A RANDOMIZED, OPEN-LABEL, PARALLEL-GROUP STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ABROCITINIB 100 MG AND 200 MG TABLETS IN PARTICIPANTS AGED 12 YEARS AND OLDER WITH MODERATE TO SEVERE ATOPIC DERMATITIS IN INDIA

Study Intervention Number:	PF-04965842
Study Intervention Name:	Abrocitinib
US IND Number:	N/A
EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
Protocol Number:	B7451094
Phase:	3

Brief Title: A Safety and Efficacy Study of Abrocitinib Tablets in Participants Aged 12 Years and Older with Atopic Dermatitis in India

Document History

Document	Version Date
Amendment 1	23 March 2022
Original Protocol	21 December 2021

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

Protocol Amendment Summary of Changes Table

Amendment 1 (23-March-2022)

Overall Rationale for the Amendment: This protocol is being amended to reflect recommendations from India BoH: to revise protocol into Phase 3; to add SCORAD assessment; to indicate that photography should be utilized to capture the AD lesions. Detailed changes are summarized below in a tabular form.

Section # and Name	Description of Change	Brief Rationale
• Cover Page	**Revision** of study phase from 3b/4 to 3	Per India BoH's recommendation
• Section 1.1 (Synopsis); • Section 1.3 (SoA); • Section 3 (Objectives, endpoints and estimands); • Section 8.1.4 (SCORAD, Newly Added); • Section 9.1.1.2 (Secondary Estimands); • Section 9.3.3 (Secondary Endpoint Analysis) • Section 10.9 (Abbreviations)	**Added** SCORAD efficacy assessment for atopic dermatitis as a secondary endpoint	Per India BoH's recommendation
• Section 1.3 (SoA) • Section 8.1.2 (IGA) • Section 8.1.3 (EASI)	**Added** Photography in SoA **Added** 1 new section for Photography;	Per India BoH's recommendation

Section # and Name	Description of Change	Brief Rationale
• Section 8.1.6 (Photography, Newly Added)	**Removed text** from Sections 8.1.2 and 8.1.3: "Photographic images of the lesion will be taken as part of source documentation, wherever possible."	
• Section 1.3 (SoA); • Section 10.10.2 (Substudy SoA)	**Added** contraception check at each visit	Updates in SoA and substudy SoA
• Section 8.2.5 Clinical Safety Laboratory Assessments • Section 10.2 (Appendix 2: Clinical Laboratory Tests); • Section 10.10.2 (Substudy SoA); • Section 10.10.7.2 (Substudy Early Termination/End of Treatment Visit)	**Added** laboratory tests at EoT visit of the substudy. **Updated** substudy SoA and relevant sections**.**	Updates in substudy SoA and relevant sections
• Section 10.10.2 (Substudy SoA)	**Added** text in time frame for substudy follow-up visit	Updates in substudy SoA for clarity
• Section 1.3 (SoA)	**Added** Weight measurement at Baseline	Updates in SoA
• Section 10.10.2 (Substudy SoA)	**Added** vital signs measurement at all visits	Updates in substudy SoA
• Section 1.1 (Synopsis) • Section 9.4 (Interim Analysis) • Section 10.10.10.4 (Substudy Interim Analysis)	**Added** text: As this is an open-label study, the sponsor may conduct reviews of the data, **including MRI data, (newly added)** during the course of the study for the purpose of safety assessment **or to support regulatory**	To clarify on interim analysis, and further define the range and purpose of data review

Section # and Name	Description of Change	Brief Rationale
	submissions (newly added). There will be no **formal (newly added)** interim analysis for this substudy. **The sponsor may conduct reviews of the data, including MRI data, during the course of the study for the purpose of safety assessment or to support regulatory submissions (newly added).**	
• Section 9.3.3 (Secondary Endpoint Analysis)	**Added text:** **"**Descriptive statistics for change from baseline in POEM and ADCT scores will be derived at all scheduled timepoints, for each treatment arm."	To clarify on secondary PRO endpoint analysis
• Section 1.1 (Synopsis) • Section 2.3 (Benefit/Risk Assessment) • Section 3 (Objectives, Endpoints, and Estimands) • Section 4.1 (Overall Design) • Section 10.10.1.1 (Substudy Background and Rationale) • Section 10.10.3 (Substudy Objectives and Endpoints) • Section 10.10.4 (Substudy Design)	**Revised** "Abnormal developmental bone findings related to study intervention", "abnormal bone findings", "abnormal findings" in knee MRI-related sections **to** "Bone safety findings"	To correct an editorial error and keep consistency with the program objective

Section # and Name	Description of Change	Brief Rationale
• Section 10.10.8.1 (Bone Safety Findings Identified in Central Evaluation of Knee MRI Images) • Section 10.10.10.3 (Substudy Safety Analyses)		

Minor editorial changes throughout the document.

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomized, open-label, parallel-group study to evaluate the safety and efficacy of abrocitinib 100 mg and 200 mg tablets in participants aged 12 years and older with moderate to severe atopic dermatitis in India

Brief Title: A Safety and Efficacy Study of Abrocitinib Tablets in Participants Aged 12 Years and Older with Atopic Dermatitis in India

Rationale:

The causes of AD are varied. Both a genetic predisposition and numerous trigger factors play an important role in the first manifestation and in exacerbations of the disease.

As per the Indian consensus statement for management of AD, patients with AD suffer from dry skin and defective skin barrier function, that manifests mainly as pruritus. Systemic therapy is used to treat patients with moderate to severe AD on failure of topical treatments. Currently approved systemic agents in India have modest efficacy in patients with moderate to severe AD but are associated with adverse events that often limit long-term use.

Abrocitinib is an oral, once daily JAK1 selective inhibitor under investigation for the treatment of moderate to severe AD. Selective inhibition of JAK1 with abrocitinib modulates signaling by IL-4, IL-13, and other cytokines (eg, IL-31, IL-22, and TSLP) involved in the pathogenesis of AD and pruritus while sparing JAK2 inhibition and minimizing the risk for neutropenia and anemia. Inhibition of neuronal JAK1 dependent pathways has also been shown to ameliorate pruritus.[1]

This study is planned to provide additional safety and efficacy data for abrocitinib in India.

Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To evaluate the safety of abrocitinib in participants aged 12 years and older with moderate to severe AD.	• Incidence of AEs and SAEs.	• The primary estimand for safety is the incidence of AEs and SAEs in participants aged 12 years and older with moderate to severe AD, from the time of first dose to Week 16, regardless of dosing compliance or treatment discontinuation.
Secondary:	**Secondary:**	**Secondary:**
• To assess the efficacy of abrocitinib in participants aged 12 years and older with moderate to severe AD.	• Response based on IGA score of clear (0) or almost clear (1) and greater than or equal to 2 points improvement from baseline at Week 12. • Response based on achieving ≥75% improvement from baseline in the EASI total score (EASI-75) at Week 12. • Response based on ≥75% improvement in SCORAD (SCORAD75) at Week 12. • Change from baseline in POEM at Week 12 and at all scheduled time points. • Change from baseline in ADCT at Week 12 and at all scheduled time points.	• The secondary estimand is the treatment effect of abrocitinib on participants aged 12 years and older with moderate to severe AD, based on IGA response, EASI-75 response and SCORAD75 response from baseline to Week 12, considering patients who discontinued treatment as non-responders and based on outcome measures of POEM and ADCT from baseline to Week 12 and at all scheduled time points. Data collected after treatment discontinuation is excluded.
Primary substudy objective(s):	**Primary substudy endpoint (as secondary endpoints for B7451094):**	**Primary substudy estimand(s):**
• To evaluate the potential effects of abrocitinib on bone development in adolescent participants 12 to <18 years of age, as assessed by knee MRI.	• The proportion of bone safety findings in knee MRI 1 year after randomization in adolescent participants exposed to abrocitinib 100 mg and 200 mg QD.	• The primary substudy estimand is the incidence of bone safety findings in knee MRI after 1 year of being exposed to abrocitinib in adolescent participants 12 to <18 years of age, regardless of dosing compliance or treatment discontinuation.

Overall Design

Brief Summary

This is a randomized, open-label, parallel-group study to assess the safety and efficacy of orally administered tablets of abrocitinib 100 mg and 200 mg QD in participants aged 12 years and older with moderate to severe AD in India. There is a planned treatment duration of 12 weeks, with 4 weeks of off-treatment safety follow up thereafter. Study participants will be screened within 28 days prior to the first dose of study intervention to confirm that they meet the eligibility criteria for the study.

This study protocol also includes a substudy evaluating whether abrocitinib has any potential effects on adolescent bone with regard to bone safety findings in knee MRI. Adolescent participants (12 to <18 years of age) will continue to receive study intervention until 1 year after randomization into the main study. Section 10.10 (Appendix 10) contains complete information regarding the substudy.

Number of Participants

Approximately 200 participants will be enrolled and randomized to study intervention at approximately 10 sites in India. Adolescent participants 12 to <18 years of age will be enrolled in the knee MRI substudy.

Intervention Groups and Duration

Participants who meet eligibility criteria at baseline will be randomized in a 1:1 ratio to receive abrocitinib 200 mg in tablet form (100 mg tablet × 2) (n=100) or abrocitinib 100 mg (100 mg tablet × 1) (n=100) taken once daily by mouth. The total treatment duration will be 12 weeks with a 4-week off-treatment safety follow-up period for the main study, and 1 year treatment period for adolescent participants enrolled in the knee MRI substudy.

Data Monitoring Committee or Other Independent Oversight Committee: Yes

Safety Adjudication Committees:

To independently assess the specific, complex safety events related to malignancies, cardiovascular events, and opportunistic infections (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 will be defined 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. A separate safety adjudication committee will be established for the MRI substudy for bone findings.

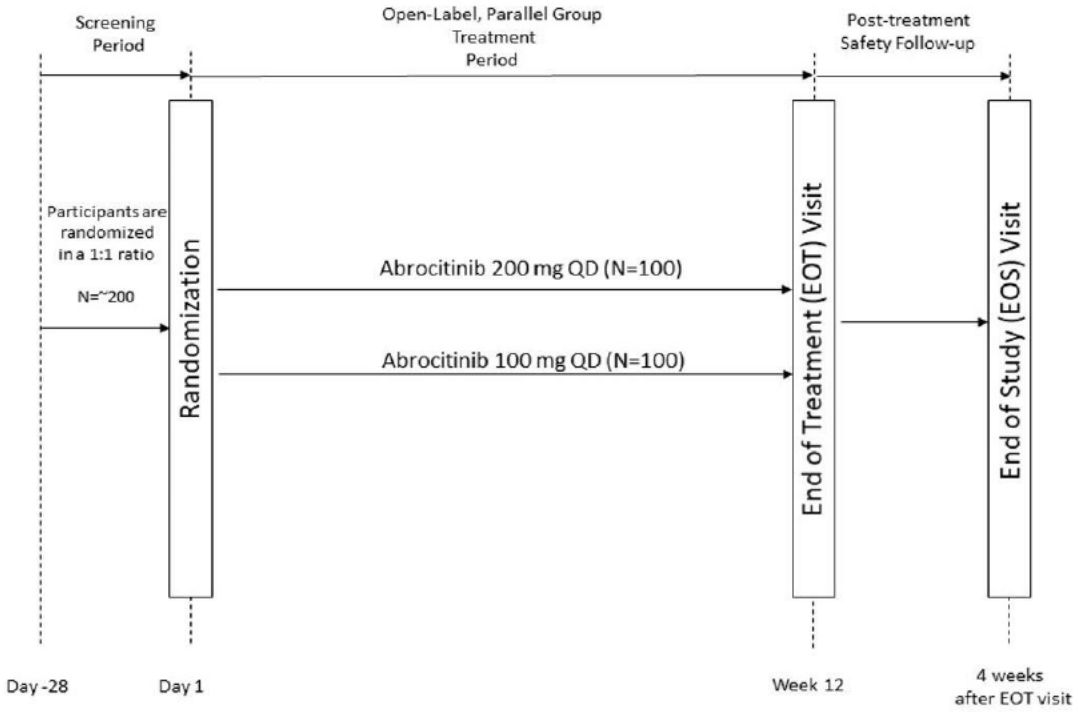
Statistical Methods

A sample of 200 participants (100 randomized participants per treatment arm) would allow estimation of the incidence rate of any AE with maximum margin of error of 10%, in each treatment arm. All randomized participants who receive at least 1 dose of abrocitinib will be included in the analyses. The number and percentage of treatment-emergent AEs will be summarized according to type, frequency, severity, seriousness and relationship to abrocitinib in each treatment arm. The response rates, together with the corresponding

95% CI (using the normal approximation or Clopper-Pearson exact method, whichever is appropriate) will be estimated for each treatment arm.

