Protocol Title: A PHASE 3B RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE CONTROLLED MULTI-CENTER STUDY ASSESSING THE EFFICACY AND SAFETY OF ABROCITINIB COMPARED WITH DUPILUMAB IN ADULT PARTICIPANTS ON BACKGROUND TOPICAL THERAPY WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Protocol Number: B7451050

Amendment Number: 2

Compound Number: PF-04965842

Study Phase: Phase 3

Short Title: A Study to Assess the Safety and Efficacy of Abrocitinib Compared with Dupilumab in Adult Participants with Moderate to Severe Atopic Dermatitis

Acronym: JADE DARE

Sponsor Name: Pfizer, Inc

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 2	14-Aug-2020	Study endpoints updated to reflect a more rigorous efficacy threshold and the associated statistical methods were revised: EASI-75 in the primary, key secondary and secondary endpoints was changed to EASI-90 to reflect a more rigorous efficacy threshold and statistical analysis methods have been revised. EASI-90 in one of the secondary endpoints was changed to EASI-75. Clarified that the estimand is PP-NRS4 (previously PP-NRS) since the endpoint is based on achieving at least a 4-point improvement in the severity of PP-NRS4 from baseline. Sample size determination was updated to reflect the change from EASI-75 to EASI-90 in the primary and key secondary endpoints. Clarified the CMH analyses method for the primary endpoint. The tipping point analysis was changed to multiple imputations under the assumption of missing at random. Per updated safety information, participants with increased risk of developing venous thromboembolism are excluded. Inclusion criterion updated to require a clinical diagnosis of AD at least 6 months prior to Day 1 instead of at least 1 year. The duration of AD diagnosis has not been associated with the magnitude of treatment effect of other AD therapies. Given other current inclusion criteria, such as the requirement for recent inadequate response to topical therapies and/or treatment with (or consideration for) systemic therapies, reducing this inclusion criterion to 6 months is not anticipated to affect the study results. Exclusion of prior use of dupilumab has been expanded to include all IL-4 and IL-13 antagonists. Dupilumab is

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		an IL-4 and IL-13 antagonist and the criterion currently only excludes prior dupilumab use. By expanding the criterion to include the drug class, we avoid inadvertently enriching the patient population with participants who are non-responders to this mechanism. Revised the baseline infection study terminology from "viral studies" to "infection studies" to allow for testing of other types of microorganisms. Added additional infection studies sample to be taken at each study visit. This will allow for testing of SARS-CoV-2 or another emergent microbial organisms. Language and an appendix were added to address COVID-19 and to describe alternative measures to be taken during public emergencies. This is in reference to the April 2020 PACL. Added statement that if the participant experiences nausea, consideration should be given to administering oral study intervention with food. A food effect and lower incidence of nausea in a fed state has been observed in some participants. Healthcare Resource Utilization (HCRU) assessment was moved from Week 16 to Week 12. There is a 3-month recall so if you assess at WK12 you are capturing the resource use from baseline to WK12 and then you capture the rest of the HCRU (more or less) when you assess at WK26. If we kept it at WK16 then we would miss the first 4 weeks post-baseline. Added Asthma Control Questionnaire (ACQ) for participants with a prior diagnosis of asthma. Asthma is a common comorbidity in patients with AD and this questionnaire will provide information about whether abrocitinib has any effect on asthma control. New clinical trial data from the abrocitinib study B7451013 and from the dupilumab CAFÉ and CHRONOS studies have been added to the protocol introduction. Updates made per updated protocol template: Clarified inclusion criterion 3 for female participants.

