TITLE PAGE

Protocol Title: A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTI-CENTER STUDY TO INVESTIGATE THE MECHANISM OF ACTION OF ABROCITINIB MONOTHERAPY IN ADULT PARTICIPANTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number: B7451037

Amendment Number: 3

Compound Number: PF-04965842

Study Phase: Phase 2a

Short Title: Study evaluating the mechanism of action of abrocitinib monotherapy for participants with moderate-to-severe atopic dermatitis

Acronym: JADE MOA

Sponsor Name: Pfizer, Inc.

Legal Registered Address: 235 East 42nd Street, New York, NY 10017-5755, USA

Regulatory Agency Identifier Number(s)

Registry	ID
IND	123554
EudraCT	Not Applicable

Approval Date: 12 November 2020

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	**11 Nov 2020**
Amendment 2	**10-Dec-2019**
Amendment 1	**05-Sep-2019**
Original Protocol	**22-Feb-2019**

Amendment 3 (30-Oct-2020)

Overall Rationale for the Amendment 3:

Section # and Name	Description of Change	Brief Rationale
Exclusion criteria#4	Added the following text: • Have increased risk of developing venous thromboembolism, e.g. deep vein thrombosis or pulmonary embolism: o History of venous thromboembolism, or o First-degree relative with unprovoked venous thromboembolism (i.e. without known underlying cause such as trauma, surgery, immobilization, prolonged travel, pregnancy, hormone use, or plaster cast), that would suggest participant is at increased risk of inherited	Per updated safety information, participants with increased risk of developing venous thromboembolism are excluded.

Section # and Name	Description of Change	Brief Rationale
	coagulation disorder (e.g. Factor V Leiden).	
Exclusion criteria #2 and 8.2.9	The participant must have a risk assessment done by a qualified Mental Health Professional (MHP) to assess whether it is safe to participate in the trial if the participant's responses on any of the screening instruments or other screening information indicate	Language changed from "should" to "must" and changed from "on more than 2 occasions" to "on 2 occasions"
8.2.9. Suicidal Ideation (Columbia Suicide Severity Rating Scale)	Participants who have recurrent SIB during the trial must be discontinued from the study and treated appropriately. If a participant endorses a 4 or 5 on the ideation subscale or any behavioral item of the C-SSRS on 2 occasions and is confirmed to have active SIB on both occasions by a risk assessment conducted by a qualified MHP, then the participant must be discontinued from the study and treated appropriately.	Language changed from "should" to "must" and changed from "on more than 2 occasions" to "on 2 occasions"
9.1. Estimands and Statistical Hypotheses	Text added: Participants need to have a baseline and week 12 assessment to be included in the analysis.	Added clarification to estimands and statistical hypotheses
9.5 Interim analysis	Text removed: There are no formal interim analyses planned. There will be a program-level EDMC (see below) who will periodically review the safety data from the study. Text added: After the first 15 participants have completed the study, there will be an interim analysis to examine platelet values. A longitudinal analysis will be conducted to determine if there is a change from baseline in platelet values. The data will remain blinded so that no one will know the participants' assigned treatment and thus the analysis will not analyse for any treatment differences. Correlation analyses may also be conducted to look for potential relationships	Added interim analysis

Section # and Name	Description of Change	Brief Rationale
	between platelet values and other laboratory measures, such as TPO. There will not be any decision rules associated with this interim analysis, so there will be no changes to the conduct or continuation of the trial based on these analyses.	
10.1.5	Added hepatic	Hepatic committee has been added on a program level
CCI [redacted]	[redacted]	[redacted]
Appendix 13. Alternative Measures During Public Emergencies Appendix	Added Alternative Measures During Public Emergencies Appendix	Language and an appendix were added to address COVID-19 and to describe alternative measures to be taken during public emergencies.
Sections 7.2, 8.3, and 10.3	Language from new protocol template has been incorporated.	Language updated per new protocol template.
Appendices 12, 13, 14, 15, 16 have been removed	Appendices have been removed to avoid any copyright issues when the protocol is publicly disclosed and in case any changes are made to the approved version.	Appendices removed per SciOPs recommendations.

Amendment 2 (10-Dec-2019)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	CCI [redacted]	[redacted]
1.3. Schedule of Activities	Addition of hematology assessment at Day 4.	Added timepoint considered important in understand time course of any changes.
1.3. Schedule of Activities	Blood collection for biomarker evaluation – updated to differentiate sample types and timepoints.	Amended for clarity.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	CCI [redacted]	[redacted]
1.3. Schedule of Activities	CCI [redacted]	[redacted]
2.0 Introduction - Abrocitinib Involvement in Hematopoiesis	Text amended and 'Both platelets and RBC derive from the same progenitor. Hence, changes in one compartment can affect the other.' added.	Amended for clarity.
3. Objectives, Estimands and Endpoints	CCI [redacted]	[redacted]
4.1 Overall Design	CCI [redacted]	[redacted]
4.1 Overall Design	CCI [redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]
8.1.6 Investigator's Global Assessment (IGA)	IGA amended to no longer exclude scalp, palms, and soles from the assessment/scoring.	To be consistent with other protocols in program.

Section # and Name	Description of Change	Brief Rationale
8.1.7 Eczema Area and Severity Index (EASI)	EASI amended to no longer exclude scalp, palms, and soles from the assessment/scoring.	To be consistent with other protocols in program.
8.1.7.1 Body Surface Area Efficacy	Assessment amended to include scalp, palms, and soles.	To be consistent with other protocols in program.
8.1.8 Hematopoiesis evaluation	Text amended and moved in part to section 8.8.	Amended for clarity.
CCI [redacted]	[redacted]	[redacted]
8.5 Pharmacokinetics	Sample volume amended from 'minimum 3.2 mL' to approximately 4 mL	To be consistent with other protocols in program.
[redacted]	CCI [redacted]	[redacted]
[redacted]	CCI [redacted]	[redacted]
8.8.2 Specified protein research	Section removed – details provided in section 8.8.	Removes duplication.
8.8.3 Specified gene expression research	Section removed – details provided in section 8.8.	Removes duplication.
[redacted]	CCI [redacted]	[redacted]

Amendment 1 (05-Sep-2019)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Columbia Suicide Severity Rating Scale (C-SSRS) assessments added to screening, baseline, Week 8, Week 12, and Week 16 visits.	Columbia-Suicide Severity Rating Scale (C-SSRS) has been added to on-study visits as a monitoring instrument for SIB for all participants in recognition of the heightened background risk of SIB in the patient population. Patients with medically significant SIB concerns identified during the study will be referred for an evaluation by a mental health professional to determine the appropriateness of continuing in the study.
1.3. Schedule of Activities	Addition of Patient Health Questionnaire – 8 Items (PHQ-8) to be administered at screening.	Patient Health Questionnaire – 8 Items will be administered at screening to assess participants' depression level.
1.3. Schedule of Activities	CCI [redacted]	[redacted]
2.2.3. Summary of abrocitinib Clinical Pharmacokinetics	Addition of the following text: Plasma profiling from the [14C] abrocitinib human mass balance study (B7451008) indicated parent as the most prevalent circulating species (26%), with 3 major and more polar mono-hydroxylated metabolites identified: PF-06471658 (3-hydroxypropyl, 11%), PF-07055087 (2-hydroxypropyl, 12%), and PF-07054874 (pyrrolidinone pyrimidine, 14%).	Background section has been updated by adding description of mass balance Study B7451008 findings.
3. Objectives, Estimands, and Endpoints	CCI [redacted]	CCI [redacted]
4. Study Design	CCI [redacted]	[redacted]
5.1. Inclusion Criteria	Clarification that documentation of inadequate response to topical therapy for AD must include 4 *consecutive* weeks of treatment.	Clarification that documentation of inadequate response to topical therapy for AD must include 4 *consecutive* weeks of treatment.

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Updated exclusion criteria on suicidal ideation. Removed text on active suicidal ideation from Exclusion Criterion 1 and updated Exclusion Criterion 2 to include risk assessment done by a qualified Medical Health Professional (MPH) to assess whether it is safe for the subject to participate in the trial. Addition of criteria for PHQ-8 assessment of clinically significant depression.	Exclusion criteria have been broadened, removing the exclusion of patients with suicidal ideation and behavior (SIB), to ensure patients with more severe AD are considered eligible for the study, thus improving the generalizability of the study. Patients with medically significant SIB concerns identified during screening will be referred for an evaluation by a mental health professional to determine the appropriateness of participation in the study.
5.2. Exclusion Criteria	Deleted text on details of Hepatitis B and Hepatitis C testing in Exclusion Criterion 7 and moved to Appendix 2.	Criterion was updated for greater clarity – details of reflex testing moved to Appendix 2.
5.2. Exclusion Criteria	Updated Exclusion Criterion 19 to change marked prolongation of QTcF interval from >450 to >500 milliseconds on the screening ECG and to delete text on history of additional risk factors for Torsade de Pointes and use of concomitant medications that prolong the QT/QTcF interval.	Criterion was updated based on results of thorough QT study.
5.4. Screen Failures	Added the following text: Individuals for whom screen failure is related to failing the disease severity (including extent of disease) inclusion criterion and who subsequently experience worsening AD, which in the investigator's judgement would make them eligible for participation, may be considered for re-screening. Such cases should be discussed with the Pfizer Medical Monitor (or designee) to determine if re-screening is appropriate.	Section was updated to clarify circumstances under which rescreening may be permitted.
6.5.2. Prohibited Medications and Treatments	Addition that excluded prior treatment with *systemic* JAK inhibitors and deleted parenthetical text of oral or topical.	Section was updated for consistency with eligibility criteria.
8.1.1. Rater Qualifications	Updated text to specify that clinical evaluations of atopic dermatitis (AD) should be performed by medical professional with experience in the conduct of *dermatology* clinical trials (not necessarily AD clinical trials) when designated by the primary site investigator.	Section was updated to allow less restrictive requirements for raters.

Section # and Name	Description of Change	Brief Rationale
8.1.9.1. Peak Pruritus Numerical Rating Scale (NRS)	Added the following text: The Peak Pruritus NRS as it is assessed on the day of the baseline visit will be included in the evaluation of Inclusion Criterion 2.	Section was updated for greater clarity.
8.2.8.1. Hepatitis Testing	Added text on the interpretation of Hepatitis B and Hepatitis C testing results for clarity.	Section was updated for greater clarity.
8.2.9. Suicidal Ideation	Updated text on administering and evaluation of C-SSRS and PHQ-8. Added text indicates that participants should have a risk assessment done by a qualified MHP to assess whether it is safe to participate in the trial if the participant's responses on any of the screening instruments or other screening information indicate this based on criteria provided.	Columbia-Suicide Severity Rating Scale (C-SSRS) has been added to on-study visits as a monitoring instrument for SIB for all participants in recognition of the heightened background risk of SIB in the patient population. Patients with medically significant SIB concerns identified during the study will be referred for an evaluation by a mental health professional to determine the appropriateness of continuing in the study.
8.2.9.1. Columbia Suicide Severity Rating Scale	Updated text on use of C-SSRS in SIB risk monitoring.	Section was updated to describe on-study monitoring of SIB risk factors
8.2.9.2. Patient Health Questionnaire - 8 Items (PHQ-8)	Addition of section to describe the administration of PHQ-8 to assess the subject’s depression level.	Section was updated to describe on-study monitoring of SIB risk factors
8.5. Pharmacokinetics	Updated text to change blood sample volumes from 8 mL to 3.2 mL, and additional text to include measurement of abrocitinib metabolites PF-06471658, PF-07055087, and PF-07054874.	Updated text to reflect analysis of abrocitinib metabolites.
8.8.2. Banked Biospecimens for Biomarkers	Change blood volume for Prep B2.5 from two 9 mL blood samples to one 4 mL blood sample.	Section was updated to correct the blood volume for Prep B2.5.
10.2. Appendix 2: Clinical Laboratory Tests	Removed routine analysis of specific gravity for consistency with abrocitinib program.	Section was updated for consistency with abrocitinib program.
10.2. Appendix 2: Clinical Laboratory Tests	Added HBV DNA testing for all countries; removed details that are explained elsewhere (redundancies).	Section was updated to clarify that HBV DNA reflex testing should be done regardless of geographic location.
10.10. Appendix 10: Monitoring and Discontinuation Criteria	Updated text that serious infection “must result in temporary interruption of study intervention. Study intervention cannot be restarted until the serious infection has resolved, and	Section was updated to provide investigators with greater clarity on how to handle potential discontinuations related to serious infection.

Section # and Name	Description of Change	Brief Rationale
	unless restarting study intervention has been discussed and agreed with the Pfizer medical monitor. If the participant cannot be restarted on study intervention within 21 days, or the infection is not resolved, or there is no agreement received from the Pfizer medical monitor to restart study intervention then the participant must be permanently discontinued from study intervention".	
Throughout	Minor typographical changes have been made throughout.	Typographical changes include biomarker names, eligibility criteria, cross-references, PK schedule and storage, and analysis set description.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTI-CENTER STUDY TO INVESTIGATE THE MECHANISM OF ACTION OF ABROCITINIB MONOTHERAPY IN ADULT PARTICIPANTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS
Short Title: Study evaluating the mechanism of action of abrocitinib monotherapy for participants with moderate-to-severe atopic dermatitis

Rationale:
Abrocitinib is a Janus kinase 1 (JAK1) inhibitor and is being developed as an oral treatment for participants with moderate-to-severe atopic dermatitis (AD).

Objectives, Estimands and Endpoints

Primary Objective	Primary Endpoint
• To assess the effects of abrocitinib on lesional and non-lesional skin biomarkers of adult participants with moderate-to-severe AD.	• Changes from baseline in AD biomarkers in skin, including biomarkers for general inflammation (MMP12), hyperplasia (K16), Th2 immune response (CCL17, CCL18, CCL26), and Th22 immune response (S100A8, S100A9, S100A12).
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of abrocitinib on gene expression (evaluated by mRNA PCR and/or gene arrays).	• Changes from baseline in gene expression (evaluated by mRNA PCR and/or gene arrays) over time in skin lesions.
• To evaluate the effect of abrocitinib on inflammatory infiltrates (T-cell and dendritic cells) using immunohistochemistry (IHC) in skin biopsies.	• Changes from baseline in cellular (T-cells and dendritic cells) markers using IHC in skin biopsies at various time points.
• To evaluate the effect of abrocitinib on epidermal hyperplasia using IHC and RT-PCR in skin biopsies.	• Changes from baseline in hyperplasia markers (thickness, K16, Ki67) in skin biopsies.
• To assess the effect of abrocitinib on blood biomarkers (OLINK proteomic in serum).	• Changes from baseline in blood biomarkers (OLINK proteomic

	microassay for inflammation and immune response in serum).
• To assess changes in T-cell lymphocyte subset populations in blood using flow cytometry.	• Changes from baseline in T-cell lymphocyte subset populations in blood using flow cytometry.
• To evaluate the effect of abrocitinib on pruritus and its correlation to IHC and genetic markers in lesional skin.	• Response based on at least 4 points improvement in the severity of Peak Pruritus numerical rating scale (NRS) from baseline and change from baseline in IHC and genetic markers in lesional skin.
Efficacy Objective	Efficacy Endpoints
• To evaluate the effect of abrocitinib on clinical efficacy outcomes.	• Response based on the Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at all scheduled time points. • Response based on the Eczema Area and Severity Index ≥75% improvement from baseline (EASI-75) response at all scheduled time points. • Response based on at least 4 points improvement in the severity of Peak Pruritus NRS from baseline at all scheduled time points. • Response based on a ≥50% and ≥90% improvement in the EASI total score (EASI-50 and EASI-90) at all scheduled time points. • Change from baseline in the percentage Body Surface Area (BSA) affected at all scheduled time points.
Safety Objective	Safety Endpoints
• To evaluate the safety and tolerability of abrocitinib during 12 weeks of treatment.	• Incidence of treatment-emergent adverse events (TEAEs). • Incidence of serious AEs (SAEs).