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct reviews of the data, including MRI data, during the course of the study for the purpose of safety assessment or to support regulatory submissions. Interim safety and efficacy data after approximately 50% of the total sample size has been randomized in the study will be prepared and summarized to support presentation of initial results to India BoH.

1.2. Schema



1.3. Schedule of Activities

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

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

Visit Identifier	Day -28 Screening	Day 1 Baseline	Day 15±1 Week 2	Day 29±2 Week 4	Day 57±3 Week 8	Day 85±3 Week 12 EOT	EOS, 4 weeks post EOT±3 days
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Follow-up
Informed Consent and Assent, as applicable	X						
Demographics, Medical History	X						
Inclusion/Exclusion Criteria	X	X					
Physical Examination[a]	X	X				X	
Vital Signs	X	X	X	X	X	X	X
Height	X						
Weight	X	X					
Chest X-ray	X						
ECG	X					X	
Clinical Chemistry, Hematology (including coagulation panel), Lipid Profile[b]	X			X		X	
HIV, HBsAg, HCV	X						
TB test (as per site standards)	X						
Knee MRI for adolescent participants 12 to <18 years of age[c]	X						

Visit Identifier	Day -28 Screening	Day 1 Baseline	Day 15±1 Week 2	Day 29±2 Week 4	Day 57±3 Week 8	Day 85±3 Week 12 EOT	EOS, 4 weeks post EOT±3 days
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Follow-up
Serum Pregnancy test (for WOCBP) or FSH	X						
Urine Pregnancy test (for WOCBP only)		X	X	X	X	X	X
IGA	X	X	X	X	X	X	
EASI	X	X	X	X	X	X	
SCORAD	X	X	X	X	X	X	
Photography for AD lesion[d]		X				X	X
POEM		X	X	X	X	X	
ADCT		X	X	X	X	X	
PP-NRS[e]	X						
Randomization		X					
Dispense Investigational Product		X	X	X	X		
Investigational Product Administration		X	X	X	X	X	
Investigational Product Accountability			X	X	X	X	
Contraception check[f]	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X
AEs, SAEs and Concomitant Medication Monitoring	X……...……...……..X						

Visit Identifier	Day -28 Screening	Day 1 Baseline	Day 15±1 Week 2	Day 29±2 Week 4	Day 57±3 Week 8	Day 85±3 Week 12 EOT	EOS, 4 weeks post EOT±3 days
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Follow-up

a. Complete physical examinations will be conducted at Screening and EOT. Brief physical examinations will be conducted at Baseline. Refer to Section 8.2.1 for details of physical examinations.
b. Clinical chemistry includes: urea, sCr, sCysC (at Screening only), estimated creatinine clearance, AST, ALT, TBili, alkaline phosphatase. The lipid profile will include total cholesterol, LDL, VLDL, HDL, and triglycerides. Hematology includes: hemoglobin, WBC, neutrophils (%, absolute), lymphocytes (%, absolute), platelets, and coagulation panel (APTT, PT/INR). Laboratory tests with abnormal results may be repeated once during the screening period; the last value will be used to determine eligibility. Fasting lipid profile panel require at least an 8 hour fast. If possible, participants should comply with fasting requirements at those visits detailed above.
c. This only applies for participants who were <18 years of age at the screening visit. Further substudy details like post baseline MRI conduct and other activities will be mentioned in Section 10.10 (Appendix 10).
d. Refer to Section 8.1.6 for details of photography.
e. PP-NRS evaluation will be conducted at Screening to evaluate AD severity.
f. 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 for contraceptive guidance.

2. INTRODUCTION

Abrocitinib is a JAK1 inhibitor that is being investigated as a treatment for patients with AD.

Abrocitinib is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the ATP binding site and has a high degree of selectivity for JAK1 when compared, 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. The selective inhibition of JAK1 will lead to modulation of multiple cytokine pathways involved in the pathophysiology of AD including IL-4, IL-5, IL-13, IL-22, IL-31, TSLP, and IFN-γ.

2.1. Study Rationale

Abrocitinib is currently being developed as a novel treatment for AD. Data from phase 3 studies (B7451012, B7451013, B7451014, B7451029, B7451036, B7451050) that evaluated abrocitinib 100 mg and 200 mg in patients with moderate to severe AD reported statistically significant improvement in efficacy endpoints in both treatment groups compared to the placebo group with an acceptable safety profile. The purpose of the study is to provide additional safety and efficacy data for abrocitinib in India.

2.2. Background

2.2.1. Atopic Dermatitis

AD, also known as atopic eczema, is a chronic, relapsing inflammatory skin condition characterized by dry, pruritic skin lesions which can affect any part of the body. Distribution and morphology of AD skin lesions are distinguishably different between pediatric and adult populations [2,3] with lesions in infants occurring mainly on the face and extensor surfaces of limbs, while adolescents/adults often present with lichenified and excoriated plaques at flexures, and with involvement of the head, neck, upper trunk, shoulders, and scalp. The lifetime prevalence of AD in children is 10%-20% with 70% of cases occurring in children <5 years of age. Most cases (approximately 75%) improve by adulthood, while approximately 25% of AD patients have symptoms throughout their life. Key cytokines implicated in the pathophysiology of AD including IL-4, IL-5, IL-13, IL-22, IL-31, and IFN-γ, require JAK1 for signal transduction, suggesting that selective JAK1 inhibitors, that modulate the activity of these cytokines, represent a compelling approach to the treatment of inflammatory skin diseases such as AD.[4]

AD affects up to 25% of children and 2%-4% of adults worldwide.[5] Research suggests that approximately 17% of adolescents and 58% of adults with AD have moderate-to-severe disease,[6,7] the burden of which is multidimensional. For example, persons with moderate-to-severe AD experience sleep disturbances, physical pain, and psychological distress.[8] In addition to disease-related atopic comorbidities, those with moderate-to-severe AD also experience greater health care resource utilization and incur significant economic burdens when compared with non-AD controls.[9]

As per the Indian consensus statement for management of AD, patients with AD suffer from dry skin and defective skin barrier function, that manifests mainly as pruritus. Systemic therapy is used to treat patients with moderate to severe AD on failure of topical treatments. Current immunosuppressive agents have modest efficacy in patients with moderate-to-severe AD but are associated with AEs that often limit long-term use.

2.2.2. Clinical Efficacy and Safety of Abrocitinib

Abrocitinib is being developed as an oral treatment for patients with moderate to severe AD based on unmet need for an effective oral systemic treatment for moderate-to-severe AD with a manageable safety profile, its novel mechanism of action, and the clinical results obtained in Phase 1, Phase 2, and Phase 3 studies. Selective inhibition of JAK1 with abrocitinib modulates signaling by IL-4, IL-13, and other cytokines (eg, IL-31, IL-22, and TSLP) involved in the pathogenesis of AD and pruritus while sparing JAK2 inhibition and minimizing the risk for neutropenia and anemia. Inhibition of neuronal JAK1 dependent pathways has also been shown to ameliorate pruritus.[1]

Phase 2b in AD

B7451006 was a Phase 2b POC trial in 269 adults (ages 18-75) with moderate-to-severe AD investigating doses of abrocitinib 10, 30, 100, and 200 mg or placebo taken once daily for up to 12 weeks. The primary endpoint in this study was the proportion of participants achieving an 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 abrocitinib 100 mg and 200 mg dose groups were significantly greater than placebo in patients with moderate to severe AD. The IGA response rates of the 200 mg and 100 mg groups were 44.5% and 27.8%, respectively. The IGA response rate in the placebo group was 6.3% and 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 changes from baseline in EASI scores at Week 12 were significantly higher for both the 200 mg and 100 mg groups compared to placebo. The estimated percent change from baseline in EASI score was 35.2% in the placebo group, 82.6% in the 200 mg group and 59.0% in the 100 mg group.

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. Response rates at Week 12 for the 10 mg and 30 mg groups were not significantly different from placebo. A key differentiating feature for the JAK1 inhibitor is rapid resolution of itch associated with AD. Significant separation from placebo was achieved for the Pruritus 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 Pruritus NRS score).

Abrocitinib appeared generally safe and well tolerated in this study. Overall, AEs and 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 SOCs of infections and infestations, skin and subcutaneous tissue disorders and gastrointestinal disorders, 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). There were dose dependent decreases in platelet counts observed in the study, which plateaued at Week 4. Further details of the clinical Phase 2 development program can be found in the IB.

Phase 3 in AD

B7451012 and B7451013 were replicate randomized, double-blind, placebo-controlled, parallel-group, Phase 3 studies which evaluated the efficacy and safety of abrocitinib monotherapy in 387 and 391 participants, respectively, aged 12 years and older, with moderate to severe AD. The treatment duration for both studies was 12 weeks. Eligible participants were randomized in a 2:2:1 ratio to receive abrocitinib 200 mg or 100 mg QD or matching placebo. Randomization was stratified by baseline disease severity (moderate [IGA=3] and severe [IGA=4] AD) and age (age <18 and ≥18 years).

The co-primary efficacy endpoints were response based on the IGA score of clear (0) or almost clear (1) and a reduction from baseline of ≥2 points at Week 12 and response based on ≥75% improvement from baseline in EASI score (EASI-75) at Week 12. The key secondary efficacy endpoints were response based on ≥4 points improvement from baseline in the peak pruritus NRS (PP-NRS) for severity at Weeks 2, 4, and 12 and change from baseline in PSAAD at Week 12.

Both studies met both co-primary endpoints. Specifically, abrocitinib 200 mg QD was superior to placebo at Week 12 for both IGA and EASI-75 responses.

- In B7451012, IGA response rate was 43.8% in the 200 mg QD arm and 7.9% for the placebo arm. The EASI-75 response rate was 62.7% in the 200 mg QD arm and 11.8% for the placebo arm. The treatment difference (95% CI) for IGA was 36% (26.2, 45.7), p<0.0001 and that for EASI-75 was 51% (40.5, 61.5), p<0.0001.

  At Week 12, abrocitinib 100 mg QD was also superior to placebo for both IGA and EASI-75 responses. The IGA and EASI-75 response rates were 23.7% and 39.7%, respectively, in the 100 mg QD arm. The treatment difference (95% CI) for IGA was 15.8% (6.8, 24.8), p=0.0037 and that for EASI-75 was 27.9% (17.4, 38.3), p<0.0001.

- In B7451013, the IGA response rate was 38.1% in the 200 mg QD arm and 9.1% for the placebo arm. The EASI-75 response rate was 61.0% in the 200 mg QD arm and 10.4% for the placebo arm. The treatment difference (95% CI) for IGA was 28.7% (18.6, 38.8), p<0.0001 and that for EASI-75 was 50.5% (40.0, 60.9), p<0.0001.

  At Week 12, abrocitinib 100 mg QD was also superior to placebo for both IGA and EASI-75 responses. The IGA and EASI-75 response rates were 28.4% and 44.5%, respectively, in the 100 mg QD arm. The treatment difference (95% CI) for IGA was

19.3% (9.6, 29.0), p=0.0008 and that for EASI-75 was 33.9% (23.3, 44.4), p<0.0001. In addition, the treatment difference for abrocitinib 200 mg QD relative to abrocitinib 100 mg QD was 9.7% (-0.7, 20.0) for IGA and 16.5% (5.6, 27.4) for EASI-75 at Week 12.

Both studies met the key secondary endpoints. Both abrocitinib doses showed statistically significant separation from placebo in response rates at all visits after baseline. In addition, response rates in the 200 mg QD arm were consistently higher than in the 100 mg QD arm.

Change from baseline in the total PSAAD score at Week 12 was statistically significant for both abrocitinib doses relative to placebo. In addition, the change from baseline in the 200 mg QD arm was greater in magnitude than in the 100 mg QD arm.