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		Exploratory objective related to banked biospecimens was removed. Section 8.3 Adverse events and Serious Adverse Events Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Recording. Appendix 4 Contraceptive Guidance. Appendix 10 Prohibited concomitant medications. Changes made for improved instruction and process clarity: Requirements for mental health professional assessments and recurrent suicidal ideation and behavior have been clarified. The research supporting accelerometry has been described. Added instruction for when to collect the eDiaries from participants. Added instruction to clarify that banked biospecimens are collected for all participants (as local regulations and IRBs/ECs allow). Dispensing and administration instructions for study intervention have been clarified. Study-specific definitions of medication errors have been updated. Tuberculosis testing procedures have been clarified. Evaluation of hand eczema has been added to the rater qualifications and has been clarified. Data collection requirements for adverse events of conjunctivitis have been added.

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		Electronic diary review has been added to the Week 24 and Week 26 (EOT/ED) visits. Clarified that the BSA for a subset of body regions (scalp, palms, and soles of feet) evaluated in EASI will be entered in the eCRF. Temporary discontinuation timeframe updated for the injectable study intervention and requirement added for participants who need systemic rescue therapy to temporarily discontinue the study intervention while taking systemic rescue therapy. Participants need to temporarily discontinue the study intervention while taking systemic rescue therapy because the medications taken together could further suppress the participant's immune system and, therefore, cause an increased safety risk. Clarified that participants who use rescue therapy will be defined as "non-responsive" after start of rescue therapy. Added isoniazid as a prohibited concomitant medication. Clarified that the block randomization method will be used. Recall period has been updated for the Medical Outcomes Study Sleep Scale (per the December 2019 PACL). Anchors have been updated for the Skin Pain Numerical Rating Scale (per the December 2019 PACL). Informal interim analyses for internal decision-making have been added. Collection of prior marijuana use has been removed. The information would not be used in analyses. Country-specific addition for the United Kingdom: Per agency requirement, added requirement for sites to contact participants who are WOCBP and are not entering the long-term extension study (B7451015) at 12 weeks after the last dose of study intervention to

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		confirm adherence to contraception guidelines per protocol. Country-specific addition for France: Requirements for study sites located in France have been added. References have been updated. Study acronyms have been updated.
Amendment 1 (Czech Republic only)	14-Jul-2020	Country-specific changes for the Czech Republic: Section 5.2: Patients with increased risk of developing venous thromboembolism are excluded. This exclusion criterion was added as a result of the updated April 2020 IB. Section 6.5.2.: If a participant requires high potency topical therapy or systemic rescue therapy, they are to be permanently discontinued from the study intervention, have an End of Treatment visit and enter the 4-week follow-up period. This was a request from the Czech Republic. Section 10.4.: Definition of postmenopausal female was revised to specify that the main condition is the absence of bleeding for 12 months without an alternative medical cause (removed portion of definition that allowed for participants age 60 or older to be considered postmenopausal). FSH level must be assessed in women in the postmenopausal range under the age of 60 and not using hormonal contraception or HRT (“may” changed to “must”). This was revised per the Czech Republic request and to be consistent with the current protocol template.
Original Protocol	04 November 2019	

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

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A PHASE 3B RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE CONTROLLED MULTI-CENTER STUDY ASSESSING THE EFFICACY AND SAFETY OF ABROCITINIB COMPARED WITH DUPILUMAB IN ADULT PARTICIPANTS ON BACKGROUND TOPICAL THERAPY WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Short Title: A Study to Assess the Safety and Efficacy of Abrocitinib Compared with Dupilumab in Adult Participants with Moderate to Severe Atopic Dermatitis

Rationale:
Atopic dermatitis (AD), also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in quality of life. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the United States (US).[1,2] AD is one of the most common, chronic, relapsing childhood dermatoses, impacting 15-30% of all children in the US and many have disease that persists into adulthood with a lifetime prevalence of those affected in childhood reported to be 34%.[3] Earlier reports indicated that, in up to 70% of cases, the disease greatly improves or resolves by late childhood, however more recent findings suggest that disease activity remains manifest for a prolonged period of time. Based on a total of 7157 participants enrolled in the Pediatric Eczema Elective Registry (PEER) study, comprising a total of 22,550 person-years, it was concluded that symptoms associated with AD seem to persist well into the second decade of life and likely longer.[4] At every age, more than 80% of PEER study participants had symptoms of AD and/or were using medication to treat their AD.