	• Incidence of AEs leading to discontinuation. • Incidence of clinical abnormalities and changes from baseline in clinical laboratory values, and vital signs.
Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
• CCI [redacted]	[redacted]
• To assess the effect of abrocitinib on Night Time Itch.	• Changes from baseline in the Night Time Itch Scale at all scheduled time points.
• CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The primary objective of this study is to assess the effects of abrocitinib on lesional and non-lesional skin biomarkers of adult participants with moderate-to-severe AD. The following estimand attributes will be considered:

- Population: Participants with moderate-to-severe AD as defined by the inclusion criteria;

- Variable: Fold-change from baseline in the biomarkers for general inflammation (MMP12), hyperplasia (K16), type 2 helper T cell (Th2) immune response (CCL17,

CCL18, CCL26), and type 22 helper T cell (Th22) immune response (S100 calcium binding protein A [S100A8], S100A9, S100A12);

- Intercurrent event: All data collected will be utilized;
- Population-level summary: Mean fold-change from baseline within each treatment group.

Overall Design:
This is a randomized, double-blind, placebo-controlled, parallel-group, Phase 2a study to investigate the mechanism of action of abrocitinib by correlating efficacy outcomes with changes from baseline in key skin and blood biomarkers in adult participants ≥18 years of age with moderate-to-severe AD. Participants will be screened within 28 days prior to the first dose of study intervention to confirm study eligibility. A total of approximately 51 participants will be randomized in a 1:1:1 ratio to receive abrocitinib 200 mg once daily (QD), abrocitinib 100 mg QD, or matching placebo QD for 12 weeks.

The double-blind treatment period will last from Baseline/Day 1 to Week 12. Lesional skin biopsy (punch biopsy) collections are required at Baseline/Day 1 (Week 0), Day 29 (Week 4), and Day 85 (Week 12), with an optional lesional skin biopsy collection at Day 15 (Week 2). Non-lesional skin biopsy collection is required at Baseline/Day 1 (Week 0), with an optional non-lesional skin biopsy collection at Day 85 (Week 12).

The skin biopsy samples will be analyzed using immunohistochemistry (IHC) and gene expression by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), including Taqman Low Density Array (TLDA) PCR, for 48 genes including 2 housekeeping genes (18S and ribosomal protein lateral stalk subunit P0 [RPLP0]), as well as single gene PCR for a few genes that are often below detection level on TLDA. CCI [redacted]

Blood for analyses of changes in inflammatory and cardiovascular markers will be collected at various time points. CCI [redacted] Red Blood Cell and platelets derive from a common progenitor. Blood for platelet and red blood cell (RBC) counts will be collected and analyzed at all scheduled time points to characterize the potential mechanism by which platelet counts decrease in a dose-dependent and self-limited manner after abrocitinib administration. OLINK proteomics will be used to analyze biomarkers in serum, including 4 panels of inflammatory and cardiovascular measures.

At the end of the 12-week study treatment, qualified participants will have the option to enter the long-term extension (LTE) Study B7451015. Participants discontinuing early from this study will undergo a 4-week off-treatment follow-up period.

Disclosure Statement:
This is a Parallel Treatment study with 3 Arms that is Investigator, sponsor, and participant blinded.

Number of Participants:
A total of approximately 51 participants will be randomized in the study.

Intervention Groups and Duration:
Eligible participants will be randomized into 3 intervention groups in the study:

Group 1 (N=17): abrocitinib 200 mg QD for 12 weeks.

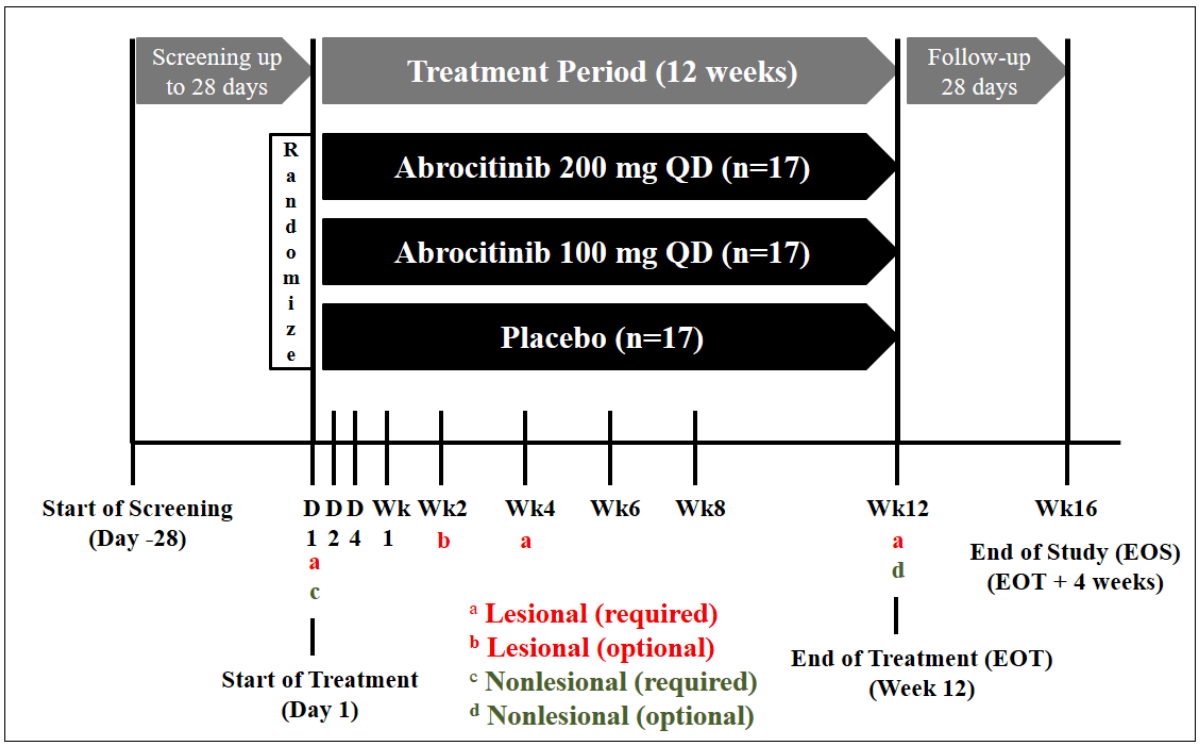
Group 2 (N=17): abrocitinib 100 mg QD for 12 weeks.

Group 3 (N=17): placebo QD for 12 weeks.

The total duration of participation in the study is up to 20 weeks, including up to 4 weeks for screening, 12 weeks study intervention, and a follow-up period of 4 weeks after study intervention (for those participants who do not enter the LTE study).

Data Monitoring Committee: Yes

1.2. Schema


Screening up to 28 days
Treatment Period (12 weeks)
Follow-up 28 days
Randomize
Abrocitinib 200 mg QD (n=17)
Abrocitinib 100 mg QD (n=17)
Placebo (n=17)
Start of Screening (Day -28)
D1 a c
D2
D4
Wk1
Wk2 b
Wk4 a
Wk6
Wk8
Wk12 a d
Wk16
End of Study (EOS) (EOT + 4 weeks)
Start of Treatment (Day 1)
End of Treatment (EOT) (Week 12)
[a] Lesional (required)
[b] Lesional (optional)
[c] Nonlesional (required)
[d] Nonlesional (optional)

1.3. Schedule of Activities (SoA)

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Base line**	**Day 2 Week 0**	**Day 4 Week 0**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 43 Week 6 (by Phone)**	**Day 57 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
Visit Window (days)	**None**	**None**	**None**	**±1**	**±1**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	
Enrollment Procedures												
Informed consent	X											
Register participant using IRT	X											See Section 6.3
Inclusion and exclusion criteria	X	X										See Section 5.1 and Section 5.2
Demographics, medical history, tobacco and alcohol history, AD disease history and prior AD treatments	X											See Section 8.2.1
Review prior/concomitant medications & treatments	X	X	X	X	X	X	X	X	X	X	X	

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1** **Week 0** **Base line**	**Day 2** **Week 0**	**Day 4** **Week 0**	**Day 8** **Week 1** **(by Phone)**	**Day 15** **Week 2**	**Day 29** **Week 4**	**Day 43** **Week 6** **(by Phone)**	**Day 57** **Week 8**	**Day 85** **Week 12** **(EOT/ET)**	**Day 113** **Week 16** **(EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
Provide patient emergency contact card	X											
Medical Procedures												
Complete physical examination	X									X		See Section 8.2.1
Targeted physical exam		X				X	X		X		X	
Vital signs (blood pressure, pulse rate, respiratory rate, temperature)	X	X				X	X		X	X	X	See Section 8.2.2
Weight	X									X		See Section 8.2.1
Height	X											See Section 8.2.1
Chest X-Ray	X											See Section 8.2.3
ECG (12-lead)	X											See Section 8.2.7
Laboratory Procedures												

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Base line**	**Day 2 Week 0**	**Day 4 Week 0**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 4 3 Week 6 (by Phone)**	**Day 5 7 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
Serum chemistry	X	X				X	X		X	X	X	See Appendix 2. See Section 8.2.8 for guidance on abnormal lab results
Hematology including Reticulocyte Count and Coagulation panel.	X	X		X		X	X		X	X	X	See Appendix 2. See Section 8.2.8 for guidance on abnormal lab results
Lipid panel		X								X		8-hour fast required
CCI [redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Blood collection for biomarker evaluation – Serum proteomics		X				X	X			X		See Section 8.8
CCI [redacted]		[redacted]					[redacted]			[redacted]		See Section 8.8

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Base line**	**Day 2 Week 0**	**Day 4 Week 0**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 4 3 Week 6 (by Phone)**	**Day 5 7 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
CCI [redacted]		[redacted]		[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	See Section 8.1.8
CCI [redacted]							[redacted]			[redacted]		[redacted] ee Section 8.5
Lymphocyte subsets		X		X		X			X	X	X	See Appendix 2
Urinalysis	X	X				X	X		X	X	X	See Appendix 2
Serum pregnancy test	X											Required for all WOCBP
Urine Pregnancy Test (conducted at study site)		X				X	X		X	X	X	

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Base line**	**Day 2 Week 0**	**Day 4 Week 0**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 4 3 Week 6 (by Phone)**	**Day 5 7 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
Banked Biospecimen Sample (Prep D1)		X										See Section 8.7.2 If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.
Banked Biospecimen Sample (Prep B1.5)		X								X		See Section 8.8.2
Banked Biospecimen Sample (Prep B2.5)		X								X		See Section 8.8.2
Blood samples collection for viral studies		X										Only analyzed on suspected viral infection/reactivation. See Section 8.2.8.2
HIV testing	X											See Appendix 2

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Base line**	**Day 2 Week 0**	**Day 4 Week 0**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 4 3 Week 6 (by Phone)**	**Day 5 7 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
Hepatitis B (HBsAg, HBsAb and HBcAb) and Hepatitis C (HCV Ab, HCV RNA)	X											See Section 8.2.8.1
HBV DNA (Only when HBsAg-, HBcAb+, HBsAb+ at screening)	X									X		See Section 8.2.8.1
Tuberculosis test	X											See Section 5.2 and Section 8.2.4
Study Treatment												
Randomization		X										
Drug dispensing		X					X		X			
Drug accountability						X	X		X	X		

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1** **Week 0** **Base line**	**Day 2** **Week 0**	**Day 4** **Week 0**	**Day 8** **Week 1** **(by Phone)**	**Day 15** **Week 2**	**Day 29** **Week 4**	**Day 43** **Week 6** **(by Phone)**	**Day 57** **Week 8**	**Day 85** **Week 12** **(EOT/ET)**	**Day 113** **Week 16** **(EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
Study intervention treatment		X----------X										At Weeks 4 and 12, study intervention treatment should be taken at the study site to accommodate PK analysis. See Section 8.5
Assess eligibility for LTE Study B7451015										X		
Clinical Assessments												
Fitzpatrick Skin Type Assessment		X										See Section 8.2.6
Investigator's Global Assessment (IGA)	X	X				X	X		X	X	X	See Section 8.1.6
Eczema Area and Severity Index (EASI)	X	X				X	X		X	X	X	See Section 8.1.7
Skin Biopsies												

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Base line**	**Day 2 Week 0**	**Day 4 Week 0**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 4 3 Week 6 (by Phone)**	**Day 5 7 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
Target lesion(s) identification		X										See Section 8.1.2
Lesional skin punch biopsy sampling		X				X (Optional)	X			X		See Section 8.1.2
Non-lesional skin punch biopsy sampling		X								X (Optional)		See Section 8.1.2
Examination of Post-biopsy Site(s)		X	X	X		X	X		X	X	X	See Section 8.1.2
CCI [redacted]		[redacted]	[redacted]			[redacted]	[redacted]			[redacted]		[redacted]
CCI [redacted]		[redacted]				[redacted]	[redacted]			[redacted]		[redacted]
Photography		X					X			X		See Section 8.1.5

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1** **Week 0** **Base line**	**Day 2** **Week 0**	**Day 4** **Week 0**	**Day 8** **Week 1** **(by Phone)**	**Day 15** **Week 2**	**Day 29** **Week 4**	**Day 43** **Week 6** **(by Phone)**	**Day 57** **Week 8**	**Day 85** **Week 12** **(EOT/ET)**	**Day 113** **Week 16** **(EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
Patient-reported Outcomes (PRO)												
Peak Pruritus Numerical Rating Scale (NRS)	X-----X	X----------X					X		X	X	X	See Section 8.1.9.1. During screening, assessed for the 7 days prior to Day 1 and also each day from Day 1 to Day 15.
Night Time Itch Scale	X-----X	X----------X					X		X	X	X	See Section 8.1.9.2. During screening, assessed for the 7 days prior to Day 1 and also each day from Day 1 to Day 15.
Safety												
C-SSRS	X	X							X	X	X	See Section 8.2.9.1

	Screening	Intervention Period									Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Base line**	**Day 2 Week 0**	**Day 4 Week 0**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 43 Week 6 (by Phone)**	**Day 57 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 11 is 4 weeks after last dose in case of early study termination.
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	
PHQ-8	X											See Section 8.2.9.2
Serious and non-serious adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	
Contraception check	X	X	X	X	X	X	X	X	X	X	X	Required for all females

Abbreviations: AD = atopic dermatitis; C-SSRS = Columbia Suicide Severity Rating Scale; EASI = Eczema Area and Severity Index, ECG = electrocardiogram; EOS = End of Study, EOT = End of Treatment; ET= early termination; HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HBcAb = hepatitis B core antibody; HBV DNA = hepatitis B viral deoxyribonucleic acid, HCV Ab = hepatitis C antibody; HCV RNA = hepatitis C viral ribonucleic acid; HIV = human immunodeficiency virus; CCI [redacted], IGA = Investigator's Global Assessment; IRT = Interactive Response System; LS = lesional; LTE = long-term extension; NL = non-lesional; NRS = Numerical Rating System; PHQ-8 = Patient Health Questionnaire - 8 Items; PK = Pharmacokinetic; WOCBP = women of childbearing potential.

2. INTRODUCTION

Abrocitinib is a Janus kinase 1 (JAK1) inhibitor that is being investigated as a treatment for patients with moderate-to-severe AD.

