Abbreviation	Term
CS	corticosteroid
CSF	cerebral spinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia suicide severity rating scale
CT	computed tomography/clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CT SAE	clinical trial serious adverse event
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DB	double-blind
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DLCO	diffusing capacity of lung for carbon monoxide
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index
EASI-50	≥50% reduction from Baseline in Eczema Area and Severity Index
EASI-75	≥75% reduction from Baseline in Eczema Area and Severity Index
EASI-90	≥90% reduction from Baseline in Eczema Area and Severity Index
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
E1	estimand 1
E2	estimand 2
ELISA	Enzyme Linked Immunosorbent Assay
EoE	eosinophilic esophagitis
EOS	end of study
EOT	end of treatment
ERS	European Respiratory Society
eSAE	electronic serious adverse event

Abbreviation	Term
ESAT6	Early Secreted Antigenic Target 6 kDa
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FA	fluorescein angiogram
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV ab	hepatitis C antibody
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IAC	independent adjudication committee
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IGA	Investigator's Global Assessment
IGRA	Interferon-Gamma Release Assays
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	Internet Protocol
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRT	Interactive Response Technology
JAK	janus kinase
JCV	John Cunningham Virus
JTC	Jump-to-Control

Abbreviation	Term
KDIGO	Kidney Disease: Improving Global Outcomes
LBBB	left bundle branch block
LFT	liver function test
LLQ	lower limit of quantification
LSM	Least squares mean
MDR	multi-drug resistance
MOA	mechanism of action
MMRM	mixed model repeated measures
MQI	medically qualified individual
MRI	magnetic resonance imaging
MS	multiple sclerosis
ms	millisecond
NCT	National Clinical Trials identifier
NIMP	noninvestigational medicinal product
NRS	numerical rating scale
OCT	optical coherence tomography
OL	open label
OLE	open label extension
PACL	Protocol Administrative Change Letter
PCP	primary care physician
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PDE-4	phosphodiesterase 4
PFT	pulmonary function test
PI	principal investigator
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
POEM	Patient-Oriented Eczema Measure
PPD	Purified Protein Derivative
PP-NRS	Peak Pruritus Numerical Rating Scale
PR	pulse rate
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
QD	once daily
QFT-G	QuantiFERON -TB Gold
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia’s formula
QTL	quality tolerance limit
qual	qualitative
RBC	red blood cell

Abbreviation	Term
RR	respiration rate
S1P	sphingosine 1-phosphate
$S1P_{1,4,5}$	S1P receptors 1, 4, and 5
S1PRM	sphingosine 1-phosphate receptor modulator
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr/Screat	serum creatinine
Scys	serum cystatin C
SE	standard error
SFU	safety follow-up
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TBNK	T and B lymphocyte and natural killer cell
T bili	total bilirubin
TCS	topical corticosteroids
Th2	type 2 helper cells
TOC	table of contents
UACR	urine albumin-to-creatinine ratio
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
vIGA	validated investigator's global assessment
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

10.13. Appendix 13: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 1 (07 December 2022)

Overall Rationale for the Amendment: Removal of inclusion of participants with a known history of HIV based on new clinical data of relevance for the investigator; clarifications for documentation and minor administrative changes.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
5.2 Exclusion Criteria	Removal of inclusion of participants with a known history of HIV	Based on new clinical data of relevance for the investigator.	Substantial
1.3.1, 1.3.2, 1.3.3 Schedule of Activities 10.2 Table 7 Clinical Laboratory Tests	Removal of testing specific for participants with a known history of HIV	Based on new clinical data of relevance for the investigator.	Substantial
5.2 Exclusion Criteria	Added exclusion of active diabetic retinopathy, macular edema or uveitis	Based on new clinical data of relevance for the investigator.	Substantial:
8.3.2 Blood Pressure and Pulse Rate 10.10.3. First-Dose Cardiac Monitoring	Clarification that pulse rate is collected as part of vital signs, and heart rate is collected as part of ECG.	Required for proper documentation.	Nonsubstantial
10.10.3.1 Cardiac Monitoring Schedule After First Dose	Clarification of required monitoring timepoints.	Required for proper documentation.	Nonsubstantial
6.9.2 Prior Treatments; 6.9.3 Prohibited	Clarification that live-attenuated replication-competent vaccines are prohibited.	Clarification of prohibited vaccines	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
During the Study; 6.9.5 Permitted During the Study			
6.1.1 Administration	Included missed doses during Week 16	Week 16 is the first Open Label dose of etrasimod	Nonsubstantial
6.5 Study Intervention Compliance	Removal of the possibility of dose reductions	Clarification since dose reduction is not allowed.	Nonsubstantial
Synopsis 4.1 Overall Design 9.4 Interim Analysis	Clarification that Sponsor conducts Interim Analysis and removed specific timing for the decision to start Part 2	For consistency between Sections 4.1 and 9.4	Nonsubstantial
8.2.1 Rater Qualifications	Clarification.	Administrative	Nonsubstantial
1.3.1, 1.3.3 Schedule of Activities	Study Day correction	Administrative	Nonsubstantial

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