Of the currently available therapies, none offers a cure; therefore, the main aims of existing treatments are to reduce skin lesions, reduce the occurrence of acute flares, to increase the time between relapses, and to reduce pruritus and the resulting sleep disturbance.[5,6]

Non-medicated topical therapies include emollients. Medicated topical therapy for moderate to severe AD include topical corticosteroids (TCS) (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (TCI) (eg, pimecrolimus, tacrolimus), and coal tar preparations. TCS are limited in terms of the treatment duration (eg, corticosteroid use is limited to 2 to 4 weeks) and the body region of treatment, due to consistent skin toxicities, as well as having risks associated with their broad immunosuppressive actions. TCI have a limited role as a second-line treatment, due to their limitations in the duration and the body region of treatment, inhibition of tumor surveillance in the skin, and safety concerns with malignancies. Crisaborole was approved as a medicated topical therapy (phosphodiesterase 4 [PDE4] inhibitor) in December 2016 by the Food and Drug Administration (FDA) for use in patients with mild to moderate AD and is being evaluated for approval in several other regions. Additional treatments generally reserved for severe AD include phototherapy (eg, ultraviolet A light [UVA] with or without psoralen, ultraviolet B-light [UVB] narrowband or broadband) and systemic agents (eg, corticosteroids, cyclosporine, recombinant interferon

gamma (IFN-γ), mycophenolate mofetil, methotrexate [MTX], azathioprine, intravenous immunoglobulin).[7]

There are a limited number of approved systemic treatments for moderate to severe AD and in the US, the only approved systemic drugs are corticosteroids and dupilumab. Per the American Academy of Dermatology (AAD) guidelines, the use of steroids should be avoided for the treatment of AD and should be exclusively reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapies.[8]

Dupilumab, an injectable human monoclonal antibody targeting interleukin (IL) -4 and -13, was approved by the FDA in March 2017 and received marketing authorization in Europe in September 2017, for the treatment of moderate to severe AD. Treatment with systemic corticosteroids has known and well documented adverse effects. Treatment with dupilumab has the risk of injection site reactions, allergic reactions, eye and eyelid inflammations and cold sores. Another potential limitation of dupilumab is the possibility for the development of antidrug antibodies, which may result in loss of efficacy over time and the development of safety concerns such as serum sickness-like reactions. Furthermore, dupilumab is delivered via subcutaneous injection, which may not be a method of administration tolerated well by all patients. During a 1-year, randomized, double-blinded study with dupilumab, in the dupilumab 300 mg every 2 weeks (marketed maintenance dose) plus TCS group, the estimated difference from placebo of the Investigator's Global Assessment (IGA) response rate and Eczema Area and Severity Index (EASI)-75 response rate (≥75% improvement from baseline in EASI score) were 26% and 46%, respectively. The placebo response rate for IGA and EASI-75 was 12% and 23%, respectively.[9] The dupilumab response rate for a ≥4-point improvement from baseline in PP-NRS4 at Week 2 and ≥90% improvement from baseline in EASI score (EASI-90) was 18% and 40%, respectively.[9] There is a need for therapies for those patients who do not respond to dupilumab or who after responding, fail to improve with dupilumab. The development of potential treatments with further improvements in efficacy remains desirable.

In Europe, cyclosporine is approved for use in patients with severe AD when systemic therapy is required. Cyclosporine use is associated with several undesirable side effects and due to its narrow therapeutic index, occasional therapeutic drug monitoring is recommended. Known adverse effects include infections, renal toxicity, hepatotoxicity, skin malignancies, lymphoma and other malignancies.