The Janus kinase (JAK) family, including JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival, and function. Cytokine receptors demonstrate restricted association with JAKs such that different receptors or receptor classes preferentially utilize a given JAK dimer combination to transduce their signal. JAK1 pairs with JAK3 to mediate γ-common cytokine signaling and also with JAK2 or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses, including interleukin (IL)-4, IL-5, IL-6, IL-13, IL-21, IL-31, interferon-gamma (IFN-γ), and IFN-alpha (IFN-α). JAK2 homodimers are critical for the signaling of hematopoietic cytokines and hormones, including thrombopoietin (TPO), erythropoietin (EPO), IL-3, granulocyte-macrophage colony-stimulating factor, and prolactin. IL-12, EPO, and IL-23 are dependent on TYK2 and JAK2 for transmitting their signals.

Following cytokine activation, receptor-associated JAKs are phosphorylated and in turn phosphorylate specific sites on the receptor intracellular domain. Phosphorylation of specific sites on the intracellular domain of the receptor allows for the recruitment of signal transducers and activators of transcription (STATs) that can subsequently be phosphorylated by JAKs. Phosphorylated STAT molecules are released from the receptor, translocate to the nucleus where they bind to specific sites on deoxyribonucleic acid (DNA), and regulate gene transcription.

The inflammatory skin disorder AD is characterized by epidermal barrier dysfunction and active AD lesions are accompanied by underlying immune activation.[1,2,3] Skin lesions have shown increased infiltration by T cells, dendritic cells (DCs), and eosinophils; increased production of cytokines and chemokines; and reactive epidermal hyperplasia, in which epidermal differentiation products (ie, filaggrin and loricrin) are highly suppressed.[4,5,6] Although AD has been classified as a Th2-dominated disease, other T-cell subsets (eg, Th22, Th17, and Th1 cells) might also contribute to pathogenesis.[2,3] Key cytokines implicated in the pathophysiology of AD include IL-4, IL-5, IL-13, IL-31, and IFN-γ. These cytokines require JAK1 for signal transduction suggesting that selective JAK1 inhibitors, which modulate the activity of these cytokines, represent a compelling approach to the treatment of inflammatory skin diseases such as AD.[7]

Data from a Phase 2b proof of concept (POC) study (B7451006) that evaluated participants with moderate-to-severe AD showed positive efficacy with the JAK1 inhibitor abrocitinib, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program. Abrocitinib is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. Abrocitinib has a high degree of selectivity in vitro against other kinases: 28-fold selectivity over JAK2, >340-fold over JAK3 and 43-fold over TYK2, as well as a good selectivity profile over the broader range of human kinases.

Abrocitinib Involvement in Hematopoiesis

In Study B7451006 there were dose-dependent decreases in mean platelet counts in the abrocitinib 200 mg once daily (QD) and 100 mg QD doses with a nadir at Week 4 (200 mg QD: -29.84%; 100 mg QD: -11.42%). Platelet counts resolved on treatment and returned to baseline by 4 weeks after end of treatment. The majority of participants maintained platelet counts within the normal range. No participant had an AE related to sequelae from thrombocytopenia (ie, bleeding or bruising). In addition, changes in total reticulocytes (absolute) were observed in all treatment groups, but were generally not clinically relevant. The abrocitinib 200 mg QD group had the greatest mean percent change from baseline in reticulocytes, for which decreases from baseline were observed during Week 1 to Week 6 with a maximal decrease at Week 2, and increases from baseline were observed during Week 8 to Week 16.

The human body produces and removes 10^{11} platelets daily to maintain a normal steady-state platelet count. Platelet production must be tightly regulated to avoid spontaneous bleeding or arterial occlusion and organ damage. Multifaceted and complex mechanisms control platelet removal and production in physiological and pathological conditions. Production of red blood cells (RBCs) is a highly regulated process; however, the time of RBCs in circulation is longer (approximately 120 days) than that of platelets (8-9 days). Reticulocytes (immature RBCs that mature to RBCs in 2-3 days) have a shorter time, and as such, may be a more sensitive indicator of JAK inhibition on RBC production. Both platelets and RBC derive from the same progenitor. Hence, changes in one compartment can affect the other.

The Ashwell-Morrell receptor (AMR) recognizes senescent, desialylated platelets under steady-state conditions.[8] Desialylated platelets and the AMR are the physiological ligand-receptor pair regulating hepatic TPO messenger ribonucleic acid (mRNA) production, resolving the longstanding question of steady-state TPO regulation. The AMR-mediated removal of desialylated platelets regulates TPO synthesis in the liver by recruiting JAK2 and STAT3 to increase thrombopoiesis. Inhibition of TPO production downstream of the hepatic AMR-JAK2 signaling cascade could additionally contribute to thrombocytopenia associated with JAK1/2 treatment.

2.1. Study Rationale

Abrocitinib is being developed as an oral treatment for patients with moderate-to-severe AD based on the clinical results obtained in Phase 1 and Phase 2 studies. Additional information for the Phase 1 and Phase 2 study results previously completed may be found in the Investigator's Brochure (IB). Phase 3 studies are ongoing to evaluate abrocitinib as monotherapy or when co-administered with background medicated topical therapy in adults or adolescents with AD.

This study (B7451037) is designed specifically to evaluate abrocitinib monotherapy in adults with AD to characterize the mechanism of action of abrocitinib and assess the effects of abrocitinib on the molecular signature of JAK1 inhibition in lesional and non-lesional skin and its correlation to clinical efficacy outcomes. The JAK1 AD Study B7451006 showed dose-dependent, self-limited decrease in platelet counts, but did not provide any mechanistic

insights. CCI [redacted]

2.2. Background

Atopic dermatitis, also known as eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in quality of life. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the United States (US).[9,10] AD is one of the most common, chronic, relapsing childhood dermatoses, impacting 15-30% of all children in the US and many have disease that persists into adulthood. Earlier reports indicated that, in up to 70% of cases, the disease greatly improved or resolved by late childhood, however more recent findings suggest that disease activity remains manifest for a prolonged period of time. Based on a total of 7157 patients enrolled in the Pediatric Eczema Elective Registry (PEER) study, comprising a total of 22,550 person-years, it was concluded that symptoms associated with AD seem to persist well into the second decade of life and likely longer.[11] The majority of studies conducted across multiple age groups suggest a continued decrease in prevalence with older age.[12] Adult-onset AD does also occur, though it is less common. The prevalence of AD in adults is estimated to be approximately 10%.[13]

Although much progress has been made in understanding the causes of AD, the complex pathophysiology of AD is still not completely understood. It has been established that the pathophysiology of AD includes a defective skin barrier function, abnormal immune responses, defective antimicrobial immune defense, and a genetic predisposition. The predominant symptoms of AD, pruritus and the resulting scratching, typically sets off an amplification cycle of atopic skin inflammation. Activation of T lymphocytes, dendritic cells, macrophages, keratinocytes, mast cells, and eosinophils results in a release of numerous pro-inflammatory cytokines and chemokines. This amplification cycle sustains the inflammatory responses characteristic of the AD lesions.[14]

Non-medicated topical therapies include emollients. Medicated topical therapies for moderate-to-severe AD include topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) (eg, pimecrolimus, tacrolimus). Additional treatments generally reserved for severe AD include phototherapy (eg, ultraviolet A light [UVA] with or without psoralen, ultraviolet B light [UVB] narrowband or broadband) and systemic agents.[15] For AD patients not responding to medicated topical therapies and phototherapy, on- and off-label use of systemic agents, which include oral corticosteroids, oral immunosuppressants, or the injectable human monoclonal antibody targeting IL-4 and IL-13, dupilumab, remain the last viable AD treatment options.

Currently available therapies for the treatment of AD have multiple limitations and drawbacks. For example, TCI have a limited role as a second-line treatment, due to their limitations in terms of the duration of treatment and the body region of treatment, and safety

concerns with malignancies. Also, systemic therapy options are associated with potentially severe adverse effects and require careful monitoring; therefore, the use of these agents is limited to short courses or intermittent therapy. Furthermore, the globally approved dosing for dupilumab as an initial dose of 2 × 300 mg subcutaneous injection followed by 300 mg every other week injections may limit the desirability of this route of treatment.

Of the currently available therapies, none offers a cure; therefore, the main aims of existing treatments are to reduce the occurrence of acute flares, to increase the time between relapses, and to reduce pruritus and the resulting sleep disturbance.[16,17]

Abrocitinib is an orally active JAK1 inhibitor that has demonstrated clinical efficacy in the Phase 2 Study B7451006. As mentioned above, a variety of pro-inflammatory cytokines such as IL-4, IL-5, IL-13, thymic stromal lymphopoietin (TSLP), IL-31 and IFN-γ, have been suggested to have a role in the pathogenesis of AD. Many of these pathogenic cytokines use JAK1 for signaling. Therefore, JAK1 is an attractive therapeutic target for AD. However, a dose-dependent platelet decrease has been observed during the JAK1 development program, and the mechanism causing this is poorly understood. Data from this study will describe the molecular signature of JAK1 inhibition in healthy and AD lesional skin, as well as investigating the mechanism by which abrocitinib might decrease platelet counts in participants with moderate-to-severe AD.

2.2.1. Non-Clinical and Phase 1 Data

Data from nonclinical and Phase 1 programs supports the planned clinical trials with abrocitinib and further information is in the current version of the IB.

2.2.2. Phase 2b in AD (B7451006)

B7451006 was a Phase 2b proof-of-concept trial in 269 adults (ages 18-75) with moderate-to-severe AD investigating doses of 10, 30, 100, and 200 mg abrocitinib or placebo taken once daily for up to 12 weeks. The primary endpoint was the proportion of participants achieving an Investigator's Global Assessment (IGA) score of clear (0), or almost clear (1), and a ≥2-point improvement from baseline at Week 12. The baseline was defined as the IGA score on Day 1 pre-dose.

At Week 12, IGA response rates of the abrocitinib 200 mg and 100 mg dose groups were significantly greater than the placebo group, 44.5%, 27.8% and 6.3%, respectively. As a result, the estimated differences from placebo in the 200 mg and 100 mg groups were 38.2% (P=0.0032) and 21.5% (P=0.0184), respectively. The percent change from baseline in Eczema Area and Severity Index (EASI) scores at Week 12 were significantly higher for both the 200 mg and 100 mg groups compared to placebo, 63.7%, 41.6%, and 15.6% respectively. At Week 12, the proportion of participants achieving EASI-75 response was 15.6% in the placebo group, 63.7% in the 200 mg group and 41.6% in the 100 mg group. As a result, the difference from placebo was 41.8% (P<0.0001) for the 200 mg group and 26.0% (P=0.0043) in the 100 mg group. Response rates at Week 12 for the 10 mg and 30 mg groups were not significantly different from placebo.

At Day 15, the proportion of response based on achieving Peak Pruritus numerical rating scale 4 points improvement from baseline (NRS4) of abrocitinib 100 mg and 200 mg dose groups was greater than placebo. The estimated proportion of Peak Pruritus NRS4 responses at Day 15 were 69.8%, 41.1% and 15.7% for 200 mg, 100 mg and placebo groups, respectively.

Abrocitinib demonstrated a rapid onset of action. In the 200 mg group, IGA and EASI scores improved until Week 4 and Week 6, respectively, and maintained their effect through 12 weeks of treatment. A key differentiating feature for the JAK1 inhibitor is rapid resolution of itch associated with AD. Significant separation from placebo was achieved for the Peak Pruritus numerical rating scale (NRS) score as early as 2 days after initiation of treatment for the 200 mg dose group.

Overall, the results demonstrated dose dependent increases in responses at Week 12 for key efficacy endpoints (IGA, EASI and Peak Pruritus NRS).

Abrocitinib was generally safe and well tolerated in this study. Overall, adverse events (AEs) and serious AEs (SAEs) were numerically higher in participants receiving abrocitinib compared to placebo, but did not appear to increase with dose. The most common AEs were in the Infections and infestations, skin and subcutaneous tissue disorders and Gastrointestinal disorders system organ class, and the majority of the AEs were mild. There were 2 cases of herpes zoster, one in the 10 mg group (not treatment-related), and one in the 30 mg group (treatment-related). In the AD Phase 2 Study B7451006, there were dose-dependent decreases in mean platelet counts in the 200 mg QD and 100 mg QD doses with a nadir at Week 4 (200 mg QD: -29.84%; 100 mg QD: -11.42%). Platelet counts were resolving on treatment and returned to baseline by 4 weeks after end of treatment. Further details of the clinical Phase 2 development program can be found in the IB.

2.2.3. Summary of Abrocitinib Clinical Pharmacokinetics

Abrocitinib was rapidly absorbed following single dose oral solution/suspension administration over the dose range 3 mg to 200 mg with time to maximum absorption (T_{max}) ranging between 0.55 to 0.77 hours (B7451001). Median T_{max} at doses of 400 mg and 800 mg was 1.5 and 3.9 hours, respectively, which indicated slower absorption compared to lower doses. Abrocitinib showed a monophasic decline at dose <100 mg with biphasic profiles at doses ≥100 mg. Observed abrocitinib maximum plasma concentrations (C_{max}) following the single dose administration generally increased in proportion to the dose from 3 mg to 800 mg. In contrast, both area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}) and area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUC_{last}) were dose proportional in the range of 3 mg to 200 mg, while a greater than proportional increase was observed at doses of 400 and 800 mg. The arithmetic mean terminal phase half-life ($t_{½}$) was 1.9 to 4.9 hours.

Following QD administration over the dose range 30 mg to 400 mg and 100 mg and 200 mg twice a day (BID) for 10 days, median T_{max} ranged between 0.50 to 0.77 hours (B7451001). After attainment of C_{max}, the disposition of abrocitinib was consistent with that

observed following single-dose administration, showing a biphasic decline following all but the lowest dose and an arithmetic mean terminal phase $t_{½}$ between 2.8 to 5.0 hours. The observed accumulation ratio (R_{ac}) for area under the curve over dosing interval tau (AUC_{tau}) and C_{max} following QD dosing was minimal (between 1.1 and 1.5), consistent with the prediction from $t_{½}$. Urinary recovery of abrocitinib was low, with <5% of the dose recovered unchanged in urine across all doses and regimens in all cohorts.

At a single 800 mg dose, the geometric mean percent coefficient of variation (%CV) C_{max} (ng/mL) was similar in Western (n=5; 3819 [26]) and Japanese participants (n=10; 3660 [48]). However, geometric mean AUC_{inf} (ng*hr/mL) was 26% higher in Western participants (n=5; 27540 [35]) than that observed in Japanese participants (n=9; 21860 [43]) (B7451001). Geometric mean (%CV) C_{max} and AUC_{tau} following multiple dose administration of 200 mg BID were 17% and 56% higher, respectively, in the Western participants (n=5) than in Japanese participants (n=6).

Co-administration of 400 mg with food resulted in equivalent geometric mean AUC_{inf} between fasted and fed conditions and a small mean decrease (<5%) in C_{max}. Overall, abrocitinib can be administered with or without food.

Plasma profiling from the [14C] abrocitinib human mass balance study (B7451008) indicated parent as the most prevalent circulating species (26%), with 3 major and more polar mono-hydroxylated metabolites identified: PF-06471658 (3-hydroxypropyl, 11%), PF-07055087 (2-hydroxypropyl, 12%), and PF-07054874 (pyrrolidinone pyrimidine, 14%).

2.2.4. Population Pharmacokinetics

Population pharmacokinetics (PK) analysis was conducted by pooling data from two Phase 1 studies (B7451001, first-in-human study, and B7451004, relative bioavailability study) in healthy volunteers and the proof-of-concept study (B7451006) in AD patients. A total of 2465 PK observations from 354 participants were included in the analysis and the data were described using a 2 compartment model with first-order absorption. The estimates of systemic clearance/fraction of dose absorbed (CL/F) and volume of distribution/fraction absorbed (V/F) were 44.8 L/hr and 147 L with inter individual variability (IIV) values of 63% and 35% (expressed as %CV), respectively. Apparent clearance (CL/F) of AD patients was estimated to be ~38% lower than that of healthy participants; residual variability was estimated to be higher in AD patients compared to the value in healthy participants (66% vs. 36% CV). Baseline body weight, race, age and sex were tested as covariates on clearance and did not appear to impact the PK of abrocitinib.