Safety results in both studies show that both doses of abrocitinib were well-tolerated, and there were no unexpected safety events. The proportion of participants experiencing AEs was higher in the abrocitinib group compared with the placebo group. The proportion of participants experiencing SAEs and severe AEs was similar across all treatment arms. The discontinuation rates due to an AE were low in each treatment arm compared to placebo.

B7451014 was a randomized, responder-enriched, double-blind, placebo-controlled, Phase 3 dosing regimen study to evaluate the efficacy and safety of abrocitinib monotherapy in participants aged 12 years and older with chronic moderate to severe AD as defined per the inclusion criteria and a body weight ≥40 kg. The study met its primary endpoint (ie, assessment of loss of response requiring rescue treatment during the blinded treatment period). By Week 52, participants in each abrocitinib group had a significantly higher probability of not flaring compared to placebo. Abrocitinib was well tolerated. The observed safety events were consistent with those seen in other abrocitinib studies.

Two Phase 3 studies evaluated 100 mg and 200 mg of abrocitinib in combination with topical medicated therapy. Study B7451029 in adults evaluated abrocitinib in context with dupilumab for 16 weeks in a double-blind, double-dummy design. Both doses were statistically superior to placebo with respect to the co-primary endpoint of IGA 0-1 and EASI-75, and met the key secondary endpoint showing a statistically significant difference from dupilumab in the relief of itch. Study B7451036 evaluated abrocitinib 100 mg and 200 mg QD in a 12-week, double-blind placebo-controlled fashion in adolescents, and showed similar results as those observed in adolescents from the monotherapy studies. Both doses met the co-primary endpoints of IGA and EASI-75 responses at Week 12 and the 200 mg dose met the key secondary endpoint showing statistically significantly greater proportions of PP-NRS4 responders compared with the placebo group at Weeks 2, 4, and 12. Safety results show that both doses of abrocitinib were well-tolerated, and there were no unexpected safety events. The discontinuation rates due to an AE were low in both abrocitinib treatment arms (5.8% for both 100 mg and 200 mg) compared to placebo (9.1%).

The B7451050 study has evaluated abrocitinib 200 mg QD in a head to head manner compared with dupilumab in adult participants. Both primary endpoints were met; abrocitinib 200 mg QD was clinically and statistically superior to dupilumab at Week 2 in regard to proportion of PP-NRS4 responders and at Week 4 with regard to proportion of EASI-90

responders. Additionally, the prespecified and error controlled key secondary endpoint was met; abrocitinib 200 mg QD is clinically and statistically superior to dupilumab in regard to proportion of responders at Week 16 attaining EASI-90.

2.3. Benefit/Risk Assessment

There was clinically meaningful benefit demonstrated with abrocitinib in the Phase 2b POC study (B7451006) in adult participants with moderate to severe AD and the completed Phase 3 studies (B7451012, B7451013, B7451014, B7451029, B7451036, B7451050). Similar benefit-risk profile has been observed in adolescents with AD. The potential risks of treatment include those that were noted in Phase 2b and Phase 3 studies and those based on the pharmacology of JAK inhibitors and include venous thromboembolism, viral reactivation, serious and opportunistic infections, hematopoietic effects (including reduced platelet count), and malignancy and immunoproliferative disorders. The most common events were gastrointestinal disorders, nervous system disorders, and skin/subcutaneous tissue disorders.

An abrocitinib-related long bones finding was observed in repeat-dose short duration (up to 1 month) toxicity studies in young rats. This microscopic finding of bone dystrophy that was noted in young rats is not expected to pose a risk in patients ≥12 years of age at clinically relevant therapeutic doses and exposures. This is because the microscopic long bones finding was considered reversible, nonprogressive, and the NOEL exposure margin at which no bone finding was noted was at least 6 × the unbound human AUC at the maximum clinical dose of 200 mg QD (the bone finding was noted at ≥23×). No abrocitinib-related clinical observations, macroscopic, or microscopic, by histopathological examination, long bones findings were observed in rats at any dose in the 6-month toxicity study (up to 26 × the unbound human AUC at the maximum clinical dose of 200 mg QD) or in young or adult monkeys in any of the toxicity studies up to 9 months in duration (up to 31 × the unbound human AUC at the maximum clinical dose of 200 mg QD). The doses used in rats exceeded the relevant human equivalent exposures. In addition, young monkey is a sensitive nonclinical species for the detection of potential effects on bone growth and development relevant to adolescent humans (Section 10.10) and no adverse effects on bone were found in monkeys. The risk-benefit for adolescents to participate in this study remains favorable. The preclinical findings indicate a low risk of potential effects in human adolescents, however, in order to fully investigate this possibility, a substudy has been added to this protocol (Appendix 10) to evaluate whether abrocitinib has any potential effects on bone with regard to bone safety findings in knee MRI in adolescent participants with moderate to severe AD in India.

Appropriate risk evaluation and mitigation strategies have been incorporated into this protocol.

Overall, there is a favorable benefit-risk profile to support the continued development of abrocitinib in the treatment of participants with AD for both the 100 mg and 200 mg doses.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of abrocitinib is provided in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Abrocitinib		
1) Serious infection and opportunistic infections are a potential risk of abrocitinib.	1) The potential risk has been reported for other JAK inhibitors. Refer to the IB for more information.	1) Participants with acute and chronic skin infections, history of specific recurrent infections and/or latent infections will be excluded from the study including participants with evidence of active, latent, or inadequately treated infection with Mycobacterium TB. Participants with a known immunodeficiency disorder will be excluded. Through regular clinic visits, the investigator will closely monitor the participant for the development of signs and symptoms of infection during study participation. Participants who develop serious infections will be evaluated for potential discontinuation.
2) Viral reactivation is a potential risk of abrocitinib.	2) The potential risk has been reported for other JAK inhibitors. Refer to the IB for more information.	2) Participants known to be infected with HIV, Hepatitis B, or Hepatitis C are excluded from study. Participants with a history of disseminated herpes zoster or disseminated herpes simplex are excluded from the study.
3) Malignancy and lymphoproliferative disorders.	3) The potential risk has been reported for other JAK inhibitors. Refer to the IB for more information.	3) Participants who 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 will be excluded. At regular clinic visits, the investigator will complete skin examinations.
4) Decreased lymphocyte counts.	4) The potential risk has been reported for other JAK inhibitors. Refer to the IB for more information.	4) Participants with an absolute lymphocyte count of $<0.50 \times 10^9$ /L ($<500/mm^3$) will be excluded from the study. Lymphocyte counts will be monitored throughout the study via laboratory assessments.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) Abrocitinib		
5) Decreased platelet counts.	5) The potential risk has been reported for other JAK inhibitors. Refer to the IB for more information.	5) Participants with any of the following will be excluded from the study: platelet counts of <150 × 10^9/L (<150,000/mm^3); current or past medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction. Additionally, platelet counts will be monitored throughout the study.
6) Alterations in lipid profile.	6) The potential risk has been reported for other JAK inhibitors. Refer to the IB for more information.	6) Investigators will monitor lipid profiles in participants throughout the study.
7) Venous thromboembolism.	7) The potential risk has been reported for other JAK inhibitors. Refer to the IB for more information.	7) Participants with an increased risk of developing VTE will be excluded from the study and discontinued if they develop VTE or become high risk for VTE during study treatment.
8) DDI risk with medications that are strong inhibitors and inducers of CYP2C9 and CYP2C19 enzymes.	8) The risk is based on results of DDI studies. Refer to the IB for more information.	8) Concomitant use of inhibitors and inducers of CYP2C9 and CYP2C19 enzymes is not allowed in the study.

2.3.2. Benefit Assessment

All adolescent and adult participants in this study will receive treatment with abrocitinib (100 mg and 200 mg QD) which has previously demonstrated efficacy and an acceptable safety profile in Phase 3 studies and has been approved for the treatment of moderate to severe AD in Great Britain and Japan. It is possible that a study participant's AD symptoms may improve during treatment with abrocitinib, but there is no guarantee of benefit. Participants may also benefit from protocol participation by gaining knowledge about their health status through study tests (eg, physical examinations, laboratory assessments, vital sign measurements) conducted at regular intervals during the trial.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with abrocitinib are justified by the anticipated benefits that may be afforded to participants with moderate to severe AD who have inadequate treatment options. The study will collect safety and efficacy data in a population representative of those who will receive the study intervention if approved by regulatory authorities.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To evaluate the safety of abrocitinib in participants aged 12 years and older with moderate to severe AD.	• Incidence of AEs and SAEs.	• The primary estimand for safety is the incidence of AEs and SAEs in participants aged 12 years and older with moderate to severe AD, from the time of first dose to Week 16, regardless of dosing compliance or treatment discontinuation.
Secondary:	**Secondary:**	**Secondary:**
• To assess the efficacy of abrocitinib in participants aged 12 years and older with moderate to severe AD.	• Response based on IGA score of clear (0) or almost clear (1) and greater than or equal to 2 points improvement from baseline at Week 12. • Response based on achieving ≥75% improvement from baseline in the EASI total score (EASI-75) at Week 12. • Response based on ≥75% improvement from baseline in SCORAD (SCORAD75) at Week 12. • Change from baseline in POEM at Week 12 and at all scheduled time points. • Change from baseline in ADCT at Week 12 and at all scheduled timepoints.	• The secondary estimand is the treatment effect of abrocitinib on participants aged 12 years and older with moderate to severe AD, based on IGA response, EASI-75 response and SCORAD75 response from baseline to Week 12, considering patients who discontinued treatment as nonresponders and based on outcome measures of POEM and ADCT from baseline to Week 12 and at all scheduled timepoints. Data collected after treatment discontinuation is excluded.

Objectives	Endpoints	Estimands
Primary substudy objective(s):	**Primary substudy endpoint (as secondary endpoints for B7451094):**	**Primary substudy estimand(s):**
• To evaluate the potential effects of abrocitinib on bone development in adolescent participants 12 to <18 years of age, as assessed by knee MRI.	• The proportion of bone safety findings in knee MRI 1 year after randomization in adolescent participants exposed to abrocitinib 100 mg and 200 mg QD.	• The primary substudy estimand is the incidence of bone safety findings in knee MRI after 1 year of being exposed to abrocitinib in adolescent participants 12 to <18 years of age, regardless of dosing compliance or treatment discontinuation.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, open-label, parallel-group study to assess the safety and efficacy of orally administered tablets of abrocitinib 100 mg and 200 mg QD in participants aged 12 years and older with moderate to severe AD in India. A total of approximately 200 participants will be enrolled from approximately 10 sites in India. Approximately 200 participants will be randomly assigned to study intervention. Safety endpoints will be assessed throughout the entire study. Secondary efficacy assessments are conducted from Screening to EOT visit.

After providing informed consent or, for minor age participants, informed consent of the legally authorized representative (parent/guardian) and assent of the study participant, participants will be assessed for study eligibility at the Screening visit. Participants will undergo screening within 28 days prior to randomization. Use of screening procedures exceeding 28 days prior to randomization should be discussed with the Pfizer medical monitor.

During the screening period, systemic treatments for AD will be washed out, as applicable, according to eligibility requirements (refer to Inclusion and Exclusion Criteria in Section 5.1 and Section 5.2, respectively). Eligible participants must have a documented history, within 6 months of the screening visit, of inadequate response or intolerance to treatment with medicated topical therapy for at least 4 weeks or must have required systemic therapies for control of their disease.

Eligible participants must meet the eligibility criteria at baseline. Participants who meet eligibility criteria at baseline will undergo Day 1 assessments and be randomized in a 1:1 ratio to receive abrocitinib 200 mg QD or abrocitinib 100 mg QD in an open-label fashion.

The total treatment period is 12 weeks. All participants will undergo a 4week offtreatment safety follow-up period thereafter.

This study protocol also includes a substudy evaluating whether abrocitinib has any potential effects on adolescent bone with regard to bone safety findings in knee MRI. All adolescent

participants 12 to <18 years of age will continue to receive study intervention until 1 year after randomization in the main study. Section 10.10 (Appendix 10) contains complete information regarding the substudy.

For study estimands, refer to Section 3.

4.2. Scientific Rationale for Study Design

This study will investigate the safety and efficacy of abrocitinib in participants with moderate to severe AD in Indian population if approved by the India regulatory authority, as India was not part of the global trials. This study is designed to specifically evaluate abrocitinib in participants 12 years of age or older with AD in India.