The predominant unmet medical need is for a conveniently administered therapy with an acceptable safety profile, for continuous and intermittent use, which is effective for moderate to severe AD. Patients with moderate to severe AD require other systemic treatment options beyond those which are currently approved. Abrocitinib is an oral tablet, providing a more convenient route of administration compared with the subcutaneous injection required for dupilumab and so it does not have the potential risk of injection site reactions. Unlike dupilumab, abrocitinib is a small molecule and there is no anticipated immunogenicity to abrocitinib, and so it is unlikely to generate antidrug antibodies and may be used intermittently.

Key cytokines implicated in the pathophysiology of AD include IL-4, IL-13, IL-31, and IFN-γ, and require Janus kinase 1 (JAK1) for signal transduction; this suggests 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.[9] Broader inhibition of cytokines, including those important in the pathogenesis of AD, may result in an increased proportion of responders, with an acceptable safety profile.

Abrocitinib (formerly known as PF-04965842) is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. Abrocitinib has a high degree of selectivity for JAK1 when compared, in vitro, against other kinases: 28-fold selectivity over Janus kinase 2 (JAK2), >340-fold over Janus kinase 3 (JAK3) and 43-fold over tyrosine kinase 2 (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-13, IL-31 and IFN-γ. Data from a Phase 2b proof of concept (POC) study (B7451006) that evaluated participants with moderate to severe AD have shown positive efficacy with both 100 and 200 mg, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

Abrocitinib has been in Phase 3 development since December 2017 treating participants with moderate to severe AD with or without topical treatment. The first Phase 3 studies, B7451012 and B7451013, that evaluated 100 and 200 mg QD abrocitinib in participants with moderate to severe AD, which completed in 2019, reported statistically significant improvement in efficacy endpoints in both treatment groups compared to the placebo group, with an acceptable safety profile.

This Phase 3b study will investigate whether abrocitinib provides comparable or improved efficacy and safety compared with duplilumab in the treatment of moderate to severe AD.

Statistical Methods

The objective of the study is to demonstrate superiority of abrocitinib 200 mg once daily (QD) to dupilumab 300 mg every other week (Q2W) as measured by Peak Pruritus Numerical Rating Scale (PP-NRS4) response at Week 2 and EASI-90 response at Week 4. Additionally, this study is intended to demonstrate that abrocitinib 200 mg QD is non-inferior to dupilumab 300 mg Q2W and if non-inferior, to demonstrate the superiority to dupilumab as measured by EASI-90 response at Week 16. A total sample of 600 participants, with 300 participants randomized to abrocitinib, 300 participants randomized to dupilumab (1:1 randomization) is planned. The proposed sample size provides adequate power for all superiority hypotheses, as follows:

- **Week 2**: this sample size would provide at least 99% power to detect a difference assuming a difference of at least 25% in PP-NRS4 between abrocitinib and dupilumab and assuming the dupilumab response rate is 11% at Week 2.

- **Week 4**: this sample size will provide approximately 97% power to detect a difference assuming a difference of at least 15% in Week 4 EASI-90 between abrocitinib and dupilumab and assuming the dupilumab response rate is 12%.

- **Week 16:** this sample size will provide at least 99% power to show the difference is no more than 10% favoring dupilumab in EASI-90 at Week 16 (non-inferiority (NI) with a 10% margin), assuming the abrocitinib response rate is 53% and the dupilumab response rate is 43% at Week 16. This sample size will also provide approximately 70% power to demonstrate superiority of abrocitinib 200 mg QD to dupilumab as measured by EASI-90 response at Week 16.

The Type I error rate is set at 5% (two sided). The familywise Type I error rate (for testing the primary and key secondary endpoints) will be strongly controlled at 5% using a sequential testing approach. This is described in further detail in Section 9 of the protocol and in the statistical analysis plan (SAP).

For analysis of the primary and key secondary endpoints, the Cochran-Mantel-Haenszel test adjusted by disease severity group (moderate and severe) will be used. For participants who drop out for any reason or use rescue therapy (Section 6.5.2) at any time during the treatment period, the response will be defined as "non-responsive" after that point.