2.3. Benefit/Risk Assessment

There was clinically meaningful benefit demonstrated for abrocitinib 200 mg QD and 100 mg QD in the Phase 2b POC study in adult participants with moderate-to-severe AD. The potential risks of treatment include those that were noted in Phase 2b and/or those based on the known pharmacology of other well studied JAK inhibitors (such as tofacitinib) and include viral reactivation, serious and opportunistic infections, hematopoietic effects (including decreases in platelet counts), malignancy and immunoproliferative disorders.

Overall, there is a favorable benefit-risk profile to support the continued development into Phase 3 of abrocitinib for the treatment of participants with AD.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of abrocitinib is provided in the IB, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Primary Objective	Primary Endpoint
• To assess the effects of abrocitinib on lesional and non-lesional skin biomarkers of adult participants with moderate-to-severe AD.	• Changes from baseline in AD biomarkers in skin, including biomarkers for general inflammation (MMP12), hyperplasia (K16), Th2 immune response (CCL17, CCL18, CCL26), and Th22 immune response (S100A8, S100A9, S100A12).
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of abrocitinib on gene expression (evaluated by mRNA PCR and/or gene arrays).	• Changes from baseline in gene expression (evaluated by mRNA PCR and/or gene arrays) over time in skin lesions.
• To evaluate the effect of abrocitinib on inflammatory infiltrates (T-cell and dendritic cells) using immunohistochemistry (IHC) in skin biopsies.	• Changes from baseline in cellular (T-cells and dendritic cells) markers using IHC in skin biopsies at various time points.
• To evaluate the effect of abrocitinib on epidermal hyperplasia using IHC and RT-PCR in skin biopsies.	• Changes from baseline in hyperplasia markers (thickness, K16, Ki67) in skin biopsies.
• To assess the effect of abrocitinib on blood biomarkers (OLINK proteomic in serum).	• Changes from baseline in blood biomarkers (OLINK proteomic microassay for inflammation and immune response in serum).
• To assess changes in T-cell lymphocyte subset populations in blood using flow cytometry.	• Changes from baseline in T-cell lymphocyte subset populations in blood using flow cytometry.

• To evaluate the effect of abrocitinib on pruritus and its correlation to IHC and genetic markers in lesional skin.	• Response based on at least 4 points improvement in the severity of Peak Pruritus numerical rating scale (NRS) from baseline and change from baseline in IHC and genetic markers in lesional skin.
Efficacy Objective	Efficacy Endpoints
• To evaluate the effect of abrocitinib on clinical efficacy outcomes.	• Response based on the Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5 point scale) and a reduction from baseline of ≥2 points at all scheduled time points. • Response based on the Eczema Area and Severity Index ≥75% improvement from baseline (EASI-75) response at all scheduled time points. • Response based on at least 4 points improvement in the severity of Peak Pruritus NRS from baseline at all scheduled time points. • Response based on a ≥50% and ≥90% improvement in the EASI total score (EASI-50 and EASI-90) at all scheduled time points. • Change from baseline in the percentage Body Surface Area (BSA) affected at all scheduled time points.
Safety Objective	Safety Endpoints
• To evaluate the safety and tolerability of abrocitinib during 12 weeks of treatment.	• Incidence of treatment-emergent adverse events (TEAEs). • Incidence of serious AEs (SAEs). • Incidence of AEs leading to discontinuation. • Incidence of clinical abnormalities and changes from baseline in clinical laboratory values, and vital signs.

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
• CCI [redacted]	[redacted]
• To assess the effect of abrocitinib on Night Time Itch.	• Changes from baseline in Night Time Itch Scale at all scheduled time points.
• CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The primary objective of this study is to assess the effects of abrocitinib on lesional and non-lesional skin biomarkers of adult participants with moderate-to-severe AD. The following estimand attributes will be considered:

- Population: Participants with moderate-to-severe AD as defined by the inclusion criteria;
- Variable: Fold-change from baseline in the biomarkers for general inflammation (Matrix Metallopeptidase [MMP]12), hyperplasia (Keratin [K]16), Th2 immune response (C-C motif chemokine ligand [CCL]17, CCL18, CCL26), and Th22 immune response (S100 calcium binding protein A [S100A]8, S100A9, S100A12);
- Intercurrent event: All data collected will be utilized;

- Population-level summary: Mean fold-change from baseline within each treatment group.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel-group, Phase 2a study to investigate the mechanism of action of abrocitinib by correlating efficacy outcomes with changes from baseline in key skin and blood biomarkers in adult participants ≥18 years of age with moderate-to-severe AD. Participants will be screened within 28 days prior to the first dose of study intervention to confirm study eligibility. A total of approximately 51 participants will be randomized in a 1:1:1 ratio to receive abrocitinib 200 mg QD, abrocitinib 100 mg QD, or matching placebo QD for 12 weeks. Refer to Section 1.2 for a study schema.

The total duration of participation in the study is up to 20 weeks, including up to 4 weeks for screening, 12 weeks study intervention, and a follow-up period of 4 weeks after study intervention. Qualified participants completing 12 weeks of treatment with study intervention will have the option to enter the long-term extension (LTE) study B7451015. Participants discontinuing early from this study will undergo a 4-week off-treatment follow-up.

Participants who have chronic moderate-to-severe AD as defined per the inclusion criteria will be enrolled in this study. Eligible participants must have a documented history, within 6 months of the screening visit, of inadequate response to treatment with medicated topical therapy, or must have required systemic therapies for control of their disease. Investigators, participants, and the sponsor study team will be blinded as to treatment group assignment. Prior to any study procedure the informed consent will be obtained at the screening visit.

Participants will be screened within 28 days prior to the first dose of study intervention to confirm study eligibility. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. All treatments for AD must have been washed out prior to Day 1 (see Section 5.2). Participants who continue to meet eligibility criteria at baseline will undergo Baseline/ Day 1 assessments and will be randomized in a 1:1:1 ratio to receive abrocitinib 200 mg (N=17) or abrocitinib 100 mg QD (N=17) or matching placebo QD (N=17) from Day 1.

The double-blind treatment period will last from Baseline/Day 1 to Week 12. For all participants, one 4.5 mm skin biopsy (punch biopsy) will be collected from each target treatment area at the specified time points. Lesional skin biopsies will be collected at Baseline/Day 1 (Week 0), Day 29 (Week 4), and Day 85 (Week 12), with an optional lesional skin biopsy collection at Day 15 (Week 2). A non-lesional skin biopsy will be collected at Baseline/Day 1 (Week 0), with an optional non-lesional skin biopsy collection at Day 85 (Week 12). CCI [redacted]

Biopsy samples will be used to perform gene expression by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), including Taqman Low Density Array (TLDA) PCR, for 48 genes including 2 housekeeping genes (18S and RPLP0), as well as single gene PCR for a few genes that are below detection level on TLDA (see Table 1). CCI [redacted] Immunohistochemistry (IHC) analysis will be performed for cellular infiltrates, Keratin 16 (K16) staining, and hematoxylin and eosin (H&E) staining.

Many of the genes to be analyzed in this study are considered key biomarkers associated with AD pathways. For this study, the following biomarkers were selected for the primary endpoint: general inflammation (MMP12), hyperplasia (K16), Th2 immune response (CCL17, CCL18, CCL26), and Th22 immune response (S100A8, S100A9, S100A12).

CCI [redacted]

The efficacy outcomes (eg, IGA, EASI, % body surface area [%BSA], and peak pruritus numerical rating scale [PP-NRS]) are collected so that any associations between biomarker changes and these efficacy outcomes may be evaluated. The clinical improvement will be correlated with the suppression of individual immune pathways, cellular infiltrates, and changes in epidermal biomarkers. Differences between groups and changes from baseline will be estimated. Tests of hypotheses for differences between treatment groups will not be performed.

Safety will be assessed by physical exams, standard laboratory testing, and collection of AEs.

Refer to the Schedule of Activities for a complete list of assessments to be performed during the study.

4.2. Scientific Rationale for Study Design

This study is part of the global clinical development program for abrocitinib investigating the safety and efficacy of doses of 200 mg QD and 100 mg QD. This study is designed to specifically evaluate the mechanism of action of abrocitinib in adults with AD.

4.3. Justification for Dose

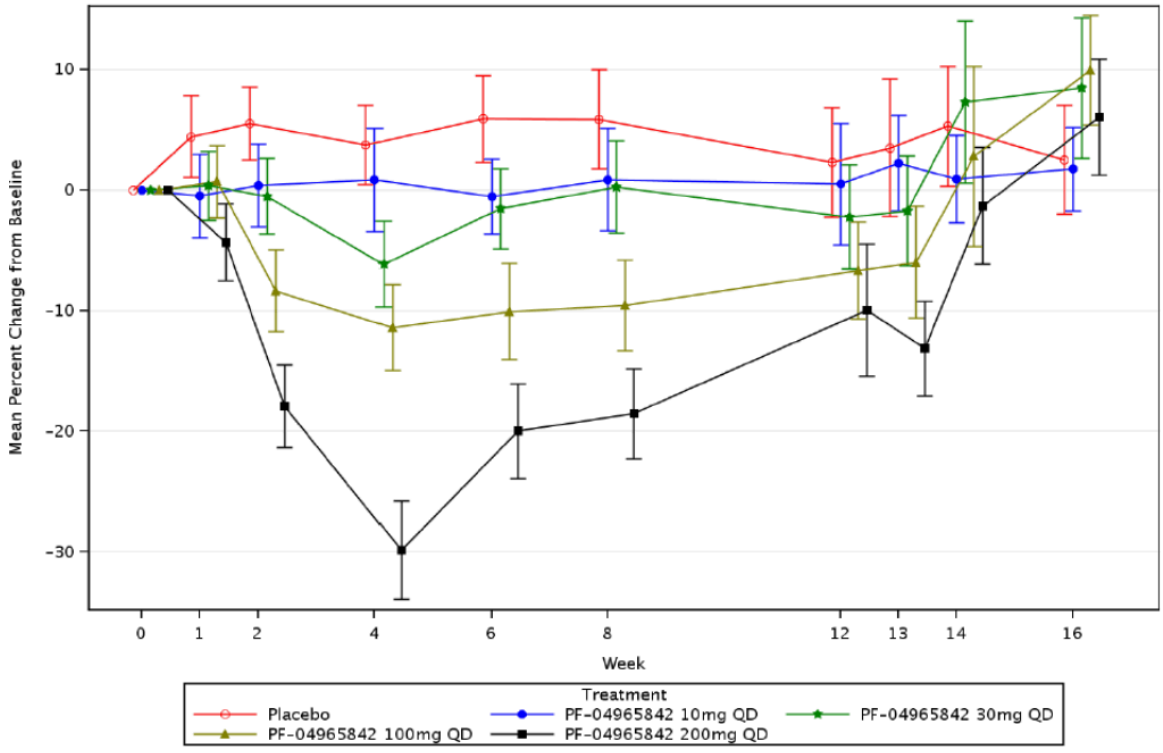
Dose selection for Phase 3 was based on efficacy and safety of abrocitinib from a dose-ranging Phase 2b study, B7451006 that evaluated a 20-fold dose range (10 mg to 200 mg QD) in adults with moderate-to-severe AD.

Specifically for this study, both doses used in the Phase 3 program (100 mg QD and 200 mg QD) were selected based on the observed efficacy and the separation observed between doses

in the IGA and of EASI responses, as well as the dose-dependent changes observed in different hematologic parameters from this study. The inclusion of both doses will enable the assessment of efficacy and safety outcomes, skin molecular signatures, and the impact on markers of hemostasis, platelet counts, and other cell types.

In Study B7451006, both the abrocitinib 200 mg QD and 100 mg QD doses demonstrated acceptable safety and tolerability. A dose-dependent decrease in the mean platelet count from baseline was observed with a nadir at Week 4 (Figure 1). At Week 4, the mean platelet count and the 90% confidence interval (CI) were within the normal reference range for the 100 mg dose and 200 mg dose. The mean platelet counts increased towards baseline after Week 4. In addition, there was a decrease in mean reticulocyte count in the 200 mg QD group with a nadir at Week 2 (-14.73%). The mean reticulocyte count returned to baseline on treatment by Week 8. Leukopenia, neutropenia, and thrombocytopenia were reported by 1 participant in the 200 mg group, all of which were moderate and treatment-related. The platelet level in this participant was less than 0.5 × lower limit of normal. There were no reported adverse clinical effects (eg, bleeding events) potentially associated with reduced platelet counts observed in Study B7451006. Further details are available in the IB.

Figure 1. Mean (90% CI) Percent Change from Baseline Versus Time for Platelets



4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including follow-up assessments after the End of Treatment (EOT) or rolled over into LTE Study B7451015 after EOT. Details of early termination are provided in Section 7.

The end of the study is defined as the date of the last study visit shown in the Schedule of Activities for the last participant at the study sites.

5. STUDY POPULATION

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

1. Participant must be ≥18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who meet the following AD criteria:

   - Clinical diagnosis of chronic moderate-to-severe AD (also known as atopic eczema) for at least 1 year prior to Day 1 and has confirmed AD at the screening and baseline visits according to the Hanafin and Rajka criteria for AD[20] (see Appendix 11).

   - Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with medicated topical therapy for AD for at least 4 consecutive weeks or who have required systemic therapies for control of their disease.

     NOTE: Medicated topical therapy is defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over-the-counter [OTC] or prescribed product).

   - Moderate-to-severe AD (affected BSA ≥10%, IGA ≥3, EASI ≥16, severity Peak Pruritus NRS ≥4 at the baseline visit).

3. Must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet (UV) light sources during the study.
4. If receiving concomitant medications for any reason other than AD, must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to Day 1 and through the duration of the study.

Sex

5. Male or Female

Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:

No contraceptive measures required.

b. Female participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP) (see definition in Appendix 4)

  OR

- Is a WOCBP (all female participants, regardless of whether or not they have experienced/reported menarche, are considered WOCBP unless they are permanently sterile or confirmed infertile). A WOCBP who is sexually active must use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the intervention period and for at least 28 days after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive (Appendix 2) serum pregnancy test at the screening visit. A urine pregnancy test with a sensitivity of at least 25 mIU/mL, will be performed before the first dose of study intervention and at every site visit including the EOT and follow-up visits to confirm the participant has not become pregnant. 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 from participation if the serum pregnancy result is positive.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

6. Capable of giving signed informed consent/assent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
7. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

5.2. Exclusion Criteria

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

Medical Conditions

1. Other acute or chronic medical condition or laboratory abnormality that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.
2. The participant must have a risk assessment done by a qualified Mental Health Professional (MHP) to assess whether it is safe to participate in the trial if the participant's responses on any of the screening instruments or other screening information indicate:
    - 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) (Section 8.2.9);
    - Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS;
    - Any lifetime history of serious or recurrent suicidal behavior (non-suicidal self-injurious behavior is not a trigger for a risk assessment unless in the investigator's judgement it is indicated);
    - Clinically significant depression: PHQ-8 when the total score is ≥ 15;
    - The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria;
    - In the investigator's judgment a risk assessment or exclusion is required.
3. A current or past medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction.
4. Have increased risk of developing venous thromboembolism, e.g. deep vein thrombosis or pulmonary embolism:
    a. History of venous thromboembolism, or
    b. First-degree relative with unprovoked venous thromboembolism (i.e. without known underlying cause such as trauma, surgery, immobilization, prolonged travel, pregnancy, hormone use, or plaster

cast), that would suggest participant is at increased risk of inherited coagulation disorder (e.g. Factor V Leiden).