4.2.1. Safety Adjudication Committee

To facilitate standardization of assessments within the abrocitinib program, a safety event adjudication committee of independent clinical experts will assess malignancies, cardiovascular events, and opportunistic infections (including eczema herpeticum and other infections of special interest) in this study. A separate adjudication committee will be established for the MRI substudy to evaluate bone-related events.

Events requiring review may be identified by the Pfizer study team or designee during the review of participant data listings or monitors during routine monitoring of participants' study records. The Pfizer study team or designee will notify relevant investigators of any events identified. Investigators will be responsible for obtaining and submitting the documentation to be reviewed by the safety event adjudication committee. Documentation includes, but is not limited to, hospital progress notes, laboratory reports, and diagnostic reports. These documents may be reviewed by Pfizer.

Further information about this safety event adjudication committee is provided in a charter, including a description of the scope of the committee's responsibilities, the process and definitions to be utilized by the committee for adjudication, and communication plan including timelines.

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

4.2.2. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for abrocitinib, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required for WOCBP (see Appendix 4).

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 AD. The 200 mg QD dose is expected to provide efficacy similar to that of currently approved systemic treatments in moderate-to-severe AD, and was therefore selected as the high dose for evaluation in Phase 3 studies. An additional dose of 100 mg QD was also selected for evaluation in Phase 3, since this dose is expected to provide clinical efficacy in IGA response, while differentiating from the higher dose in terms of expected efficacy and systemic exposure. Both 100 mg and 200 mg QD doses demonstrated acceptable safety and tolerability in the Phase 2 study, and the 200 mg dose also demonstrated acceptable safety and tolerability in the completed Phase 3 studies (B7451012 and B7451013). Further details are available in the IB. Both abrocitinib 100 mg and 200 mg QD doses have been approved for the treatment of moderate to severe AD in Great Britain and Japan, for adults and adolescents. Indian patients are not expected to have altered PK or altered response to the drug.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial.

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

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Participants must be of 12 years of age or older, at the time of informed consent.

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

Type of Participant and Disease Characteristics:

2. Meet all the following AD criteria:

    - Clinical diagnosis of chronic AD (also known as atopic eczema) for at least 1 year prior to Day 1 and has confirmed AD (Hanifin and Rajka criteria of AD[10]).

- Moderate to severe AD (affected BSA ≥10%, IGA ≥3, EASI ≥16, and PPNRS ≥4 at the baseline visit);
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks), or who have required systemic therapies for control of their disease.

3. Negative pregnancy test for females of childbearing potential at Screening. Female participants of childbearing potential must agree to use a highly effective method of contraception for the duration of the active treatment period and for at least 28 days after the last dose of study intervention.

Weight:

4. Body weight ≥25 kg at Baseline.

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol. Evidence of a personally signed and dated ICD indicating that the participant (or a legally acceptable representative, parent(s)/legal guardian) has been informed of all pertinent aspects of the study. For minors under the age of legal consent in India, assent of the participating child needs to be documented for the age range 12 to 18 years in addition to the parental informed consent.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Currently have active forms of other inflammatory skin diseases or have evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, lupus).

2. A current or past medical history of conditions associated with thrombocytopenia, coagulopathy or platelet dysfunction or QT interval abnormalities.

3. Have increased risk of developing venous thromboembolism, eg, deep vein thrombosis or pulmonary embolism:

   - History of venous thromboembolism, or

   - First degree relative with unprovoked venous thromboembolism (ie, 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 (eg, Factor V Leiden).

4. Have a history of any lymphoproliferative disorder such as EBV related lymphoproliferative disorder, history of lymphoma, leukemia, or signs or symptoms suggestive of current lymphatic or lymphoid disease.

5. Past history or active infection with Mycobacterium TB, disseminated herpes zoster or disseminated herpes simplex, HIV, Hepatitis B, or Hepatitis C.

6. 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.

7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgement, make the participant inappropriate for the study. Any psychiatric condition including recent or active suicidal ideation or behavior that met any of the following criteria when screened for during the main study:

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

    - 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;

    - The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria;

    - In the opinion of the investigator or Pfizer (or designee) exclusion is required.

Prior/Concomitant Therapy:

8. Prior treatment with systemic JAK inhibitors.

9. Participants who are vaccinated with live attenuated vaccine within the 6 weeks prior to the first dose of abrocitinib or who are expected to be vaccinated with these vaccines during treatment or during the 6 weeks following discontinuation of abrocitinib.

10. Have received any of the following treatment regimens specified in the timeframes outlined below:

    Within 1 year of first dose of study intervention:

    - Prior treatment with non B cell-specific lymphocyte depleting agents/therapies (eg, 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 CD 19/20+ counts by FACS analysis.

    Within 12 weeks of first dose of study intervention:

    - Biologic drugs that have immunomodulatory properties or could be used to treat AD: within 12 weeks of first dose of investigational product or 5 half-lives (if known), whichever is longer.

    Other biologics without immunomodulatory properties (eg, insulin) are permissible at the judgement of the Investigator.

    Within 4 weeks of first dose of study intervention:

    - Use of oral immunosuppressive drugs (eg, 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: Systemic corticosteroids must be discontinued before Study Day 1, but a specific timeframe for discontinuation prior to first dose of abrocitinib is not required.

    NOTE: Corticosteroid inhalers and intranasal sprays are permissible.

    NOTE: Ophthalmic corticosteroids are permissible.

    Within 1 week of first dose of study intervention:

    - Anti-platelet drugs.

    Note: low dose acetyl salicylic acid (<100 mg QD) is permitted, for the purpose of cardiovascular prophylaxis, at the discretion of the investigator.

11. Require treatment with prohibited concomitant medication(s) or have received a prohibited concomitant medication.

Prior/Concurrent Clinical Study Experience:

12. Participation in other studies involving investigational drug(s) or vaccine within 8 weeks or within 5 half-lives (if known) whichever is longer, prior to study entry and/or during study participation.

Diagnostic Assessments:

13. Any of the following abnormalities in clinical laboratory tests at Screening:

    - Absolute neutrophil count of $<1.0 \times 10^9$/L ($<1000/mm^3$);
    - Platelet count of $<150 \times 10^9$/L ($<150,000/mm^3$);
    - Absolute lymphocyte count of $<0.50 \times 10^9$/L ($<500/mm^3$);
    - Estimated Creatinine Clearance <60 mL/min using the CockcroftGault method;
    - AST or ALT values >2 times the ULN;
    - TBili ≥1.5 times the ULN.

Other Exclusions:

14. Pregnant or breastfeeding women, or women of childbearing potential who are unwilling to use highly effective contraception consistently and correctly for the entire duration of the study and for at least 28 days after the last dose of study intervention.

15. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

1. On study visit days, participants must not administer study intervention until instructed to do so by the investigator or designated study site staff. The study sites need to ensure clinical assessments are performed before dose is administered.

2. On study visit days, showering or bathing is permitted prior to attending the study visit, but participants must not moisturize or apply emollient.

3. On study visit days, topical therapies (ie, non-medicated topical therapy and medicated topical therapy, per protocol guidelines as described in Section 6.8.2) 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 6.8.1).

5.3.1. Meals and Dietary Restrictions

On study visit days as per the SoA participants should comply with fasting requirements for at least 8 hours prior to the visit, if possible. Water and permitted non-study medications are allowed (Section 6.8.1).

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. Vaccine and Exposure to Infections Guidelines

5.3.3.1. Participant Specific Recommendations

It is recommended that all participants should be up-to-date with respect to standard-of-care vaccinations (as defined by their country health ministry or AD guidelines). This includes approved/emergency use authorization COVID-19 vaccinations. Vaccination of participants with live attenuated vaccine is prohibited within the 6 weeks prior to first dose of abrocitinib, during treatment with abrocitinib, and during the 6 weeks following discontinuation of abrocitinib. Routine inactivated or other types of vaccines are allowed before and during the study.

5.3.4. Contraception

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 from the permitted list of contraception methods (see Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception) considering that their risk for pregnancy may have changed since the last visit. 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 or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 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(S) AND CONCOMITANT THERAPY

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

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

6.1. Study Intervention(s) Administered

Study Intervention		
Intervention Name	Abrocitinib	Abrocitinib
ARM Name	Abrocitinib 200 mg QD	Abrocitinib 100 mg QD
Type	Small molecule	Small molecule
Dose Formulation	Tablet	Tablet
Unit Dose Strength	100 mg	100 mg
Dosage Level	100 mg x 2 tablets	100 mg x 1 tablet
Route of Administration	Oral	Oral
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.

Study Arms		
Arm Title	Abrocitinib 200 mg QD	Abrocitinib 100 mg QD
Arm Type	Experimental	Experimental
Arm Description	Participants will receive abrocitinib 200 mg QD for 12 weeks.	Participants will receive abrocitinib 100 mg QD for 12 weeks.
Associated Intervention Labels	Abrocitinib	Abrocitinib

6.1.1. Administration

Orally administered study intervention, abrocitinib 100 mg tablet(s), will be administered QD from Day 1 to Week 12. Participants will be dispensed bottles of study intervention at Day 1, Week 2, Week 4 and Week 8 visits. Study intervention administration details for substudy participants is mentioned in Section 10.10 (Appendix 10).

Participants will be given clear dosing instructions to take either 1 tablet or 2 tablets of study intervention once daily by mouth with meals, preferably in the morning whenever possible,

at approximately the same time of day. On study visit days, participants (and caregivers, if applicable) are to be instructed to refrain from dosing at home and are to administer study intervention in the clinic under observation, at the end of the study visit.

Participants will swallow the oral study intervention whole and will not manipulate or chew the medication prior to swallowing. If the participant experiences nausea, might consider administering the oral study intervention at night.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

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

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

7. 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), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the

investigator by the participant. Returned study intervention must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

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

6.3. Measures to Minimize Bias: Randomization and Blinding

There will be no blinding measures, because the study is open label.

6.3.1. Allocation to Study Intervention

This is an open-label study and the specific study intervention dispensed to the participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the study intervention assignment on the applicable CRF, if required. Potential bias will be reduced by the following steps: central randomization. Re-randomizations are not allowed. In case a participant is randomized in error, the participant must be discontinued from study before any study intervention is dispensed.

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

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

Returned study intervention must not be redispensed to the participants.

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

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit by delegated site personnel. Compliance will be assessed by combination of counting returned tablets and

discussion with the participant during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

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

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

- Participants administering >8 tablets in 1 day or administering ≥4 tablets/day for 4 consecutive days;
- Participants who have an overall compliance of <80% or >120% between visits for oral study intervention;

Any deviation from protocol specified dosing should be recorded as a protocol deviation and the investigator or designee is to counsel the participant and parent(s)/legal guardian (if applicable) and ensure steps are taken to improve compliance. In addition, if the compliance deviation reaches the thresholds defined above it should also be recorded as a medication error (see Section 8.3.10).

6.5. Dose Modification

Dose modification is not allowed in this study.

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

No intervention will be provided to study participants at the end of their study participation. Investigator may consider alternative forms of therapy for their participant until abrocitinib is potentially available.

6.7. 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.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study intervention (whichever is longer). Closely monitor the participant for any AEs/SAEs.

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

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

5. A plasma sample for PK analysis may be requested by the Pfizer clinician (determined on a case-by-case basis).

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

6.8. 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.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (refer to Appendix 4).

Participants will abstain from all prohibited concomitant medications as described in Section 6.8.2 and Appendix 7. Medications that are taken in the Screening 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 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 prompt evaluation for potential new or worsening adverse events.

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. Following Day 1, the addition of concomitant medications or any change in the dosage should be limited to those considered medically essential.

The concomitant medication for any reason must be a locallyapproved medication and dose.

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

6.8.1. Permitted Concomitant Treatments

The following concomitant AD therapies are permitted during the study:

- Oral antihistamines;
- Non-medicated emollients and all topical medications for AD at the discretion of the investigator and in accordance with their usual practice.