5. Currently have active forms of other inflammatory skin diseases, ie, not AD or have evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, lupus) at the time of Day 1 that would interfere with evaluation of AD or response to treatment.
6. Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of investigational product, or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of investigational product.
7. Have a history of any lymphoproliferative disorder such as Epstein Barr virus (EBV)-related lymphoproliferative disorder, history of lymphoma, leukemia, or signs or symptoms suggestive of current lymphatic or lymphoid disease.
8. Infection History:

    - Have a history of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1;

    - Have active chronic or acute skin infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to Day 1, or superficial skin infections within 1 week prior to Day 1.

    - A participant known to be infected with human immunodeficiency virus (HIV), Hepatitis B, or Hepatitis C (Section 8.2.8.1).

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

9. Have a history of alcohol or substance abuse within 6 months prior to Day 1 that in the opinion of the investigator will preclude participation in the study.
10. Have a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.
11. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.
12. Have evidence of active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB) as evidenced by any of the following:

    - A positive QuantiFERON®-TB Gold (QFT-G) In-Tube test or positive Mantoux/Purified Protein Derivative (PPD)/ tuberculin skin test (if appropriate per Section 8.2.4) performed at or within the 12 weeks prior to Day 1 is exclusionary; a negative test is required for eligibility. QFT-G is

the preferred testing method. If the QFT-G test cannot be performed, or if the results cannot be determined by the reference laboratory to be either positive or negative, then participants may be screened using the PPD test with approval of the Pfizer clinician.

- It is recommended that participants with a history of Bacille Calmette Guérin (BCG) vaccination be tested with the QFT-G test since the Mantoux/PPD/tuberculin skin test may be positive due to vaccination. A QFT-G or PPD skin test is not required if the participant has previously received a documented adequate course of therapy for either latent or active TB infection.

- A negative QFT-G or PPD skin test is required unless the participant has previously received a documented adequate course of therapy for either latent (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. 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;

- Chest X-ray (or chest computed tomography scan, or magnetic resonance imaging [MRI]) taken at screening or 12 weeks prior to Day 1 with changes suggestive of active TB infection as determined by a qualified radiologist.

- A history of either untreated or inadequately treated latent or active TB infection;

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

Prior/Concomitant Therapy

13. Require treatment with prohibited concomitant medication(s) (Section 6.5.2 and Appendix 7) or have received a prohibited concomitant medication within the specified time frame prior to the first dose of study medication.
14. Receiving anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, anti-platelets, novel oral anticoagulants (eg apixaban), antiplatelet medication (eg clopidogrel), or has a contraindication to skin biopsies, or medications known to cause thrombocytopenia, (unless considered safe to stop and washout for the duration of the study). Nonsteroidal anti-inflammatory drugs [NSAIDs] and low-dose acetyl salicylic acid will not be considered antiplatelet therapy.

15. Participants who have received prior treatment with any systemic JAK inhibitors.
16. Have received any of the following treatment regimens specified in the time frames outlined below:

Within 1 year of first dose of study intervention:

- Prior treatment with non-B-cell-specific lymphocyte depleting agents/therapies (eg, alemtuzumab [CAMPATH®], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc). Participants who have received rituximab or other selective B lymphocyte depleting agents (including experimental agents) are eligible if they have not received such therapy for at least 1 year prior to study baseline and have normal cluster of differentiation (CD) 19/20+ counts by fluorescence-activated cell sorting (FACS) analysis.

Within 12 weeks of first dose of study intervention:

- Biologics: within 12 weeks of first dose of study intervention or 5 half-lives (if known), whichever is longer.

Within 6 weeks of first dose of study intervention:

- Use of dupilumab.

Within 4 weeks of first dose of study intervention:

- Use of oral immunosuppressive drugs (eg, cyclosporine A [CsA], azathioprine, methotrexate, systemic corticosteroids, mycophenolate-mofetil, IFN-γ) within 4 weeks of first dose of study intervention or within 5 half-lives (if known), whichever is longer;

  NOTE: Corticosteroid inhalers and intranasal sprays are permissible for participants receiving a stable dose.

  NOTE: Ophthalmic corticosteroids are permissible for participants receiving a stable dose.

- Use of CYP2C9 and CYP2C19 inducers within 5 half-lives of the inducer plus 14 days prior to the first dose of study intervention. For example, the average half-life of Carbamazepine after repeat dosing is 15 hours. The washout period is calculated as the sum of 5 half-lives (approximately 3 days) and an additional 14 days for a total of 17 days prior to the first dose of study intervention.

  Note: Half-life refers to the half-life of the parent drug and its metabolites, which are inhibitors or inducers. The longest half-life should be used to calculate the period necessary to washout a medication prior to the first dose of study intervention. For example, fluoxetine and its metabolite norfluoxetine are both

inhibitors of CYP2C19. The terminal half-life of fluoxetine is up to 6 days. However, norfluoxetine has a longer half-life, up to 16 days. Therefore, the washout period should be calculated based on the 5 times the half-life of norfluoxetine (approximately 80 days) and an additional 14 days for a total of 94 days prior to the first dose of study intervention.

- Phototherapy narrowband UVB (NB-UVB) or broad band phototherapy;
- Regular use (more than 2 visits per week) of a tanning booth/parlor;
- Herbal medications with unknown properties or known beneficial effects for AD.

Within 1 week of first dose of study intervention:

- Use of CYP2C9 and CYP2C19 inhibitors within 1 week of first dose of study intervention or within 5 half-lives (if known) of the inhibitor, whichever is longer.
- Anti-platelet drugs.

Note: low dose acetyl salicylic acid is permitted, for the purpose of cardiovascular prophylaxis, at the discretion of the investigator.

Within 72 hours of first dose of study intervention:

- Topical treatments that could affect atopic dermatitis (eg, corticosteroids, calcineurin inhibitors, tars, antibiotic creams, topical antihistamines).

Prior/Concurrent Clinical Study Experience

17. Participation in other studies involving investigational drug(s) within 8 weeks or within 5 half-lives (if known) whichever is longer, prior to study entry and/or during study participation.
18. Note: Any investigational or experimental therapy taken or procedure performed for AD, psoriasis, psoriatic arthritis, or rheumatoid arthritis in the previous 1 year should be discussed with the Pfizer clinician (or designee). Participants cannot participate in studies of other investigational or experimental therapies or procedures at any time during their participation in this study.

Diagnostic assessments

19. **ANY** of the following abnormalities in the clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:
    - Absolute neutrophil count of $<1.2 \times 10^9$/L ($<1200/mm^3$);

- Hemoglobin <10.0 g/dL or hematocrit <30%;
- Platelet count of <150 x 10^9/L (<150,000/mm^3);
- Absolute lymphocyte count of <0.50 x 10^9 /L (<500/mm^3);
- Estimated creatinine clearance <40 mL/min based on the age appropriate calculation, or serum creatinine >1.5 times the upper limit of normal (ULN);
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 times the ULN;
- Total bilirubin ≥ 1.5 times the ULN; participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN.

20. A Screening 12-lead electrocardiogram (ECG) that demonstrates clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy- or brady-arrhythmias) or that are indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads, Wolff Parkinson White syndrome) or criteria associated with Q wave interval (QT)/ Fridericia-corrected Q wave interval (QTcF) abnormalities including:
    - A marked prolongation of QTcF interval (>500 milliseconds [ms]) on the screening ECG.

Other Exclusions

21. In the opinion of the investigator the participant is not a candidate for skin biopsy due to potential for complications, including but not limited to increased bleeding risk associated with history of bleeding disorders (acquired or inherited); use of antithrombotic agents; blood dyscrasias; delayed wound healing; compromised nutritional status; or uncontrolled diabetes.
22. In the opinion of the investigator or sponsor, have any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the participant's participation in the study.
23. Have undergone significant trauma or major surgery within 1 month of the first dose of study intervention.
24. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

1. On study visit days, participants must not take the dose of study intervention until instructed to do so by the investigator or designated study site staff.

2. On study visit days, showering or bathing is permitted prior to attending the study visit.

3. On study visit days, topical therapy (ie, non-medicated topical therapy, per protocol guidelines as described in Section 6.5.1) are not permitted to be applied prior to attending the study visit. Topical therapies are required to be applied after the visit (per protocol guidelines as described in Section 6.5.1).

4. At Weeks 4 and 12, study intervention treatment should be taken at the study site to accommodate PK analysis.

5. WOCBP participants who are sexually active must agree to use one highly effective method of contraception (as specified in Appendix 4), as applicable.

5.3.1. Meals and Dietary Restrictions

On study visit days (Day 1 and Week 12), participants must comply with fasting requirements for at least 8 hours prior to the visit. Water and permitted non-study medications are allowed (Section 8.2.8).

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will abstain from using tobacco products or ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for at least 30 minutes before pulse rate and blood pressure measurements.

5.3.3. Surgery

During the study, no elective surgery is permitted. However, if the proposed procedure is not judged to have any significant impact on the participant's study assessments and treatment, then their case may be discussed with the Pfizer clinician or designee and an allowance made for their continued participation. Preferably, elective surgery should occur before the study or be delayed until study participation is completed.

The Pfizer clinician or designee should be notified if a participant requires surgery (including dental surgery) during the study to determine whether the participant should discontinue from the study and/or discontinue study intervention prior to the surgical procedure. In general, planned surgical procedures should not be performed unless the study intervention has been discontinued for at least 28 days (unless otherwise advised by the Pfizer clinician or designee). The Pfizer clinician or designee should be notified as soon as possible if a participant undergoes a surgical procedure without first informing the study staff.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once after discussion with Pfizer if they fail the screening evaluation for reasons related to incidental transitory conditions. Individuals for whom screen failure is related to failing the disease severity (including extent of disease) inclusion criterion and who subsequently experience worsening AD, which in the investigator's judgement would make them eligible for participation, may be considered for re-screening. Such cases should be discussed with the Pfizer Medical Monitor (or designee) to determine if re-screening is appropriate.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The interventions are abrocitinib (also known as PF-04965842) and placebo. Abrocitinib will be administered orally at doses of 100 mg or 200 mg given QD for 12 weeks based on treatment assignment. In addition, one treatment group will be assigned to receive abrocitinib-matching placebo.

See the Schedule of Activities for drug dispensing and accountability details.

6.1. Study Intervention(s) Administered

Abrocitinib 100 mg tablets and matching placebo will be provided by the sponsor.

ARM Name	Abrocitinib 200 mg QD	Abrocitinib 100 mg QD	Placebo
Intervention Name	Abrocitinib	Abrocitinib	Placebo
Type	Small molecule	Small molecule	Placebo
Dosage Form	Tablet	Tablet	Tablet
Dose Strength	100 mg	100 mg	0 mg
Dosage	100 mg – 2 tablets	100 mg – 1 tablet Placebo – 1 tablet	Placebo – 2 tablets
Route of Administration	Oral	Oral	Oral

Sourcing	Provided centrally by the sponsor.	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.	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.

QD = once daily

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention 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 or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4. Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Product (IP) Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinded study using central randomization via IRT system.	Participants will be randomized into the study on Day 1 provided they have signed an informed consent document to participate in the study, have undergone all screening procedures, and have met all inclusion and none of the exclusion criteria for participation in the study at screening and Day 1. A computer-generated randomization schedule will be used to assign participants to the treatment groups using an Interactive Response Technology (IRT). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, protocol number, the participant number and the date of birth of the participant. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when abrocitinib / placebo study intervention is being supplied via the IRT. Treatment assignment will be based on a central randomization list consisting of

	randomly permuted blocks. The IRT system will provide a confirmation report containing the participant number and DU or container number assigned. The confirmation report must be stored in the site's files. There is a 24 hour-a-day, 365 days-a-year IRT help desk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT. Note: The IRT is the source of the participant number. The IRT system will provide the participant number at the end of the first IRT participant transaction.

Blind Break (IRT)	Investigators, participants and the sponsor study team will be blinded as to treatment group. The study will be participant (including caregiver) and investigator blinded. At all times, treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, or the sponsor's study team until following the conclusion of the study, with the exception described in this section. At the initiation of the study, the study site will be instructed on procedures for breaking the blind. Blinding codes should only be broken in emergency situations for reasons of participant safety. The method will be an electronic process. When the blind for a participant has been broken, the reason must be fully documented and entered on the Case Report Form (CRF). Whenever possible, the investigator should contact Pfizer before breaking the blind. If the blind is broken, the investigator should promptly inform the Pfizer Clinician. The participant for whom the blind has been broken will be discontinued from the study and undergo the early termination (ET) procedures.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

For self-administration of abrocitinib / placebo at home, compliance will be recorded by the participant.

When study intervention is administered at the study site (Weeks 4 and 12 to accommodate PK analysis), it will be administered under the supervision of study personnel.

Compliance with the dosing of study intervention will be monitored and verified by delegated site personnel through a combination of the accounting of unused study intervention returned by the participant at the study visits, review of the dosing diary, and discussion with the participant which will be documented in the source documents.

Study intervention should be taken in the morning. Participants should be instructed that if a dose is inadvertently missed then it should be taken as soon as remembered, but not within 12 hours of the next scheduled dose.

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

- Participants interrupting study intervention for more than 4 consecutive days or for a total of more than 7 days between visits;
- Participants administering >8 tablets in one day or administering ≥4 tablets/day for 4 consecutive days;
- Participants who have an overall compliance of <80% or >120% between visits.

Any deviation from protocol specified dosing should be recorded as a protocol deviation and the investigator or designee is to counsel the participant 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 8.3.10).

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

The Pfizer clinician should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking new prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit (see Appendix 7 for washout periods for CYP2C9 and CYP2C19 inhibitors and inducers), unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Participants will abstain from all prohibited concomitant medications as described in Section 6.5.2 and Appendix 7, of the protocol. Medications that are taken in the Screening/Washout period (after informed consent is obtained and before the first dose of study intervention) will be documented as prior medications. Medications taken after the first dose of study intervention has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in study records with indication (if AD), reference to any associated adverse event, dose, and start and stop dates of administration. Participants will be queried about concomitant medication (including topical medications and treatments, over-the-counter and prescription medications and treatments, and vaccinations) at each study visit. Any new concomitant medications or dose changes to current concomitant medications should be evaluated for potential new or worsening adverse events.

6.5.1. Permitted Concomitant Treatments

The following concomitant AD standard-of-care therapies are permitted during the study and will not be provided by the sponsor:

- Oral antihistamines;
- Topical non-medicated emollient.

The following concomitant standard-of-care medications for other conditions are permitted during the study:

- Corticosteroid inhalers and intranasal sprays are allowed for stable asthma patients;
- Ophthalmic corticosteroids are allowed for patients receiving a stable dose to treat rhinoconjunctivitis;
- Low dose acetyl salicylic acid (≤100 mg QD) is permitted, for the purpose of cardiovascular prophylaxis, at the discretion of the investigator;
- Acetaminophen/paracetamol may be used intermittently (not to exceed 1 g/day);
- Vitamin and mineral supplements of standard potency are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis).

For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, and purified food substances. Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (eg, hypervitaminosis).

Unless prohibited by the protocol, participants may be administered any other medications necessary for the treatment of medical disorders as deemed necessary by the treating physician. The addition of concomitant medications or any change in the dosage should be limited to those considered medically essential.

A participant who is receiving a permitted concomitant medication for any reason must be on a locally-approved medication and dose, and this must be documented in the CRF. Participants are not allowed any other investigational drugs or treatments during the study.

Participants should refrain from starting new or changing doses of permitted prescription or non-prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to Day 1 and prior to study visits throughout the study, unless otherwise noted below.

Participants should report any changes to permitted medications during the study to the investigator as soon as they occur. Medication changes must be documented in the participant's record and eCRF.

6.5.2. Prohibited Medications and Treatments

Participants are required to discontinue and avoid using certain medications and treatments (see Inclusion Criteria and Exclusion Criteria and Appendix 7). Participants should be instructed at each visit to contact the study site investigator promptly if there are any intended changes or additions to concomitant medications.

All medications and treatments that could affect AD must be discontinued except oral antihistamines.

Due to the potential to affect AD with ultraviolet light exposure, participants must also avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.

Participants who received prior treatment with systemic JAK inhibitors are to be excluded from the study.

Herbal medications with unknown properties or known beneficial effects for AD must be discontinued at least 4 weeks before the first dose of study intervention.

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

6.6. Dose Modification

Dose modification of the study intervention is not permitted in this study.

6.7. Intervention after the End of the Study

There is no intervention required by the protocol following the end of the study. Participants may enroll in the LTE study if eligible.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In certain instances, it may be necessary for a participant to permanently discontinue study intervention (ie, study treatment). If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for EOT assessments (per Schedule of Activities).

Note that discontinuation of study treatment does not represent withdrawal from the study. Refer to Appendix 10 for discontinuation criteria.

See the Schedule of Activities for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

Temporary interruption to dosing is not allowed in this study, except when specified in the protocol for participant safety.

7.2. Participant Discontinuation/Withdrawal from the Study

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

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

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the Schedule of Activities 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

If a participant withdraws from the study, he/she 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 should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

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 him or her 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 he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Participants will be screened (Visit 1) within 28 days prior to administration of the study intervention to confirm that they meet the participant selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each participant, in accordance with the procedures described in Section 10.1.3.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF 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 Schedule of Activities.
- Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results; the last value will be used to determine eligibility. If results return to normal within the 4-week screening period, the participant may enter the study.
- Due to possible need for PPD testing and chest radiograph, screening procedures may be performed over more than 1 visit in the 28 days prior to the Day 1 visit.
- Visit windows are based on Day 1 visit. To assure consistency and reduce variability, all study visits should occur in the morning whenever possible. On days of study visits, participants will receive their dose at the clinic during the visit.
- Participants are required to fast for at least 8 hours prior to all visits that include lipid profile panel testing (Day 1 and Week 12). During the fasting period, participants should refrain from all food and liquids (water and permitted non-study medications are allowed).
- Urine pregnancy test must be performed prior to dosing with the study intervention for WOCBP through the EOT/EOS visit specified in the Schedule of Activities.
- Prior to attending a study visit, participants are allowed to shower and bathe but should not moisturize or apply emollient.

8.1. Efficacy Assessments

8.1.1. Rater Qualifications

Clinical evaluations of AD will be performed by an experienced and qualified dermatologist (board certified or equivalent). An experienced and qualified non-dermatologist physician or experienced medical professional with experience in the conduct of dermatology clinical trials may be permitted to perform the clinical evaluations of AD 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 assure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual participant throughout the study whenever possible**; a back-up 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.

8.1.2. Skin Biopsies

One 4.5 mm skin biopsy (punch biopsy) will be collected from each target lesional skin at Baseline/Day 1 (Week 0), Day 29 (Week 4), and Day 85 (Week 12), with an optional collection on Day 15 (Week 2). The target lesional skin to be used for skin biopsy should be selected pre-dose at the Baseline/Day 1 visit. An area of non-lesional skin anatomically similar in location to the target lesional skin should also be selected for biopsy on Day 1, with optional collection on Day 85. Biopsies at all time points following the visit at Baseline/Day 1 will always be collected from the same area, even if the target treatment area has cleared, in order to assess molecular clearance.

Ideally, a single target, approximately the size of the palm of the participant's hand, should be identified and the location and borders noted in the clinic chart; anatomical markers should be used as needed to describe the target skin location. A photograph of the lesional and non-lesional site(s) will also be taken (see Section 8.1.5). The target skin should be of sufficient size to accommodate the required number of biopsies specified in the protocol (eg, 3 biopsies) while not interfering with the clinical evaluation of the lesion; the potential biopsy sites should be pre-selected.

The biopsies after Day 1 will be collected in the vicinity of the torso (upper and mid back, chest), abdomen, buttocks, upper arms and upper legs, but at least 1 cm distant from where the biopsies were collected at Day 1, even if the target lesion has cleared. Target lesions may not be located on the head, face, neck, elbows, knees, lower arms, lower legs, genital area and inguinal area, intertriginous areas, and lower back.

Each biopsy will be cut in half. One half will be used to perform reverse transcriptase polymerase chain reaction (RT-PCR) and gene array and the other half will be used for immunohistochemistry analysis.

Details of the biopsies sampling and handling will be described in a separate manual.

Tissue and derived material left over from the biopsy already being performed in this study may be used for potential further testing CCI provided material is available. Each sample will be labeled with a code so that the laboratory personnel (including biomarker laboratory personnel) testing the samples will not know the participant's identity. Any tissue or derived material left over may be stored long term for further research purposes at a Sponsor-designated facility. The samples will be used for the purposes described in the protocol and in the informed consent document; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, the samples may be stored for up to 15 years after the end of the study and then destroyed.

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8.1.5. Photography of Representative AD Lesions

For participants, photographs of treated AD will be obtained (according to the separately provided Photography Instructions) at various time points as described in the Schedule of Activities. Areas photographed should be recorded in source documents so that the same AD body region(s) will be photographed at each time point. Photographs may be optional and will be utilized for illustrative purposes and not formally evaluated as an endpoint for analysis.

Photographic services will be provided through a central photography laboratory selected by the sponsor. Detailed procedures to assure consistency will be provided separately in a central photography laboratory instruction manual.

8.1.6. Investigator's Global Assessment (IGA)

The Investigator's Global Assessment of AD is scored on a 5-point scale (0-4), reflecting a global consideration of the erythema, induration, and scaling. The clinical evaluator of AD will perform an assessment of the overall severity of AD 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. Assessments will be collected at various time points as described in the Schedule of Activities.

Table 2. Investigator's Global Assessment (IGA) 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.
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.

8.1.7. Eczema Area and Severity Index (EASI)

The EASI quantifies the severity of a participant's AD based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring by the AD 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. Assessments will be collected at various time points as described in the Schedule of Activities.

Lesion Severity by Clinical Signs: The basic characteristics of AD 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 the Eczema Area and Severity Index (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
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 AD in a body region can be used to determine the extent (%) to which a body region is involved with AD (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 Body Surface Area (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 number of handprints will be for the entire body region.

The extent (%) to which each of the 4 body regions is involved with AD 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 (EASI) Area 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. Eczema Area and Severity Index (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 AD.

8.1.7.1. Body Surface Area – Efficacy (BSA Efficacy)

BSA Efficacy will be derived from the sum of the BSA in handprints across 4 body regions assessed as part of the EASI assessment (Table 4). Handprint refers to that of each individual participant for their own measurement. The BSA Efficacy ranges from 0 to 100%, with higher values representing greater severity of AD. Assessments will be collected at various time points as described in the Schedule of Activities.

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8.1.9. Patient-reported Outcomes (PROs)

Participants will complete the PROs at the clinic prior to other clinical activities and study intervention administration. The PROs should be checked for completeness by the study site staff before proceeding with other steps of the clinical visit procedures. Compliance with scheduled PROs activities will be monitored. Delegated site staff will oversee the administration of PROs at site visits to ensure protocol compliance. Participants are given a diary to complete the Peak Pruritus NRS and Night Time Itch Scale on a daily basis. Delegated site staff will review compliance at each visit and counsel as appropriate. If a participant has repeated non-compliance, the participant should be re-trained.

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8.1.9.1. Peak Pruritus Numerical Rating Scale (NRS)

The severity of itch (pruritus) due to AD will be assessed using the Peak Pruritus NRS, a validated horizontal NRS.[21,22] Participants will be asked to assess their worst itching due to AD over the past 24 hours on an NRS anchored by the terms “no itch” (0) and “worst itch imaginable” (10). This item will be administered to all participants. Participants will enter Peak Pruritus NRS assessment into a diary. The Peak Pruritus NRS as it is assessed on the day of the baseline visit will be included in the evaluation of Inclusion Criterion 2.

The Peak Pruritus NRS should be completed as per Schedule of Activities.

8.1.9.2. Night Time Itch Scale

Severity of Night Time Itch

The severity and frequency of itch (pruritus) during the night due to AD will be assessed using the Night Time Itch Scale. Participants will be asked to assess their worst itching due to AD during their most recent night's sleep on an NRS anchored by the terms "no itch" (0) and "worst itch imaginable" (10). The frequency of itch will be assessed using a 5-point qualitative scale, with responses including "Never", "Rarely", "Sometimes", "Often" and "Almost Always". This item will be administered to all participants.

The Night Time Itch Scale should be completed as per Schedule of Activities.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities.

8.2.1. Physical Examinations and Medical History

- Complete AD disease history includes collection of details of AD at Screening: AD diagnosis, the use of topical treatments, systemic treatments and other treatments for AD. Medical history in addition to AD history including disease duration will be collected at screening. Medical history also includes history of alcohol and tobacco use. Smoking status and average weekly alcohol consumption (units/week) will be collected, where a unit contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz/150 mL (a glass) of wine, 12 oz/360 mL of beer, or 1.5 oz/45 mL of 90 proof of spirits.

- Complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose, except as noted below:

  The following timeframe prior to the planned first dose must be used for collection of the following Current/Prior Medications:

  - 1 year: Previous non-systemic drug treatments for AD including topical treatments;
  - Lifetime history of previous systemic treatment for AD and reason for stopping any systemic treatment for AD;
  - Lifetime history of intolerance/allergy to any drug, regardless of indication.

- A complete physical examination will include, at a minimum, assessments of the general appearance; skin; head, eyes, ears, nose and throat (HEENT); mouth, heart;

lungs; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; and lymph nodes. Complete physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines. Height (inches or centimeters) and weight (lbs. or kg) will be measured and recorded in the source document at the screening visit. Height and weight will be measured without the participant wearing shoes. Weight (lbs. or kg) will continue to be measured and recorded at various time points described in the Schedule of Activities.

- A targeted physical examination will include, at a minimum, assessments of the skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the participant. Targeted physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Vital signs (sitting blood pressure, pulse rate, respiratory rates, and temperature) will be measured after 5 minutes of rest as indicated in the Schedule of Activities.
- Pulse rate and blood pressure will be assessed pre-dose. The same method should be used consistently throughout the study.
- Pulse rate and blood pressure measurements will be assessed in a seated position, back supported, and arms bared (free of restrictions such as rolled-up sleeves, etc.) and supported at heart level. Measurements should be taken on the same arm at each visit (preferably non-dominant) with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Pulse rate and blood pressure measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Participants should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements.

8.2.3. Chest X-Ray

Chest X-ray (posterior-anterior and lateral views) or other appropriate diagnostic image (ie, chest computed tomography or MRI) at screening or within 12 weeks prior to Study Day 1. Such imaging must be read by a qualified radiologist and show no evidence of current, active TB. Documentation of the official reading must be located and available in the source documentation.

8.2.4. Tuberculosis Testing

At the time of screening, all participants will undergo tuberculosis (TB) testing unless performed within 12 weeks of Day 1. QFT-G is the preferred testing method. If the QFT-G test cannot be performed, or if the results cannot be determined by the reference laboratory to be either positive or negative, then participants may be screened using the PPD test with approval of the Pfizer clinician.

In addition to TB testing as specified in this clinical protocol, a chest X-ray (or other appropriate diagnostic image (see Section 8.2.3) is recommended.

QFT-G test is an in vitro diagnostic test using a peptide cocktail simulating early secretory antigen 6 (ESAT-6), cell filtrate protein 10 (CFP-10), and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon-γ by Enzyme-Linked Immunosorbent Assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. QFT-G 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 QTF-G testing. Following sample processing, the sample will be shipped to the sponsor's designated reference laboratory for testing. The procedure for processing and preparing the sample for shipment is described fully in the laboratory manual, which will be provided to investigators.

Should the PPD test be required, the test must be administered and evaluated by a health care professional 48 to 72 hours later, 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.

8.2.5. Special Safety Assessment

In the event of a suspected opportunistic infection, effort should be made to identify the pathogen utilizing laboratory or other methods appropriate to the clinical situation.

In case of a suspected viral skin infection (eg, herpes zoster, herpes simplex or eczema herpeticum), a specimen for viral DNA may be analyzed locally for confirmation and results provided to the adjudication committee to support evaluation.

For participants with a past history of oral or genital herpes simplex virus infection and a presentation consistent to prior infections, further laboratory analysis may be performed at the discretion of the investigator.

8.2.6. Skin Type Assessment

As part of baseline characteristics, a skin type assessment will be done using the Fitzpatrick Skin Type assessment (see Appendix 12). This is used to classify a person's skin type by their response to sun exposure (ie, burning or tanning).

8.2.7. Electrocardiograms

- Single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and [QTc] intervals. Refer to Appendix 10 for [QTc] withdrawal criteria. ECGs will be done locally.
- The ECG should be performed after the participant has rested quietly for at least 10 minutes in a supine position.
- A participant's screening ECG must not demonstrate clinically significant abnormalities prior to randomization.

8.2.8. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the Schedule of activities for the timing and frequency.

- Participants must abstain from all food and drink (except water and non-study medications) for an 8-hour overnight fast prior to labs that include the lipid profile panel on Day 1 and Week 12. All other labs do not require fasting.

- Sample collection, labeling, storage, and shipping information can be found in the laboratory manual.

- 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. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which 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 significantly 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 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.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.8.1. Hepatitis Testing

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

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 negative: Participant is excluded from study participation.

HBsAg negative and HBcAb positive and HBsAb positive: Participant may be eligible for the study:

- Participants who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Participants who have HBV DNA above lower limit of quantification (LLQ) will be excluded. Participants who are HBV DNA negative or below LLQ may be randomized but will have repeat HBV DNA testing at Week 12 (or Early Termination).

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:

Participants who are positive for hepatitis C viral antibody (HCVAb) and HCV RNA will be screen failed.

8.2.8.2. Viral Studies

Blood samples will be collected at Baseline for viral studies but will be analyzed only if the participant has suspected viral infection/reactivation. Additional sample collection instructions will be provided in the lab manual. The retained samples will be destroyed upon participant completion of this study or the LTE study.

8.2.9. Suicidal Ideation (Columbia Suicide Severity Rating Scale)

Site staff is to administer the C-SSRS and PHQ-8 to all participants at screening and score immediately. The participant must have a risk assessment done by a qualified MHP to assess whether it is safe to participate in the trial if the participant's responses on any of the screening instruments or other screening information indicate:

- Suicidal ideation associated with actual intent and a method or plan in the past year: “Yes” answers on items 4 or 5 of the C-SSRS.

- Previous history of suicidal behavior in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS.
- Any lifetime history of serious or recurrent suicidal behavior (non-suicidal self-injurious behavior is not a trigger for a risk assessment unless it is indicated according to the investigator's judgement).
- Clinically significant depression when the PHQ-8 total score is ≥ 15.
- The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.
- In the investigator's judgement a risk assessment or exclusion is required.

Written documentation of the risk assessment should be included in the subject's clinical record (source documentation).

At the baseline (randomization) visit, if there are "yes" answers on items 4, 5 or on any behavioral question of the C-SSRS, a risk assessment should be done prior to randomization by a qualified MHP to determine whether it is safe for the participant to continue in the trial. This risk assessment should be completed in a timeframe that would allow for the screening period to be completed within 28 days. A copy of the risk assessment should be included in the source documents.

At post-baseline visits, if there are "yes" answers on items 4, 5 or on any behavioral question of the C-SSRS, a risk assessment by a qualified MHP should be done to determine whether it is safe for the participant to continue in the trial.

Participants who have recurrent SIB during the trial must be discontinued from the study and treated appropriately. If a participant endorses a 4 or 5 on the ideation subscale or any behavioral item of the C-SSRS on 2 occasions and is confirmed to have active SIB on both occasions by a risk assessment conducted by a qualified MHP, then the participant must be discontinued from the study and treated appropriately.