The following concomitant medications are permitted during the study:

- Corticosteroid inhalers and intranasal sprays are permissible for participants receiving a stable dose;
- Ophthalmic corticosteroids are permissible for participants receiving a stable dose;
- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (Refer to Appendix 4);
- Dietary supplements (defined as vitamins and minerals, and purified food substances) of standard potency are allowed in amounts not known to be associated with adverse effects (such as hyper-vitaminosis).

6.8.2. Prohibited Medications and Treatments

Participants are required to discontinue and avoid using certain medications and treatments (refer to Inclusion Criteria [Section 5.1], Exclusion Criteria [Section 5.2], 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.

Participants who received prior treatment with systemic JAK inhibitors are to be excluded from the study. Prior treatment with topical JAK inhibitors is not exclusionary.

Restrictions on certain vaccinations are described in Section 5.3.3.

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

6.8.3. Rescue Medicine

After Week 4 if medically necessary, participants with intolerable AD symptoms may receive locally-approved rescue therapy with systemic corticosteroids for up to 14 days at a time, at the investigator's discretion, according to local product label. Participants receiving systemic rescue therapy may continue to receive abrocitinib concurrently and should

continue study visits and assessments. Rescue therapy will be obtained locally and administration must be recorded on the CRF. As possible, investigators should conduct safety and efficacy assessments (eg, safety labs, disease severity scores) before administering rescue therapy. An unscheduled visit may be used for this purpose, if necessary.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Other AE, per judgment of the investigator, requiring discontinuation from treatment (or, if necessary/desired, following discussion with sponsor).
- Pregnancy.
- Serious infection must result in temporary interruption of study intervention. Study intervention cannot be restarted until the serious infection has resolved and restarting study intervention has been discussed and agreed with the medical monitor. If the participant cannot be restarted on study intervention within 28 days, or the infection is not resolved, or there is no agreement received from the 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).
- Any AE or laboratory abnormality, that per the investigator's judgement requires temporary interruption to dosing of study intervention for >28 days.
- Any AE of venous thromboembolism.
- 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.
- Estimated Creatinine Clearance <60 mL/min using the Cockcroft-Gault method.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for end of treatment and end of study/follow-up assessments. See the SoA for

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

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

If a participant has a clinically significant, treatment-emergent, abnormality at the time of withdrawal from the study, the Pfizer Medical Monitor (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. Note that discontinuation of study treatment does not represent withdrawal from the study.

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Appendix 5 or if the investigator believes that it is in best interest of the participant.

Refer to 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.

7.2. 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 study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Behavioral, compliance or administrative reasons.

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

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.

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. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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

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

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

Immediate safety concerns should be discussed with the sponsor as soon as possible upon awareness to determine if the participant should continue or discontinue study intervention.

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

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

The estimated total blood sampling volume for a participant who is in the study intervention phase for up to 12 weeks and who completes the EOT and Follow-up/EOS visits is approximately 50 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments, and the investigator should remain mindful that the total blood volume taken during the study does not exceed limits established locally.

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. 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 atopic dermatitis and assign an IGA score and category as described in Table 1. The assessment will be a static evaluation without regard to the score at a previous visit.

Table 1. IGA Scores

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.

8.1.3. 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.

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 2.

Table 2. Clinical Sign Severity Scoring Criteria for the 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 3). When measuring, the handprint unit refers to the size of each individual participant's hand with fingers in a closed position.

Table 3. Handprint Determination of BSA

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

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

The extent (%) to which each of the four body regions is involved with AD is categorized to a numerical Area Score using a non-linear scaling method according to the following BSA scoring criteria (Table 4).

Table 4. 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 5).

Table 5. 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.

The EASI Clinical Sign Severity Scores for each of the 4 body regions and the involvement by total number of handprints for each of the 4 body regions will be recorded on the CRF.

8.1.3.1. BSA Efficacy

BSA Efficacy will be derived from the sum of the BSA affected by AD as measured in handprints across the 4 body regions assessed as part of the EASI assessment (refer to 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 body surface area affected with AD.

8.1.4. SCORAD

SCORAD is a validated scoring index for atopic dermatitis, which combines extent (0-100), severity (0-18), and subjective symptoms (0-20) based on pruritus and sleep loss, each scored using a visual analog scale (0-10).

Extent (A, maximum score of 100%)

To determine extent of AD, rule of 9 is used to calculate body surface area affected by AD as a percentage of the whole-body surface area. Body surface area as percentage of total body surface area for each body region is as follows:

- Head and neck 9%;
- Upper limbs 9% each;
- Lower limbs 18% each;
- Anterior trunk 18%;
- Back 18%;
- 1% for genitals.

The score for each body region is added up to determine the BSA affected by AD (A), which has a possible maximum score of 100%.

Severity (B, maximum score of 18)

A representative area of AD is selected. In this area, the severity of each of the following signs is assessed as none (0), mild (1), moderate (2) or severe (3).

- Erythema (reddening);
- Edema (swelling)/papulation;
- Oozing/crusting;
- Excoriation (scratch marks);
- Skin thickening (lichenification);
- Xerosis (dryness) (this is assessed in an area where there is no inflammation).

The severity scores are added together to give 'B' (maximum score of 18).

Subjective Symptoms (C, maximum score of 20)

Subjective symptoms, ie, itch and sleep loss, are each scored by the participant or caregiver using a visual analog scale (VAS) where "0" is no itch (or no sleep loss) and "10" is the worst imaginable itch (or sleep loss). The value for each should reflect the average on a 10-point scale for the last 3 days/nights. These scores are added to give 'C' (maximum score of 20).

SCORAD Total Score

The SCORAD for an individual is calculated by the formula: A/5 + 7B/2 + C (can range from 0 to 103).

8.1.5. PROs

The PROs included in this study have all been recommended by the HOME initiative as core outcomes to be measured in eczema trials. 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. In instances where an electronic device is used to collect the PRO data, the electronic version may differ slightly in format or wording compared with the paper version to facilitate electronic implementation.

All PROs should be completed as per the Schedule of Activities.

8.1.5.1. PP-NRS

The severity of itch (pruritus) due to AD will be assessed using the PP-NRS, a validated horizontal NRS.[11,12] 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 at the Screening Visit to determine eligibility criteria (See Section 5.1).

8.1.5.2. POEM

The POEM is a validated 7-item PRO measure used to assess the impact of AD recalled over the past week. This instrument is appropriate for use by participants aged 12 years and older.[13-15]

8.1.5.3. ADCT

The ADCT is a brief patient self-administered instrument designed and validated to assess patient-perceived AD control; 6 AD symptoms and impacts are evaluated over the past week, including overall severity of symptoms, days with intense episodes of itching, intensity of bother, problem with sleep, impact on daily activities, and impact on mood or emotions.[16,17]

8.1.6. Photography

Photographs of representative AD lesions should be obtained at Baseline/Day 1, EOT and EOS/follow-up visit. Areas photographed should be recorded in source documents so that the same AD body region(s) will be photographed at each time point. Photographs will be utilized for illustrative purposes and not formally evaluated as an endpoint for analysis.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.2. Vital Signs

Vital sign measurements including oral temperature, pulse rate and blood pressure will be assessed (pre-dose, if applicable). Blood pressure and pulse rate will be collected on the CRF. Temperature will not be collected on the CRF.

Blood pressure and pulse rate measurements will be assessed with the participant in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate 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 or other appropriate diagnostic image (ie, computerized tomography or magnetic resonance imaging) to aid in TB status determination may be performed up to 12 weeks prior to Day 1. Chest X-rays (posterior/anterior and lateral views) are required. Chest X-rays may also be completed at the investigator's discretion to aid in TB status determination of participants requiring TB testing. Completion of the chest X-ray (or other appropriate diagnostic image) will be recorded on the CRF, and results and documentation will need to be available from the participant's medical record upon request by the sponsor.

8.2.4. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

If a) a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QT value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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

ECG values of potential clinical concern are listed in Appendix 6.

8.2.5. Clinical Safety Laboratory Assessments

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

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

See Appendix 5 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.6. Pregnancy Testing

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

8.2.7. Knee MRI

See Appendix 10 for details of the knee MRI substudy.

8.2.8. Suicidal Ideation and Behavior Risk Monitoring

The C-SSRS is a validated tool for investigative staff to use to evaluate suicidal ideation and behavior.[18]

Trained site staff are to administer the C-SSRS to all participants at study visits and score immediately. Based on the judgment of the investigator, the participant should either be permitted to continue in the study or must have a risk assessment done by a qualified medical health professional to assess whether it is safe to continue 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 since the last assessment: “Yes” answers on items 4 or 5 of the C-SSRS.

- Previous history of suicidal behavior since the last assessment: "Yes" answer 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).

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

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

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

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

During the active collection period as described in Section 8.3.1, each participant/parent/legal guardian/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

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

8.3.1. 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.

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.

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

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

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

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and 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 Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, 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 AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.3.3. Follow-Up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

Any such exposure to the study intervention under study 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 up to 28 days after last dose of 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 EDP:
    - 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 preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion;

- 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 up to 28 days 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 ingestion.

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

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

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

8.3.9. 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 study participant.

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5. Genetics

8.5.1. Specified Genetics

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

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

Data analysis and statistical methods for the MRI substudy in adolescents are described in Section 10.10.

9.1. Statistical Hypotheses

9.1.1. Estimands

9.1.1.1. Primary Estimand

The primary estimand is defined by the following attributes:

Population: Patients aged 12 years and older with moderate to severe AD.

Variable: Binary indicator of whether any AE/SAE occurred at least once.

Treatment condition: The randomized intervention regardless of intercurrent events.

The intercurrent events "intervention discontinuation for any reason" and "intervention compliance" are both addressed by the treatment condition of interest.

Population-level summary: Incidence rate of AEs/SAEs, defined as the number of participants with AEs/SAEs from the time of first dose to Week 16 divided by the number of participants, in each treatment arm.

9.1.1.2. Secondary Estimands

The secondary estimand 1 is defined by the following attributes:

Population: Patients aged 12 years and older with moderate to severe AD.

Variable: Response based on IGA score of clear (0) or almost clear (1) and greater than or equal to 2 points improvement from baseline at Week 12; participants who discontinued intervention for any reason are considered as non-responders.

Treatment condition: The randomized intervention.

The intercurrent event "intervention discontinuation for any reason" is addressed in the variable definition.

Population-level summary: IGA response rate with 95% CI, in each treatment arm.

The secondary estimand 2 is defined by the following attributes:

Population: Patients aged 12 years and older with moderate to severe AD.

Variable: Response based on improvement of ≥75% from baseline EASI score at Week 12; participants who discontinued intervention for any reason are considered as non-responders.

Treatment condition: The randomized intervention.

The intercurrent event "intervention discontinuation for any reason" is addressed in the variable definition.

Population-level summary: EASI-75 response rate with 95% CI, in each treatment arm.

The secondary estimand 3 is defined by the following attributes:

Population: Patients aged 12 years and older with moderate to severe AD.

Variable: Response based on improvement of ≥75% in SCORAD from baseline at Week 12; participants who discontinued intervention for any reason are considered as non-responders.

Treatment condition: The randomized intervention.

The intercurrent event "intervention discontinuation for any reason" is addressed in the variable definition.

Population-level summary: SCORAD75 response rate with 95% CI, in each treatment arm.

The secondary estimand 4, is defined by the following attributes:

Population: Patients aged 12 years and older with moderate to severe AD.

Variable: Change from baseline in POEM at Week 12 and at all scheduled timepoints; data after treatment discontinuation at any time during the treatment period will be censored.

Treatment condition: The randomized intervention. The intercurrent event "intervention discontinuation for any reason" is addressed in the variable definition.

Population-level summary: Mean and standard deviation.

The secondary estimand 5 is defined by the following attributes:

Population: Patients aged 12 years and older with moderate to severe AD.

Variable: Change from baseline in ADCT at Week 12 and at all scheduled timepoints; data after treatment discontinuation at any time during the treatment period will be censored.

Treatment condition: The randomized intervention.

The intercurrent event "intervention discontinuation for any reason" is addressed in the variable definition.

Population-level summary: Mean and standard deviation.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Enrolled	All participants who sign the ICD.
Full analysis set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data.

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

Study data will be summarized and presented separately for the following treatment arms:

- abrocitinib 100 mg QD
- abrocitinib 200 mg QD.