8.2.9.1. Columbia Suicide Severity Rating Scale

The C-SSRS is a validated tool for investigative staff to use to evaluate suicidal ideation and behavior.[25] Trained site staff is to administer the C-SSRS to all participants at Screening/Baseline visits and assess the participant's eligibility based on the answers. The C-SSRS will also be administered at post-baseline visits to determine whether it is safe for the participant to continue in the trial. Refer to Section 8.2.9 for information on using this tool in SIB risk monitoring. When there is a positive response to any question on the C-SSRS, the investigator should determine whether an adverse event has occurred.

8.2.9.2. Patient Health Questionnaire – 8 Items (PHQ-8)

The PHQ-8 is a participant-reported questionnaire consisting of 8 items to assess the participant's depression level.[27] Site staff is to administer the PHQ-8 to all participants at screening and score immediately. Refer to Section 8.2.9 for information on using this tool in SIB risk monitoring.

8.2.10. Pregnancy Testing

For all WOCBP, a serum pregnancy test with a sensitivity of at least 25 mIU/mL will be performed at Screening. A urine pregnancy test will be performed at various time points described in the Schedule of Activities to confirm the participant has not become pregnant during the study. Serum and urine pregnancy test kits will be provided by the central laboratory with sample collection instructions provided in the package insert.

A negative pregnancy test result is required at the Baseline visit before the participant may receive the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Participants who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not progress further in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory with a sensitivity of at least 25 mIU/mL).

In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of the study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

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

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 it meets the criteria for classification as an SAE, or that caused the participant to discontinue the study intervention (see Section 7.1).

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

8.3.1. 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 the participant’s participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days; except as indicated below after the last administration of the study intervention.

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 definitively 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.

Follow up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.[2,3] Key cytokines implicated in the pathophysiology of AD include IL-4, IL-5, IL-13, IL-31, and IFN-γ. This is a randomized, double-blind, placebo-controlled, parallel-group, Phase 2a study to investigate the mechanism of action of abrocitinib by correlating efficacy outcomes with changes from baseline in key skin and blood biomarkers in adult participants ≥18 years of age with moderate-to-severe AD.

Investigators are not obligated to actively seek AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers 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.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 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 it being available.

8.3.1.2. Recording Non-serious 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 8.3.1, 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.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE 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.

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards 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, IRB/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.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion

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 or a 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 28 days after the last dose.

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding 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 exposure during breastfeeding 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 CT SAE Report Form is maintained in the investigator site file.

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

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may

include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. 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.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	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 participating participant.

- Refer to Section 6.4 for examples of medication errors related to compliance with study intervention.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

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

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 8 tablets within a 24-hour time period [+/- 2 hours] will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 3 days).
3. Obtain a plasma sample for PK analysis within 28 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.
5. Overdose is reportable to Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Pfizer clinician based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

During the study, blood samples (8 mL) to provide approximately 4 mL of plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2-EDTA) for measurement of plasma concentration of abrocitinib and its metabolites PF-06471658, PF-07055087, and PF-07054874 at times specified in the Schedule of Activities. The actual date and time (24-hour clock time) of each sample will be recorded.

Blood for PK analysis will be collected at the study site at the following time points:

- Prior to dosing at Week 4;
- At 0.5 hours (±15 min) postdose at Week 4;
- At 0.5 hours (±15 min) postdose at Week 12;
- At 4.0 hours (±30 min) postdose at Week 12.

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

- The plasma will be stored in appropriately labeled screw-capped polypropylene tube at approximately -80°C within 1 hour of collection.
- Further details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.
- CCI [redacted]

8.5.1. Shipment of Pharmacokinetic Samples

The central laboratory will provide collection materials and directions for packaging and shipment of samples and will manage shipment of samples to the contract analytical laboratory.

CCI [redacted]

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

A 4 mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/IECs allow.

Banked Biospecimens may be used for research related to drug response and moderate to severe atopic dermatitis. Genes and other analytes (eg, proteins, RNA, non-drug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent form whether they will allow their Banked Biospecimen(s) to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sample banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their Banked Biospecimens. The optional additional research does not require the collection of any further samples.

See Appendix 5 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

8.8. Biomarkers

CCI [redacted], the following biomarkers will be evaluated in this study.

The following genes are considered key biomarkers associated with AD pathways:

- General inflammation (MMP12);
- Hyperplasia (K16);
- Th2 (CCL17, CCL18, CCL26);
- Th22 (S100A8, S100A9, S100A12).

In addition, the following genes are considered:

Parameters studied using IHC will include epidermal thickness (performed on H&E sections), Ki-67+ cells, Keratin 16 (K16), CCI

CCI

Gene expression by TLDA RT-PCR will include the levels of the following established cytokines associated with AD: CCI

S100A7, S100A8, S100A9, S100A12, MMP12, CCI

CCL18, CCI CCL26, CCI
18S and RPLP0 as control genes.

CCI

Blood for analyses of changes in inflammatory and cardiovascular markers will be collected at Weeks 0, 2, 4, and 12.

CCI

8.8.1. Specified Gene Expression Ribonucleic Acid (RNA) Research

Specified gene expression (RNA) research is included in this study and described in Section 8.8.

8.8.2. Banked Biospecimens for Biomarkers

One 4 mL blood sample to provide serum (Prep B2.5) and a 3 mL blood sample to provide plasma (Prep B1.5) will be collected for each of the time points as per Schedule of Activities, as local regulations and IRB/ECs allow.

Banked biospecimens may be used for research related to drug response and moderate to severe atopic dermatitis. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked samples to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This

component of the sampling banking is optional for participants; they may still participate in the study even if they do not agree to the additional research on their banked samples. The optional additional research does not require the collection of any further samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the central lab manual.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable to the study.

9. STATISTICAL CONSIDERATIONS

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary objective of this study is to assess the effects of abrocitinib on lesional and non-lesional skin biomarkers of adult participants with moderate-to-severe AD. The following estimand attributes will be considered:

- Population: Participants with moderate-to-severe AD as defined by the inclusion criteria;
- Variable: Fold-change from baseline in the biomarkers for general inflammation (MMP12), hyperplasia (K16), Th2 immune response (CCL17, CCL18, CCL26), and Th22 immune response (S100A8, S100A9, S100A12);
- Intercurrent event: All data collected will be utilized;
- Participants need to have a baseline and week 12 assessment to be included in the analysis.
- Population-level summary: Mean fold-change from baseline within each treatment group.

9.2. Sample Size Determination

The sample size of this study is based on the objective to evaluate changes in key AD biomarkers in skin lesions, including biomarkers for general inflammation (MMP12), hyperplasia (K16), Th2 (CCL17, CCL18, CCL26), and Th22 (S100A8, S100A9, S100A12) with abrocitinib 200 mg QD, abrocitinib 100 mg QD, and placebo.

A total sample of approximately 51 participants, with 17 participants randomized to abrocitinib 200 mg QD, 17 participants randomized to abrocitinib 100 mg QD, 17 participants randomized to matching placebo (1:1:1 randomization) is planned.

A sample size of 17 participants per treatment group would provide about 92% chance that the 95% CI for the mean fold-change (post-baseline relative to baseline) has a half-width of no more than 3.2 (which is within 64% of an assumed maximal standard deviation of 5 for the fold-change, as based on published data). [28] Calculations are based on the assumption of a chi-square distribution for the estimated sample variance so that the width of the estimated confidence interval is a random quantity.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Full Analysis Set (FAS)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they are randomized to.
Per Protocol Analysis Set (PPAS)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Furthermore, participants must not have any major protocol violations such inclusion/exclusion criteria, inadequate protocol compliance in terms of dosing or study activities or any other major protocol violation as determined by the clinical study team prior to unblinding. Participants will be analyzed according to the intervention they are randomized to.
Safety Analysis Set (SAS)	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate.

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, for all endpoints listed in Section 3, and procedures for accounting for missing data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Analysis of the Primary Endpoint

The population for the primary analysis will be all participants in the FAS having valid biomarker data at baseline and Week 12.

The primary endpoints in this study include mean fold-changes for the following biomarkers:

- General inflammation (MMP12);
- Hyperplasia (K16);

- Th2 (CCL17, CCL18, CCL26);
- Th22 (S100A8, S100A9, S100A12).

In each participant, expression levels from RT-PCR will be normalized to the housekeeping gene RPLP0 (validated in other studies) by negatively transforming the Ct values to –dCt, obtaining an equivalent to log2 scale expression values (reporting unit: log2 [Expression/RPLP0]). The expression values below detection will be estimated for each gene as the 20% of the minimum of unlogged values across all samples (which is equivalent to subtracting 2.321928 from the –dCt minimum value). The expression levels below detection may provide important information about some markers that significantly change with treatment (eg, the expression may decrease below the level of detection after treatment), therefore this imputation is an important step in the analysis.

RT-PCR expression data in log2 scale will be modeled using a mixed effect model with Treatment, Time Point, and Tissue Type as a fixed effect and a random intercept for each participant. This model will yield unbiased estimates and valid inferences in the presence of a missing data mechanism that is missing at random (MAR). [29] This approach introduces less bias than restricting the analysis for participants with complete observations and is consistent with estimation of a hypothetical estimand. Contrasts will be used to estimate the log2 fold-changes for each treatment group. Fold-changes will be computed by obtaining the antilog of log2 fold-changes. Point estimates and 95% confidence intervals (CIs) will be obtained for the fold-change from baseline in the biomarker values for each treatment group based on this model.

Correlation analyses will be performed to assess if the fold-change from baseline in biomarkers correlates with change (from baseline) in the clinical efficacy endpoints such as IGA, EASI, and Peak Pruritus NRS.

Supportive analyses for the primary endpoint will also be performed using the PPAS.

While statistical tests of hypotheses will not be performed to compare the fold-change from baseline in the abrocitinib groups versus placebo, the point estimates and 95% CIs for the two abrocitinib dose groups will be assessed in relation to those from the placebo group. A fold-change from baseline observed in the abrocitinib groups alone (and correlated with efficacy) but not in the placebo group is likely due to the mechanism of action of abrocitinib.

9.4.2. Analysis of Other Biomarker Endpoints

CCI

Parameters studied using IHC will include epidermal thickness (performed on H&E sections), Ki-67+ cells, Keratin 16 (K16), CCI .

CCI

CCI

CCI

Gene expression by TLDA RT-PCR will include the levels of the following established cytokines associated with AD: CCI

100A7, S100A8, S100A9, S100A12, MMP12, CCI

, CCL18, CCI , CCL26, CCI

18S and RPLP0 as control genes.

CCI

CCI

CCI

CCI

9.4.2.1. Analysis of Other Endpoints

The responses based on IGA, EASI (eg, EASI-75), and severity scale of the Peak Pruritus NRS will be summarized descriptively by visit and treatment. The difference of the improvement from baseline between each abrocitinib dose and placebo will also be derived.

If a participant withdraws from the study, then this participant will be considered a non-responder after withdrawal for any binary valued clinical efficacy endpoint.

9.4.3. Safety Analyses

All safety analyses will be performed on the Safety Population. The Safety population will include any participant receiving ≥1 dose of investigational product.

All safety data will be summarized using descriptive statistics. No imputation will be made for missing safety data.

All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- Treatment-emergent AEs and SAEs;
- Withdrawals from active treatment due to AEs;
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials or met other criteria that required the event be classified as serious;

- Safety laboratory tests (eg, hematology [including coagulation panel], chemistry, and lipid profiles);
- Vital signs;
- ECG parameters if applicable.

CCI [redacted]

9.5. Interim Analyses

After the first 15 participants have completed the study, there will be an interim analysis to examine platelet values. A longitudinal analysis will be conducted to determine if there is a change from baseline in platelet values. The data will remain blinded so that no one will know the participants' assigned treatment and thus the analysis will not analyse for any treatment differences. Correlation analyses may also be conducted to look for potential relationships between platelet values CCI [redacted]. There will not be any decision rules associated with this interim analysis, so there will be no changes to the conduct or continuation of the trial based on these analyses.

9.5.1. Data Monitoring Committee (DMC)

This study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. 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 to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. Composition of the E-DMC and processes under which the E-DMC operates will be documented in the E-DMC charter.

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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations, including applicable privacy laws.

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, 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/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- 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 ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators 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 his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (parent(s)/legal guardian) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The investigator must ensure that each study participant or his or her 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 must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) and if the age of majority is reached during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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 shall 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 natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets 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 his or her actual identity. 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.

10.1.5. Committees Structure

External Data Monitoring Committee (E-DMC)

See Section 9.5.1.

Safety Adjudication Committees

To help assess the specific, complex safety events related to malignancies, cardiovascular events, hepatic and opportunistic infection (including eczema herpeticum and other infections of special interest) in this study, Safety Adjudication Committees, consisting of clinical experts in each of the relevant clinical areas, will be set up to harmonize and standardize assessments. In order to allow for an unbiased safety assessment, the members of these committees will be blinded to treatment assignment. Further information about the Safety Adjudication Committees can be found in their respective charters, including a specific description of the scope of their responsibilities, a plan where communication timelines are defined, and the exact process and definitions used by each committee to adjudicate the safety events that they will adjudicate. Other safety events for adjudication may be identified and included in the remit of the Safety Adjudication Committees as appropriate.

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 European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (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 US Basic 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. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (Clinical Study Report [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the

centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data 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 (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, remote, or on-site monitoring) are provided in the Monitoring Plan and contracts.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification 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, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, 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 so 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 sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow 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 sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide 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’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed 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.
- Definition of what constitutes source data can be found in the Clinical Monitoring Plan.

10.1.9. Study and Site Closure

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. 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 contract research organization (CRO) if requested to do so by the responsible IRB/IEC 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/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings by the Investigator after publication of the overall study results or one year after end of the study (or study termination), whichever comes first.
- The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor 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- or Pfizer intervention-related information necessary to the appropriate scientific presentation or understanding of the study results.
- For all publications relating to the study, the Investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.
- The sponsor will comply with the requirements for publication of the overall study results covering all Investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.
- If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the clinical trial management system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and study intervention identifiers, participant study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If such a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF. This is applicable for repeat tests.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
    1. Refer to Section 5.1 Inclusion Criteria and Section 8.2.10 Pregnancy Testing for screening pregnancy criteria.
    2. For details of timing of recommended pregnancy testing see the Schedule of Activities.

Table 7. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	CCI Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC RBC Morphology Reticulocyte Count	White blood cell (WBC) count with Differential: Total Neutrophils Lymphocytes Monocytes Eosinophils Basophils Coagulation Panel Activated Partial Thromboplastin Time (APTT) Prothrombin Time/International Normalized Ratio (PT/INR)	
Clinical Chemistry[1]	Blood urea nitrogen (BUN) Creatinine Creatine Phosphokinase Glucose (non-fasting) (Day 1 and Week 12 fasting) AST	ALT GGT Potassium Sodium Calcium	Chloride Uric acid Albumin Total Protein Total CO2 (bicarbonate)	Total, indirect and direct bilirubin Alkaline phosphatase Lactate dehydrogenase
Lipid Profile Panel[1]	Total cholesterol	Triglycerides	LDL	HDL
Routine Urinalysis	• pH, glucose, protein, blood, ketones, nitrite, leukocyte esterase by dipstick • Microscopic examination and/or culture[2]			
Other Tests[9]	• HIV[3] • HBsAg[3] • HBcAb[3] • HBsAb[3,4] • HBV DNA[5] • HCVAb[3,4] • HCV RNA[3,4] • Viral test at baseline • Serum Pregnancy Test[3,6] • Urine pregnancy test[6] • QFT-G or PPD (if applicable)[7] • CCI • Lymphocyte Subsets Total T cells (CD3+) CD4+ T cells (CD3+CD4+)			

Table 7. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
	CD8+ T cells (CD3+CD8+) NK cells (CD3-CD16+CD56+) B cells (CD3-CD19+)

1. Lipid profile panel requires at least an 8 hour fast. Lipid profile panel will be completed at Day 1 and Week 12, and will include total cholesterol, LDL, HDL, and triglycerides.
2. Microscopy performed at all visits and culture as appropriate.
3. At Screening only. HIV testing will be performed for all participants.
4. HBsAb reflex testing only if HBsAg negative but HBcAb positive. HCV RNA is reflex testing only if HCVAb is positive.
5. Participants who are HBsAg negative, HBcAb positive, and HBsAb positive will have reflex testing for HBV DNA.
6. Pregnancy testing for all WOCBP.
7. PPD results should be read within 48 to 72 hours.
C [redacted]
9. All study-required laboratory assessments will be performed by a central laboratory, with the exception of: urine pregnancy tests, which will be performed on the Day of the study visits per the Schedule of Activities.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 Meeting 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 laboratory 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 either an increase in frequency and/or intensity of the condition.
• New conditions 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/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the

requirements as per Section 8.3.8.1. Also, “lack of efficacy” or “failure of expected pharmacological action” does not constitute an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

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, which 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 detained (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 pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient 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.