9.3.2. Primary Endpoint Analysis

Analysis of the incidence of AEs and SAEs will be performed on the FAS. Participants will be analyzed according to the treatment they actually received. The number and percentage of treatment-emergent AEs will be summarized according to type, frequency, severity, seriousness and relationship to abrocitinib in each treatment arm. In addition, withdrawals from active treatment due to AEs and serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials or meets other criteria that require it to be classified as a serious adverse event, will be summarized descriptively.

9.3.3. Secondary Endpoint Analysis

Analysis of secondary endpoints will be performed on the FAS. Participants will be analyzed according to the treatment arm they are randomized to. The IGA, EASI-75 and SCORAD75 response rates, together with the corresponding 95% CI (using the normal approximation or Clopper-Pearson exact method, whichever is appropriate) will be estimated for each treatment arm. Descriptive statistics for change from baseline in POEM and ADCT scores will be derived at all scheduled timepoints, for each treatment arm.

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct reviews of the data, including MRI data, during the course of the study for the purpose of safety assessment or to support regulatory submissions. Interim safety and efficacy data after approximately 50% of the total sample size has been randomized in the study will be prepared and summarized to support presentation of initial results to India BoH.

9.5. Sample Size Determination

A sufficient number of participants will be screened to achieve 200 participants randomly assigned to study intervention. The sample size of 100 randomized participants per treatment arm would allow estimation of the incidence rate of any AE with maximum margin of error of 10%, in each treatment arm.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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

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

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

10.1.2. Financial Disclosure

Investigators and 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, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

The investigator must ensure that each 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 or his or her legally authorized representative 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 or his or her legally authorized representative.

The participant or his or her legally authorized representative 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/EC 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 was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or his or her legally authorized representative must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

For pediatric participants:

The investigator or his/her representative will explain the nature of the study to the participant and his/her parent(s)/legal guardian and answer all questions regarding the study. The participant and his/her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his or her own assent, the source documents must record why the participant did not provide assent (for example, minor child), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority during the study, as recognized under local law, they must be reconsented as adults to remain in the study. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, they must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. Participant's parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian and the study participant as applicable 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's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian.

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

The investigator further must ensure that each study participant's parent(s)/legal guardian is fully informed about his or her right to access and correct his or her child's personal data and to withdraw consent for the processing of his or her child's personal data keeping in mind the privacy rights that may restrict access of older adolescents medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent and as applicable, assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

10.1.4. Data Protection

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, 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 SOPs.

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (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 corresponding study results are 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 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 contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 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.

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

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

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

The investigator must permit study-related monitoring, audits, IRB/EC 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, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

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

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

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

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

10.1.8. Source Documents

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

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

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

Definition of what constitutes source data and its origin can be found in the Clinical Monitoring Plan, which is maintained by the sponsor.

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

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

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 guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

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 the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

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

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

10.1.10. 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 1 year after the 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 submits 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 for 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 for study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant’s study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

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

10.2. Appendix 2: Clinical Laboratory Tests

The laboratory tests detailed in Table 6 will be performed at times defined in the SoA section and the Substudy SoA section of this protocol and analyzed at local laboratories. Laboratory tests with abnormal results may be repeated once during the screening period; the last value will be used to determine eligibility. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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.

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:
  - Refer to Section 5.1 Inclusion Criteria and Section 8.2.6 Pregnancy Testing for screening pregnancy criteria.
  - For details of timing of recommended pregnancy testing refer to the SoA.

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Lipid Profile[a]	Other
Hemoglobin WBC count Neutrophils (%, Abs) Lymphocytes (%, Abs) Platelets Coagulation Panel (APTT, PT/INR)	Urea sCr sCysC (at Screening) Estimated Creatinine Clearance AST ALT TBili Alkaline phosphatase	Total cholesterol LDL VLDL HDL Triglycerides	At Screening only: • FSH[b] • Serum pregnancy test (β-hCG, for WOCBP only)[c] • HBsAg • HIV • HCV • TB test (as per site standards)

a. Fasting lipid profile panel requires at least an 8-hour fast. If possible, participants should comply with fasting requirements at those visits per the SoA and the Substudy SoA.
b. For confirmation of postmenopausal status only.
c. Urine pregnancy test (for WOCBP only) will be performed at all visits other than screening visits.

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 condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be

completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

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

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.
*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

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

Assessment of Intensity

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

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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.

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or VERY SEVERE to describe the maximum intensity of the AE. The severity of the AE should be determined using the Toxicity Grading Scale:

MILD	Does not interfere with participant's usual function.
MODERATE	Interferes to some extent with participant's usual function.
SEVERE	Interferes significantly with participant's usual function.
VERY SEVERE	Unacceptable and intolerable events or events which are irreversible or cause the participant to be in imminent danger of death.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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 an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic 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) 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 and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

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

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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.

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are <u>not</u> considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;

    - Documented bilateral salpingectomy;

- Documented bilateral oophorectomy.

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

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

3. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

  - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

  - A female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

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

2. Intrauterine device.

3. Intrauterine hormone releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:

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

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

    - Oral;
    - Intravaginal;
    - Transdermal;

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

    - Oral;
    - Injectable.

8. Sexual abstinence:

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

In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

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

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede 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 laboratory 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 Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.6. Appendix 6: ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.7. Appendix 7: Prohibited Concomitant Medications That May Result in DDI

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

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

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (e.g., emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

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

Drug Category	Drugs	Required Washout Period requirement
CYP2C9 Inhibitors	amiodarone fluconazole fluvoxamine miconazole oxandrolone voriconazole	1 week or 5 half-lives whichever is longer
CYP2C19 Inhibitors	esomeprazole fluconazole fluoxetine fluvoxamine isoniazid moclobemide omeprazole ticlopidine voriconazole	1 week or 5 half-lives whichever is longer
CYP2C9 Inducers	carbamazepine enzalutamide rifampicin	5 half-lives plus 14 days For example, carbamazepine: The average half-life of carbamazepine after repeat dosing is on average 15 hours, so the washout period is calculated as the sum of 5 half-lives (approximately 3 days) and an additional 14 days for a total of 17 days.
CYP2C19 Inducers	enzalutamide rifampicin	5 half-lives plus 14 days

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, for a total of approximately 80 days prior to the first dose of study intervention.

10.8. Appendix 8: 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 in India 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).

10.8.1. 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 (eg, 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 abrocitinib dosing information, 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.

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

10.8.2. Alternative Facilities for Safety Assessments

10.8.2.1. 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. The following safety laboratory evaluations may be performed at a local laboratory:

Hematology	Chemistry	Lipid Profile[a]	Other
Hemoglobin WBC count Neutrophils (%, Abs) Lymphocytes (%, Abs) Platelets Coagulation Panel (APTT, PT/INR)	Urea sCr sCysC (at Screening) Estimated Creatinine Clearance AST ALT TBili Alkaline phosphatase	Total Cholesterol LDL VLDL HDL Triglycerides	At Screening only: • FSH[b] • Serum pregnancy test (β-hCG, for WOCBP only)[c] • HBsAg • HIV • HCV • TB test (as per site standards)

a. Fasting lipid profile panel requires at least an 8-hour fast. If possible, participants should comply with fasting requirements at those visits per the SoA.
b. For confirmation of postmenopausal status only.
c. Urine pregnancy test (for WOCBP only) will be performed at all visits other than screening.

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.

10.8.2.2. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.8.3. 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.

Abrocitinib 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 abrocitinib by mail. The tracking record of shipments and the chain of custody of abrocitinib must be kept in the participant's source documents/medical records.

Examples of potentially acceptable delivery methods (not an all-inclusive list):

- Site staff delivery with confirmation of temperature monitoring and time in transit (time study intervention leaves site until delivered to participant);
- Site courier with confirmation of temperature monitoring and time in transit (time study intervention is picked up at site until delivered to participant. There must (at a minimum) be a record of verbal consent of the participant, including whether they consent to provide their personal information to a third-party vendor for this purpose.

Note: If no temperature monitoring is available, assess and document if average temperature in the geographic area is within the stability range, anticipating shipping transit times and possible travel delays – and ensure to discuss this further with the sponsor.

10.8.4. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19, if the investigator judges this as required, with or without discussion with the sponsor as required.

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

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
Abs	absolute
AD	atopic dermatitis
ADCT	Atopic Dermatitis Control Tool
AE	adverse event
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BoH	Board of Health
bpm	beats per minute
BSA	body surface area
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
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
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
EBV	Epstein Barr virus
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EMA	European Medicines Agency

Abbreviation	Term
EOS	end of study
EOT	end of treatment
EU	European Union
EudraCT	European Clinical Trials Database
FACS	fluorescence activated cell sorting
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HOME	Harmonising Outcome Measures for Eczema
HSS Pedi-FABS	Hospital for Special Surgery Pediatric Functional Activity Brief Scale
HT SDS	height standard deviation scores
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	interferon
IGA	Investigator's Global Assessment
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IP manual	investigational product manual
IR	incidence rate
IRB	Institutional Review Board
IRC	internal review committee
IRT	interactive response technology
JAK	Janus kinase
LDL	low-density lipoprotein
LFT	liver function test
MHP	medical health professional
MRI	magnetic resonance imaging
N/A	Not Applicable
NOAEL	no observed adverse effect level
NOEL	no observed effect level

Abbreviation	Term
PK	pharmacokinetic(s)
POC	proof of concept
POEM	Patient-Oriented Eczema Measure
PP-NRS	Peak Pruritus Numerical Rating Scale
PR	pulse rate
PRO	patient reported outcome
PSAAD	Pruritus and Symptoms Assessment for Atopic Dermatitis
PT	prothrombin time
PVC	premature ventricular contraction
PY	patient year
QD	once daily
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
QTL	quality tolerance limit
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCORAD	SCORing Atopic Dermatitis
sCr	serum creatinine
sCysC	serum Cystatin C
SDS	standard deviation scores
SIB	suicidal ideation and behavior
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBili	total bilirubin
TSLP	thymic stromal lymphopoietin
TYK	tyrosine kinase
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VLDL	very-low-density lipoprotein
VTE	venous thromboembolism
WBC	white blood cell
WOCBP	woman/women of childbearing potential

10.10. Appendix 10: An Imaging Substudy for Evaluation of Abrocitinib's Potential Effects on Adolescent Bone in Participants With Moderate to Severe AD in India

10.10.1. Substudy Introduction

10.10.1.1. Substudy Background and Rationale

JAK signaling plays an important role in bone development and metabolism. Data from abrocitinib and other JAK inhibitors such as baricitinib and upadacitinib indicate clear JAK class-related bone effects after in utero exposure.[19,20] However, the direct effects of JAK inhibitors on bone development remain unclear. Importantly, atopic dermatitis is associated with systemic corticosteroid use which can lead to poor bone health. AD patients may have decreased bone health including a higher fracture rate relative to controls.[21] Currently approved JAK inhibitors show differences in selectivity for individual JAK enzymes and cytokine signaling pathways, and at present there is incomplete understanding of their specific contribution to potential effects regarding bone development, or lack thereof.