10.3.3. Recording/Reporting and Follow-Up of AE and/or SAE

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

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

terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (And EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/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/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.
- 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/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: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **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 his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • 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 Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool 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 data collection tool 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 CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, 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 Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

For this study, a female participant is considered fertile (ie WOCBP) starting at 12 years of age (regardless of whether they have experienced/reported menarche) unless permanently sterile (see below).

Women with one of the following are not considered WOCBP

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

Note: Documentation for any of the above conditions 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.

Contraception Guidance:

All female participants who are considered WOCBP and who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of study intervention. The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and her partner from the permitted list of contraception methods (see below) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, 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). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the participant plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the participant.

The contraception check is an opportunity to confirm that contraception, if assigned, is used consistently and correctly. It also facilitates continual reassessment of child-bearing potential in women. This allows for implementing necessary changes to contraception; for example, investigators may need to ensure alternative contraceptive methods if new concomitant disease contraindicates a selected method of contraception, or if a participant is demonstrably no longer of child-bearing status (as per protocol) then they will no longer require contraception. Continual reassessment of contraceptive needs is imperative.

Collection of Pregnancy Information:

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the study intervention; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study intervention;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the study intervention prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the study intervention, 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. In addition, the investigator must submit

information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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 EDP supplemental form. 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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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 includes miscarriage and missed abortion;
- 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.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to abrocitinib or study interventions of this class, treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary, or may be used for internal decision-making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Samples for banking (see Section 8.7.2 and 8.8.2) will be stored indefinitely or other period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

Banked Biospecimens will be labelled with a code. The key between the code and the participant's personally identifying information (eg name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

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 drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili 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 TBili 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 TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili 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 TBili 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 TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili 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 TBili for suspected cases of Hy's Law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (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 (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, 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 and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (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.

10.7. Appendix 7: Prohibited Concomitant Medications

CYP2C19 Inhibitors	**CYP2C19 Inducers**
Fluconazole (Diflucan)	Enzalutamide (Xtandi)
Fluvoxamine (Luvox)	Rifampin
Ticlopidine (Ticlid)	
Esomeprazole (Nexium)	
Fluoxetine (Prozac)	
Moclobemide	
Omeprazole (Prilosec)	
Voriconazole (Vfend)	
CYP2C9 Inhibitors	**CYP2C9 Inducers**
Fluconazole (Diflucan)	Carbamazepine (Tegretol)
Amiodarone (Cordarone)	Enzalutamide (Xtandi)
Fluvoxamine (Luvox)	Rifampin
Miconazole	
Oxandrolone (Oxandrin)	
Voriconazole (Vfend)	

Note 1: All CYP2C9 and CYP2C19 inhibitors require at least 1 week or at least 5 half-lives (whichever is longer) washout period prior to the first dose of study intervention.

Note 2: All CYP2C9 and CYP2C19 inducers require a period of washout of at least 5 half-lives plus 14 days prior to the first dose of study intervention. For example, the average half-life of carbamazepine after repeat dosing is 15 hours. The washout period is calculated as the sum of 5 half-lives (approximately 3 days) and an additional 14 days for a total of 17 days prior to the first dose of study intervention.

Note 3: Half-life refers to the half-life of the parent drug and its metabolites, which are inhibitors or inducers. The longest half-life should be used to calculate the period necessary to washout a medication prior to the first dose of study intervention. For example, fluoxetine and its metabolite norfluoxetine are both inhibitors of CYP2C19. The terminal half-life of fluoxetine is up to 6 days. However, norfluoxetine has a longer half-life, up to 16 days. Therefore, the washout period should be calculated based on the 5 times the half-life of norfluoxetine (approximately 80 days) and an additional 14 days for a total of 94 days prior to the first dose of study intervention.

This is not an all-inclusive list. Study personnel should stay current and consult with their pharmacy to exclude all concomitant medications that are CYP2C9 or CYP2C19 inhibitors or inducers.

10.8. Appendix 8: Country-specific Requirements

Not applicable.

10.9. Appendix 9: Abbreviations

AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AMR	Ashwell-Morrell receptor
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	Area under the curve
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AUC_{tau}	area under the curve over dosing interval tau
BCG	Bacille Calmette Guérin
BID	twice a day
BSA	body surface area
BUN	blood urea nitrogen
CCI	[redacted]
CCL	C-C motif chemokine ligand
CD	cluster of differentiation
CFB	Change from baseline
CFP-10	Cell filtrate protein 10
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	clearance/fraction of dose absorbed
C_{max}	maximum plasma concentration
CO2	carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	corona virus disease 2019
CK	creatine kinase
CRF	case report form
CRO	contract research organization
CsA	cyclosporine A
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CTLA3	Cytotoxic T-lymphocyte associated protein 3
CV	coefficient of variation
DC	dendritic cell
DCT	data collection tool
DEFB4	defensin beta 4A

DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index
EBV	Epstein Barr virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
ESAT-6	Early secretory antigen 6
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FLG	filaggrin
FOXP3	forkhead box P3
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
CCI	[redacted]
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C viral antibody
HCV RNA	hepatitis C viral ribonucleic acid
HDL	high-density lipoprotein
H&E	hematoxylin and eosin
HEENT	head, eyes, ears, nose and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
CCI	[redacted]
HSV	herpes simplex virus
HTA	health technologies assessment

IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committees
IFN	interferon
IFN-α	interferon-alpha
IFN-γ	interferon-gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IgG	immunoglobulin G
IHC	immunohistochemistry
IIV	inter individual variability
IL	interleukin
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive web response
JADE	Jak1 Atopic Dermatitis Efficacy and safety program
JAK1	Janus kinase 1
K16	Keratin 16
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LCN2	lipocalin 2
LDL	low-density lipoprotein
LFT	liver function test
LLQ	lower limit of quantification
LMW	low molecular weight
LS	lesional
LSLV	last subject last visit
LTE	long-term extension
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MHP	mental health professional
MMP	matrix metallopeptidase
MNAR	missing not at random
MOA	mechanism of action
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MX1	MX dynamin like GTPase 1

N/A	not applicable
NB-UVB	narrowband ultraviolet B light
NL	non-lesional
NRS	numerical rating scale
NRS4	numerical rating scale 4 points improvement from baseline
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
OASL	2'-5'-oligoadenylate synthetase like
OTC	over-the-counter
PCA	Principal Component Analysis
PCD	primary completion date
PCP	primary care physician
PCR	polymerase chain reaction
PDL1	programmed cell death ligand 1
PEER	Pediatric Eczema Elective Registry
PGx	Pharmacogenomics
PI3	Peptidase inhibitor 3
PK	Pharmacokinetics
POC	proof of concept
PPAS	per protocol analysis set
PPD	purified protein derivative
PP-NRS	peak pruritus numerical rating scale
PRO	patient reported outcome
PT	prothrombin time
QC	quality control
QD	once daily
QFT-G	QuantiFERON®-TB Gold
QT	Q wave interval
QTc	corrected Q wave interval
QTcF	Fridericia corrected Q wave interval
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
R_{ac}	accumulation ratio
RBC	red blood cell
RNA	ribonucleic acid
RPLP0	Ribosomal protein lateral stalk subunit P0
RT-PCR	reverse transcriptase polymerase chain reaction
S100A	S100 calcium binding protein A
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
STAT	signal transducers and activators of transcription

SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
T_{max}	time to maximum absorption
TB	tuberculosis
TBili	total bilirubin
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
Th2	type 2 helper T cell
Th22	type 22 helper T cell
TLDA	Taqman Low Density Array
TPO	thrombopoietin
TSLP	thymic stromal lymphopoietin
TSLPR	thymic stromal lymphopoietin receptor
TYK2	tyrosine kinase 2
ULN	upper limit of normal
US	United States
UV	ultraviolet
UVA	ultraviolet A light
UVB	ultraviolet B light
VAS	visual analog scale
V/F	volume of distribution/fraction absorbed
WBC	white blood cell
WOCBP	women of childbearing potential

10.10. Appendix 10: Monitoring and Discontinuation Criteria

Monitoring Criteria

The following laboratory abnormalities require prompt retesting:

- Neutrophil counts <1000 neutrophils/mm^3; confirmed promptly by repeat testing, ideally within 3-5 days;
- Platelet counts <75,000 platelets/mm^3; confirmed promptly by repeat testing, ideally within 3-5 days;
- Any single hemoglobin value <9.0 g/dL or one that drops ≥2 g/dL below baseline; confirmed promptly by repeat testing, ideally within 3-5 days;
- Any single AST and/or ALT elevation >3 times the upper limit of normal regardless of accompanying symptoms or the total bilirubin should prompt repeat testing. This should also prompt review of Appendix 6 (Liver Safety); additional investigations must be conducted.

Temporary Interruption to Dosing

Temporary interruption to dosing is not allowed in this study, except when specified in the protocol for participant safety.

Discontinuation Criteria

Participants must be permanently discontinued from treatment if they meet any of the following criteria at any point in the study:

- Marked prolongation of the QTcF interval to >500 ms or >60 ms change from screening ECG.
- Serious infection (see definition for Serious Adverse Events in Section 10.3.2) must result in temporary interruption of study intervention. Study intervention cannot be restarted until the serious infection has resolved, and this has been discussed and agreed with the Pfizer medical monitor. If the participant cannot be restarted on study intervention within 21 days, or the infection is not resolved, or there is no agreement received from the Pfizer medical monitor to restart study intervention then the participant must be permanently discontinued from study intervention.
- Any bleeding event thought to be associated with a platelet count reduction per the judgement of the investigator (or, if necessary/desired, following discussion with sponsor).
- Adverse event, per judgment of the investigator, requiring discontinuation from treatment (or, if necessary/desired, following discussion with sponsor).

NOTE: any initial lab value below must be retested within 48 hours.

- Two sequential platelet counts <50,000/mm^3. If the participant has a platelet count <25,000/mm^3, study intervention should be temporarily withheld pending the confirmatory retest.
- Two sequential neutrophil counts <500/mm^3.
- Two sequential lymphocyte counts <500/mm^3.
- Two sequential hemoglobin assessments <8.0 g/dL and / or a decrease of >30% from baseline value.
- Any of the following:
  - Two sequential AST or ALT elevations >3 times the upper limit of normal with at least one total bilirubin value >2 times the upper limit of normal.
  - Two sequential AST or ALT elevations >3 times the upper limit of normal with an abnormal international normalized ratio (INR).
  - Two sequential AST or ALT elevations >3 times the upper limit of normal accompanied by symptoms consistent with hepatic injury.
  - Two sequential AST or ALT elevations >5 times the upper limit of normal, regardless of total bilirubin or accompanying symptoms.

  NOTE: Any of the above findings should prompt review of "The Potential Cases of Drug-Induced Liver Injury," Appendix 6 for which additional investigations must be conducted.
- Two sequential increases in serum creatinine that are >50% over the average of screening and baseline values AND an absolute increase in serum creatinine ≥0.5 mg/dL. At the time of study completion or discontinuation, if a participant should exhibit elevations in serum creatinine ≥33% above the average of screening and baseline values, they will be re-tested every 1 to 2 weeks until the serum creatinine elevation is fully reversed to within 10% of the average of screening and baseline values or has stabilized.

Having met Discontinuation Criteria, the participant must be permanently withdrawn from treatment, have their end of treatment visit, and will then enter the 4-week follow-up period.

Additional individual participant safety monitoring, including laboratory testing or unscheduled study visits, in addition to these guidelines is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled laboratory testing through the central laboratory may be obtained at any time during the study to assess such concerns.

If a participant has a clinically significant, treatment emergent, abnormality at the time of withdrawal from the study, the Pfizer clinician (or designee) should be notified and every effort should be made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormality. All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels or are deemed clinically stable. Follow-up for abnormal laboratory findings and adverse events by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

10.11. Appendix 11: Diagnostic Criteria for Atopic Dermatitis

Per Inclusion Criterion 2, a participant is to have a clinical diagnosis of AD according to the criteria of Hanifin and Rajka.[20]

Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

Must have three or more basic features described below:
Pruritus
Typical morphology and distribution:
Flexural lichenification in adults
Facial and extensor eruptions in infants and children
Chronic or chronically-relapsing dermatitis
Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
Must have three or more following minor features:
Xerosis
Ichthyosis/palmar hyperlinearity, keratosis pilaris
Immediate (type 1) skin test reaction
Elevated serum IgE
Early age of onset
Tendency toward cutaneous infections (esp. staph. aureus and herpes simplex), impaired cell-mediated immunity
Tendency toward non-specific hand or foot dermatitis
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor, facial erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Periofollicular accentuation
Food intolerance
Course influenced by environmental and emotional factors
White dermographism, delayed blanch

10.12. Appendix 12: Fitzpatrick Skin Type

Phototype	Sunburn and tanning history (defines the phototype)
I	Burns easily, never tans
II	Burns easily, tans minimally with difficulty
III	Burns moderately, tans moderately and uniformly
IV	Burns minimally, tans moderately and easily
V	Rarely burns, tans profusely
VI	Never burns, tans profusely

10.13. Appendix 13: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally or specific location(s) and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.13.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing 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:

- 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 8.3.
- 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 and Section 8.2.10 of this appendix regarding pregnancy tests.
- Review Patient-Reported Outcomes (PROs) and C-SSRS.

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

10.13.2. Alternative Facilities for Safety Assessments

10.13.2.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. All safety laboratory tests required per protocol could be done at local labs with an exception of hs-CRP test to avoid the risk of potential unblinding.

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.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, 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.

10.13.3. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

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

10.13.4. Home Health Visits

A home health care visit may be performed to facilitate scheduled visits per the Schedule of Activities. 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:

- 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 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Physical exam and targeted physical exam.
- Clinical AD assessments.
- Vital sign measurements.
- 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 and Section 8.2.10 of this appendix regarding pregnancy tests.

- Review Patient-Reported Outcomes (PROs) and C-SSRS.
- Skin punch biopsy, CCI [redacted] could be performed by qualified personnel at their discretion.

10.13.5. Adverse Events and Serious Adverse Events

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

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

10.13.6. Efficacy Assessments

The IGA and EASI efficacy assessments may be assessed by a qualified rater as part of a home health care visit, but cannot be completed as part of a TeleHealth visit.

PROs may be completed as part of a home health care visit or a TeleHeath visit.

10.13.7. Independent Oversight Committees

The Data Monitoring Committee will be informed of considerations during Public Health Emergencies such as COVID-19 that may impact participant participation, participant safety, or study operations.

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