Nonclinical bone microscopic finding of decreased primary spongiosa in the metaphysis bone (femur/tibia) region was noted in young rat (comparable human age of ≥12 years) short duration (up to 1 month) repeat-dose toxicity studies. This microscopic long bones finding was transient, nonprogressive and the NOEL exposure margin at which no bone finding was noted was at least 6x the unbound human AUC at the maximum clinical dose of 200 mg QD (the bone finding was noted at ≥23×). No abrocitinib related clinical observations, macroscopic, or microscopic, by histopathological examination, long bones findings were observed in rats at any dose in the 6-month toxicity study (up to 26x the unbound human AUC at the maximum clinical dose of 200 mg QD) or in young or adult monkeys in any of the toxicity studies up to 9 months in duration (up to 31 × the unbound human AUC at the maximum clinical dose of 200 mg QD). Young monkeys (comparable human age of 8 years and older) are a sensitive nonclinical species for the detection of potential effects on bone growth and development relevant to adolescent humans because: (1) young monkeys have less active growth plates compared to rats of similar age, and (2) the physiologic ambulatory activity and bone biomechanical loading are similar between young monkeys and human adolescents. Therefore, it is unlikely that the observations in the repeat-dose rat toxicity studies have a clinically significant consequence for adolescent humans. In a juvenile rat toxicity study to support using abrocitinib in children <12 years of age, bone findings (decreased femur bone length and width, bone malrotations, macroscopic femoral head and neck abnormalities including occasional long bone fractures) occurred in a time period when femoral bone neck development was still on-going in early postnatal development in these juvenile rats (postnatal day 10; comparable to approximately 3-months human age at dose initiation).[22]

Height SDS and fracture rates have been previously assessed in adolescent participants in order to assess whether the microscopic, transient nonclinical finding in rats translated to changes in adolescent bone growth and development. HT SDS is the standard for measuring changes in height in clinical trials as it allows efficient use of data across both ages and genders.[23] In the safety update data, including B7451036, at each dose and time point where the HT SDS was assessed the median change was 0, suggesting that participants remain on the growth curve that had been established prior to abrocitinib dosing. Fracture rates is a

relevant measure for assessment of a clinically meaningful impact on bone. Fracture rates are high in adolescence because there is a lag in mineralization relative to bone lengthening.[24] The fracture rates in adolescent participants in the safety update data, including B7451036, representing an IR of 0.92/100 (CI, 0.25, 2.35) patient years. To contextualize the rate of fractures in the abrocitinib development program, the IR of fracture in a large Danish Health Registry (3,909 patients with AD aged 12 to <18) was 2.72/ 100 PY (272.19/10,000 PY) [Danish Report Table 15].

This substudy will provide imaging data to further evaluate whether abrocitinib has any potential effects on adolescent bone with regard to bone safety findings in knee MRI, including to assess if there is any abrocitinib-associated effects on cartilage mineralization in the actively growing bones of adolescent participants with moderate to severe AD and to verify that epiphyseal plate closure occurs as expected in late adolescence or early adulthood. Findings of the substudy will further inform risk assessment as to whether administration of abrocitinib may affect bone in adolescents.

Knee MRI is the selected imaging modality and body site utilized in the substudy for several reasons:

- The spatial resolution for MRI provides the best opportunity to identify morphologic changes that may be related to abrocitinib exposure.
- MRI permits visualization of the ossification centers and verification of epiphyseal plate closure.
- MRI does not require ionizing radiation exposure for adolescent participants.

The knee is a suitable body site to evaluate because there are 3 ossification centers.

10.10.2. Substudy Schedule of Activities

Substudy Visit Identifier	**Substudy Screening**	**Substudy Randomization (Baseline)**	**Substudy Recurring Visit** [Week 12 (Day 85 ±**3 days**), 24 (Day 169 ±7 **days**), 36 (Day 253 ±7 **days**)]	**Substudy Early Termination/End of Treatment Visit**	**Substudy Follow-up Visit**[a]
	Main Study Screening (Day -28)	Main Study Day 1	Main study [Weeks 2, 4, 8, 12][e]	Main Study Day 1 + 365 days ±**14 days**	ET/EOT + 28 days ±**3 days**
Informed consent/assent[b]	X				
Dispense Study Intervention		X	X		
Study Intervention Administration		X	X	X	
Study Intervention Accountability			X	X	
MRI procedure[c]	X			X	
Assess knees of participant for relevant history	X				
Review Inclusion/Exclusion criteria for the substudy	X				
Monitor if any discontinuation criteria for substudy have been met or not	X	X	X		
Urine Pregnancy Test (for WOCBP only)		X	X	X	X
Assess for adverse events[d]	X	X	X	X	X
Vital Signs	X	X	X	X	X

Substudy Visit Identifier	**Substudy Screening**	**Substudy Randomization (Baseline)**	**Substudy Recurring Visit** [Week 12 (Day 85 ±**3 days**), 24 (Day 169 ±**7 days**), 36 (Day 253 ±**7 days**)]	**Substudy Early Termination/End of Treatment Visit**	**Substudy Follow-up Visit**[a]
	Main Study Screening (Day -28)	Main Study Day 1	Main study [Weeks 2, 4, 8, 12][e]	Main Study Day 1 + 365 days ±**14 days**	ET/EOT + 28 days ±**3 days**
Clinical Chemistry, Hematology (including coagulation panel), Lipid Profile[f]	X		X[f]	X	
Contraception check[g]	X	X	X	X	X
PROs					
HSS Pedi-FABS (1 month recall)	X	X		X	X
HSS Pedi-FABS (1 year recall)	X	X		X	X

a. Substudy follow-up visit should occur approximately 28 days after the substudy early termination/end of treatment visit. Note: if any participant requires MRI following the early termination/end of treatment visit, the expectation is that the MRI would be arranged as soon as feasible and that the substudy follow up visit be conducted as close to the stated visit window as possible. It will not be considered a protocol deviation as long as the substudy follow up visit occurs no more than 14 days after the completion of the MRI in such cases.
b. Informed consent and assent (if applicable) for the substudy will be included in the main study ICD or assent. Participants who subsequently reach the age of majority during the study will be required to be reconsented as an adult.
c. Participants who turn 18 years during the main study will only have baseline MRI. Participants who have completed 3 months of treatment in the main study and turn 18 years of age during the substudy will be required to attend an early termination visit with an MRI scan.
d. AEs and SAEs are recorded/reported as per Section 8.3.
e. Visits corresponding to main visits. Week 12 visit is End of treatment visit for main study. For substudy participants, activities will be performed as per the substudy schedule of activities.
f. Clinical chemistry includes: urea, sCr, sCysC (at Screening only), estimated creatinine clearance, AST, ALT, TBili, alkaline phosphatase. The lipid profile will include total cholesterol, LDL, VLDL, HDL, and triglycerides. Hematology includes: hemoglobin, WBC, neutrophils (%, absolute), lymphocytes (%, absolute), platelets, and coagulation panel (APTT, PT/INR). Laboratory tests with abnormal results may be repeated once during the screening period; the last value will be used to determine eligibility. Fasting lipid profile panel require at least an 8 hour fast. If possible, participants should comply with fasting requirements at those visits detailed above. For all adolescent participants for the substudy, laboratory tests will be performed at Screening, Week 4 and Week 12 as per the main study SoA, as well as at the ET/EOT visit of the substudy.
g. 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 for contraceptive guidance.

10.10.3. Substudy Objectives and Endpoints

Primary substudy objective(s):	Primary substudy endpoint (as secondary endpoints for B7451094):
• To evaluate the potential effects of abrocitinib on bone development in adolescent participants 12 to <18 years of age, as assessed by knee MRI.	• The proportion of bone safety findings in knee MRI 1 year after randomization in adolescent participants exposed to abrocitinib 100 mg and 200 mg QD.

10.10.4. Substudy Design

This is a substudy of the main B7451094 open label parallel group study. This substudy is being performed to evaluate whether abrocitinib has any potential effects on adolescent bone with regard to bone safety findings in knee MRI, including to assess if there is any abrocitinib associated effects on cartilage mineralization in the actively growing bones of adolescent participants with moderate to severe AD in India, and to verify that epiphyseal plate closure occurs as expected in late adolescence or early adulthood. All adolescent participants who were 12 to <18 years of age at the screening visit will be enrolled in this substudy. This substudy will continue until 1 year after all enrolled adolescent participants in the main study have been randomized to study intervention.

Prior to knee MRI at the screening visit of the main study, informed consent and assent (if applicable) will be obtained. Adolescent participants will continue to receive the assigned abrocitinib 100 mg or 200 mg QD after the 12-week treatment period in the main study, until 1 year after the participant was randomized in the main study, when a second MRI imaging will be performed at the substudy end of treatment visit. Both imaging sessions will require participants to be in a supine position in the confined space of the MRI scanner for approximately 30 minutes.

The same knee for each participant will be evaluated in the substudy. The default knee selected to be evaluated will be the participant's left knee. The right knee will only be selected and used if there is a prior history of significant trauma or abnormality of the left knee, such as any knee condition requiring surgery, any knee condition that is a birth defect, or any condition which has resulted in long-term (>6 months) knee pain, reduction in knee function, or abnormal gait (Note: This is not an all-inclusive list), or any other reason that the left knee is unsuitable for MRI in the Investigator's judgement.

MRIs will be evaluated by a central reader, and reviewers will be radiologists; who are experienced in pediatric imaging and proficient in the interpretation of pediatric bone imaging. The assessments will include evaluation of epiphyseal plate closure and mineralization of cartilage at the growth centers. The radiologist(s) will evaluate the images using a standardized case report form. If any bone safety finding(s) are determined to be present in the central evaluation of the post-dose knee MRI images at the substudy end of treatment visit or early termination visit, then the adjudication committee will adjudicate the diagnosis as per the adjudication charter. The Investigator will determine based on the MRI central read and (if relevant) any suggested further assessment/investigation made by the adjudication committee, and (if relevant) the adjudication outcome if any further follow-up or investigation is required. The Investigator will be responsible for recording any medical

history or AEs that they determine. The Investigator holds responsibility for reviewing all MRI central read reports and adjudication outcomes, and performing a general safety review based on these.

The participants of this substudy will complete all other protocol-specific procedures in the main study.

Adolescent participants who discontinue from the main study will also be discontinued from the substudy. For participants that withdraw during the main study period, an end of treatment/early termination knee MRI for the participant should be performed approximately within 1 month of the main study end of treatment/early termination visit, and then the participant should enter into the follow-up period, with a main study end-of-study visit scheduled for 4 weeks after the end of treatment visit MRI.

10.10.5. Substudy Eligibility Criteria

This substudy can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the substudy is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this substudy.

Participant eligibility should be reviewed and documented by an appropriate member of the Investigator's study team before participants are included in the substudy.

10.10.5.1. Substudy Inclusion Criteria

Participant must meet all of the following inclusion criteria to be eligible for enrollment into the substudy:

1. 12 to <18 years of age, at the time of screening visit;
2. Evidence of a personally signed and dated informed consent document, and/or informed consent of the legally authorized representative (parent/guardian), and assent of the study participant, indicating that the participant or their parent(s)/legal guardian, if applicable, have been informed of all pertinent aspects of the substudy;
3. At least one knee suitable for MRI in the Investigator's judgment, without prior history of significant trauma or abnormality eg, any knee condition requiring surgery, any knee condition that is a birth defect, or any condition which has resulted in long-term (>6 months) knee pain, reduction in knee function, or abnormal gait (Note: This is not an all -inclusive list);
4. Willing and able to comply with substudy scheduled visits and subsstudy procedures including knee MRI imaging.

10.10.5.2. Substudy Exclusion Criteria

Participant with any of the following characteristics/conditions will not be included in the study:

1. Participant who has any absolute or relative contraindication for an MRI scan, such as implants, metallic foreign bodies, claustrophobia. (Note: This is not an all inclusive list).

10.10.5.3. Substudy Enrollment Criteria

Participants will be enrolled into the substudy provided they have an appropriately signed informed consent document and have evidence of assent, if applicable (ie, current minors), to participate in the substudy, and meet all inclusion and none of the exclusion criteria for participation in the substudy at the screening/enrollment visit.

10.10.5.4. Substudy Lifestyle Requirements

There are no additional requirements for the substudy. The requirements from the main protocol apply. Please refer to the Lifestyle Considerations section (Section 5.3) of the main protocol for further details.

10.10.6. Substudy Study Treatments

There are no additional requirements for the substudy and the requirements from the main study apply, except that adolescent participants who enter the substudy will continue to receive study intervention as assigned in the main study after the 12-week treatment period, until 1 year after randomization in the main study or until they turn 18 years of age. Participants will be dispensed bottles of study intervention at Week 12, Week 24 and Week 36 visits. Please refer to the Study Intervention(s) and Concomitant Therapy section (Section 6) of the main protocol for further details.

10.10.7. Substudy Study Procedures

The study procedures for the substudy are described below.

If for whatever unanticipated reason a participant is unable to attend the site visit, the substudy procedures may be performed remotely where locally permissible and where an acceptable and feasible approach has been agreed with the study team and/or detailed per protocol.

10.10.7.1. Substudy Screening/Enrollment and Initial Knee MRI Evaluation

- Substudy details will be included in the main study informed consent, and/ or assent (if applicable). Informed consent or assent will be required prior to performing any procedure for the substudy.
- Assess knees of the participant for relevant history.
- Review substudy inclusion and exclusion criteria.

- Participants who meet the substudy eligibility and enrollment criteria may enroll in the substudy. Participants who do not meet these criteria must not enroll in the substudy and therefore cannot enroll in the main study.
- Participant substudy enrollment will be recorded in the substudy CRF.
- There will be no separate screening/enrollment visit for the substudy. An MRI should be arranged to occur pre-dosing, promptly following the main study screening/enrollment visit. After the initial MRI review if any abnormal knee MRI findings then:
    - Review findings identified by central reader MRI evaluation, and arrange any further follow-up and investigation, if relevant and required;
    - Record medical history/adverse event as appropriate.

- Monitor if any discontinuation criteria for the substudy have been met or not per the substudy Schedule of Activities (Section 10.10.2). The main study discontinuation criteria will also apply for substudy.

10.10.7.2. Substudy Early Termination/End of Treatment Visit

- A Substudy End/Early Termination Visit will be performed approximately within 1 month of the participant turning 18 years of age, OR whenever the participant discontinues from the substudy, OR 1 year after participant randomization in the main study; whichever is the sooner.
- An MRI should be arranged approximately within 1 month of the visit (but must be AFTER the participant has turned 18 years of age if participant is completing substudy due to turning 18).

- After the MRI is performed, review if any abnormal knee MRI findings then:
    - Review findings identified by central reader MRI evaluation, and (if relevant) the adjudication report, and arrange any further follow-up and investigation, if relevant and required;
    - Record medical history/adverse event/laboratory assessment abnormality as appropriate.

10.10.7.3. Substudy Follow-up Visit

- MRI may be required if any clinically significant finding is identified in knee MRI following the substudy early termination/end of treatment visit or if for any reason MRI was not performed following the end of treatment visit. This MRI, if required, must be performed **prior** to the substudy follow up visit. After the MRI is performed, review if any abnormal knee MRI findings then:
  - Review findings identified by central reader MRI evaluation, and (if relevant) the adjudication report, and arrange any further follow-up and investigation, if relevant and required;
  - Record medical history/adverse event as appropriate.

Note: if any participant requires MRI following the end of treatment visit, the expectation is that the MRI would be arranged as soon as feasible and that the substudy follow up visit be conducted as close to the stated visit window as possible. It will not be considered a protocol deviation as long as the substudy follow up visit occurs no more than 14 days after the completion of the MRI in such cases.

10.10.7.4. Substudy Discontinuation Criteria

A participant will be discontinued from the substudy and have a Substudy Early

Termination/End of Treatment Visit if:

- The participant meets any of the discontinuation criteria of the main B7451094 study;
- If the participant is no longer an active participant of the main B7451094 study;
- If the participant has turned 18 years of age during the substudy.

10.10.7.5. Substudy Participant Withdrawal

Participants may withdraw from the substudy at any time and for any reason. Participants will be withdrawn from the substudy if they are no longer an active participant of the main study. The requirements and discontinuation criteria from the main protocol apply for the substudy. Please refer to Participant Withdrawal section (Section 7.2) of the main protocol for further details.

10.10.8. Substudy Assessments

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

10.10.8.1. Bone Safety Findings Identified in Central Evaluation of Knee MRI Images

All bone safety findings will be recorded in the CRF as either medical history or treatment emergent adverse events, as determined by the Investigator.

If any bone safety finding(s) are determined to be present in the central evaluation of the postdose knee MRI images, then the adjudication committee will adjudicate the diagnosis as per the adjudication charter.. The adjudication committee may suggest further follow up or investigation for Investigator consideration. The Investigator will receive a report of the MRI central read and the adjudication outcome, and will determine if any further follow-up or investigation is required.

The Investigator will ensure the recording of any AEs as described in the Adverse Event Reporting section (Section 8.3 and Section 10.10.9), or medical history, if relevant.

If any potential bone safety findings, as per the image review charter, are determined to be present in the MRI central read report, then these findings are to be reported to Pfizer Safety as an important medical event on the CT SAE form within 24 hours of awareness of the event. These potential bone related safety findings are to initially be detailed as potentially related to study intervention under study. If subsequently determined (e.g. following further history, examination, investigation, adjudication) that the finding is unrelated to study intervention, then this must be updated by submitting a follow up CT SAE form within 24 hours of awareness.

Incidental/Unrelated Findings:

An incidental finding is one unknown to the participant and has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study, but is unrelated to the purpose and beyond the aims of the study.

MRI images will be reviewed by a central review facility. The purpose of this review will be to further evaluate whether abrocitinib has any potential effects on adolescent bone with regard to abnormal finding(s) in knee MRI*, but* are not a complete medical review of the participant. If during the central review process, any other unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding will be shared on the central read report to the Investigator. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-patient relationship. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

Related Findings:

A related finding is one that is judged by the Investigator to be possibly related to study intervention.

The Investigator will make a judgment regarding the underlying cause of all treatment emergent AEs. If necessary/required, the Investigator may discuss further with orthopedic specialist(s) or other relevant specialist(s) to help inform this judgement, but the judgement will ultimately be made by the Investigator.

10.10.8.2. Patient-Report Outcomes for the SubStudy

Participants will complete PRO assessments at the relevant substudy visit prior to other clinical activities in the main study (eg, laboratory assessments). The PRO assessments should be checked for completeness by the study site staff before proceeding further with the substudy visit. Compliance with scheduled PRO activities will be monitored. Appropriately delegated site staff will oversee the administration of the PRO assessments at site visits to ensure protocol compliance, and will transcribe participant responses into the CRF.

10.10.8.2.1. HSS Pedi-FABS

The HSS Pedi-FABS is a validated 8-item instrument designed to quantify the activity level of children between 10 and 18 years of age over a 1 month recall period.[25] Participants will be asked to indicate the frequency and intensity of their athletic activity, level of play, and coach/trainer supervision.[26] The HSS Pedi-FABS should be completed as per the substudy Schedule of Activities (Section 10.10.2).

Two versions of the PRO will be completed; each regarding a different recall period:

- HSS Pedi-FABS (1 month recall)
- HSS Pedi-FABS (1 year recall)

If for whatever unanticipated reason a participant is unable to attend the site visit, the PRO assessments may be performed remotely in an acceptable manner if permissible by local guidelines/regulations. For example, if permissible, the PRO may be securely posted to the participant by courier for completion at home and the PRO can subsequently be collected the next time the participant attends the site or can be securely posted to site by courier.

10.10.9. Substudy AE Reporting

There are no additional specific requirements for non-serious AE reporting in the substudy. The requirements from the main protocol apply. Please refer to the Adverse Event Reporting section (Section 8.3) of the main protocol for further details.

10.10.9.1. Withdrawal From the Substudy Due to AEs

Participants who discontinue from the main study will also be discontinued from the substudy. An end of treatment visit will be performed per the main study protocol and participants should enter into the follow-up period, with an end of study visit scheduled for 4 weeks after the end of treatment visit.

Please refer to Section 7.1 of the main protocol for further details.

10.10.10. Substudy Data Analysis/Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this substudy will be described in a SAP, which will be maintained by the sponsor.

10.10.10.1. Sample Size Determination

Adolescent participants 12 to <18 years of age in the main study will be eligible for enrollment into the substudy.

10.10.10.2. Substudy Efficacy Analysis

There are no efficacy analyses planned for this substudy.

10.10.10.3. Substudy Safety Analyses

Bone safety findings as adjudicated by the safety adjudication committee will be summarized by treatment group using frequency and proportions along with 95% CI for the proportions. Further details will be specified in the SAP.

10.10.10.4. Substudy Interim Analysis

There will be no formal interim analysis for this substudy. The sponsor may conduct reviews of the data, including MRI data, during the course of the study for the purpose of safety assessment or to support regulatory submissions.

10.10.11. Substudy Safety Adjudication Committees

To help assess the specific, complex safety events in this substudy, a Safety Adjudication Committee consisting of clinical experts in the relevant clinical area will be established 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 Committee can be found in the respective charter, including a specific description of the scope of their responsibilities, a plan in which communication timelines are defined, and the exact process and definition used by the 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.

11. REFERENCES

1. Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396(10246):255-266.

2. Akdis C, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. Allergy 2006;61:969-87.

3. Weidinger S, Novak N. Atopic dermatitis. Lancet 2016;387:1109-22.

4. Auriemma M, Vianale G, Amerio P, et al. Cytokines and T cells in atopic dermatitis. Eur Cytokine Netw 2013; 24(1):37-44.

5. Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71:327-49.

6. Johanssen E, Ballardini N, Bergström A, et al. Atopic and nonatopic eczema in adolescence: is there a difference? Br J Dermatol. 2015;173:962-8.

7. Egeberg A, Andersen YM, Gislason GH. Prevalence of comorbidity and associated risk factors in adults with atopic dermatitis. Allergy. 2017;72:783-91.

8. Drucker AM, Wang AR, Li WQ, et al. The burden of atopic dermatitis: Summary of a report for the National Eczema Association. J Invest Dermatol. 2017;137:26-30

9. Eckert L, Gupta S, Amand C, et al. Impact of atopic dermatitis on health-related quality of life and productivity in adults in the United States: An analysis using the National Health and Wellness Survey. J Am Acad Dermatol. 2017;77:274-9.

10. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980;(Suppl 92):44-7.

11. Yosipovitch G, Reaney M, Mastey V, et al. Validation of the peak pruritus numerical rating scale: Results from clinical studies of dupilumab in adult patients with moderate to severe atopic dermatitis. J Am Acad Dermatol 2017;76:AB278.

12. Yosipovitch G, Reaney M, Mastey V, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. Br J Dermatol 2019;181(4):761-9.

13. Charman C, Venn A, Williams HC. The Patient-Oriented Eczema Measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol 2004;140(12)(Dec):1513-9.

14. Charman CR, Venn AJ, Ravenscroft JC, et al.. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. Br J Dermatol 2013;169(6)(Dec):1326-32.

15. Spuls PI, Gerbens LAA, Simpson E, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. Br J Dermatol 2017;176(4)(Apr):979-84.

16. Pariser DM, Simpson EL, Gadkari A, et al. Evaluating patient-perceived control of atopic dermatitis: design, validation, and scoring of the Atopic Dermatitis Control Tool (ADCT). Curr Med Res Opin. 2020;36(3):367-376.

17. Simpson E, Eckert L, Gadkari A, et al. Validation of the Atopic Dermatitis Control Tool (ADCT©) using a longitudinal survey of biologic-treated patients with atopic dermatitis. BMC Dermatol. 2019 Nov 6;19(1):15.

18. Posner K, Oquendo MA, Gould M, et al. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry 2007; 164(7):1035-43.

19. Olumiant® (baricitinib) Prescribing Information. Indianapolis, IN: Lilly LLC; Revised October 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf. Accessed: 13 April 2020.

20. RINVOQ™ (upadacitanib) Prescribing Information. Sligo, Ireland: AbbVie Inc; August 2019. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211675s000lbl.pdf. Accessed: 13 April 2020.

21. Mukovozov IM, Morra DE, Giustini D et al. Atopic dermatitis and bone health: a systematic review. J Eur Acad Dermatol Venereol, 2020; 35: 615-628.

22. Kim NN, Parker RM, Weinbauer GF, et al. Points to consider in designing and conducting juvenile toxicology studies. Int J Toxicol 2017;36(4):325-39.

23. Johannsson G, Bidlingmaier M, Biller BM, et al. Growth Hormone Research Society perspective on biomarkers of GH action in children and adults. Endocrine Connections 2018;7(3):R126-34.

24. Faulkner RA, Davison KS, Bailey DA, et al. Size-corrected BMD decreases during peak linear growth: Implications for fracture incidence during adolescence. J Bone Miner Res 2006;21(12):1864-70.

25. Fabricant PD, Suryavanshi JR, Calcei JG, et al. The Hospital for Special Surgery Pediatric Functional Activity Brief Scale (HSS Pedi-FABS): Normative Data. Am J Sports Med. 2018 Apr;46(5):1228-34.

26. Fabricant PD, Robles A, Downey-Zayas T, et al. Development and Validation of a Pediatric Sports Activity Rating Scale: The Hospital for Special Surgery Pediatric Functional Activity Brief Scale (HSS Pedi-FABS). The American Journal of Sports Medicine. 2013;41(10):2421-9.