For continuous endpoints, a mixed-effect model with repeated measures (MMRM) will be used. This model will include the factors (fixed effects) for treatment group, disease severity group, visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment at each time point will be derived from the MMRM model.

All participants who receive study intervention (safety population) will be included in the safety analyses. All the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations.

Objectives, Estimands and Endpoints

1.1.1. Estimands

There are 2 estimands for the study.

Estimand 1, composite estimand:

- Population: Participants with moderate-to-severe Atopic Dermatitis (AD) as defined by the inclusion criteria to reflect the targeted participant population;

- Variable: response based on achieving at least a 4-point improvement in the severity of the PP-NRS4 from baseline at Week 2; for participants who drop out for any reason or use rescue therapy (Section 6.5.2) at any time during the treatment period, the response will be defined as "non-responsive" after that point;

- Interventional effect: Effect of randomized treatment accounting for treatment adherence, rescue therapy, and response; the intercurrent event (drop-out or use of rescue therapy) is captured through the variable definition;

- Population-level summary: differences in proportions of responders between abrocitinib and dupilumab.

Estimand 1 composite estimand is the primary estimand for the primary and key secondary endpoints: PP-NRS4 response at Week 2, EASI-90 at Week 4, and EASI-90 at Week 16. Other binary outcome measures such as response based on PP-NRS4 and EASI-90 at all other scheduled timepoints, EASI-75, and IGA, will follow the same structure.

Estimand 2, hypothetical estimand:

- Population: Participants with moderate-to-severe Atopic Dermatitis (AD) as defined by the inclusion criteria to reflect the targeted participant population;

- Variable: Percent change from baseline in SCORing Atopic Dermatitis (SCORAD) at all scheduled timepoints;

- Interventional effect: Effect of randomized treatment as if all participants maintain their randomized treatment; drop-out for any reason and use of rescue therapy are the intercurrent events; data after dropout or use of rescue therapy at any time during the treatment period will be censored;

- Population-level summary: Difference in least-square means between abrocitinib and dupilumab.

- Percent change from baseline or change from baseline to each specific post baseline scheduled time points in a continuous outcome measure such as the Hospital Anxiety and Depression Scale (HADS), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), and EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) will follow the same structure as defined for SCORAD.

Primary Objectives	Primary Endpoints
To compare the efficacy of abrocitinib 200 mg once daily (QD) versus dupilumab (as per label guidelines) in adult participants on background topical therapy with moderate to severe atopic dermatitis (AD).	- Response based on achieving at least a 4-point improvement in the severity of Peak Pruritus Numerical Rating Scale (PP-NRS4) from baseline at Week 2. - Response based on achieving the Eczema Area and Severity Index (EASI)-90 (≥90% improvement from baseline) at Week 4.
Key Secondary	

To compare the efficacy of abrocitinib 200 mg once daily versus dupilumab on additional efficacy endpoints in adult participants on background topical therapy with moderate to severe atopic dermatitis (AD).	- Response based on achieving the Eczema Area and Severity Index (EASI)-90 (≥90% improvement from baseline) at Week 16.

Overall Design:

This is a randomized, double-blind, double-dummy, active controlled, multi-center study to assess the efficacy and safety of abrocitinib 200 mg QD compared with dupilumab (administered per label guidelines) in adult participants on background topical therapy, with moderate to severe AD. The treatment duration is 26 weeks. A total of approximately 600 participants will be enrolled from approximately 220 sites globally. There are primary efficacy assessments at Week 2 and Week 4, and a key secondary efficacy assessment at Week 16. Efficacy and safety endpoints will be assessed throughout the entire study. Participants who complete the study through the Week 26 visit and are deemed eligible may enter the long-term extension (LTE) Study B7451015. A study design schematic is presented in Section 1.2.

After providing informed consent, participants will be assessed for study eligibility at the screening visit. Participants will undergo screening within approximately 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. Eligible participants must have a documented history, within 6 months of the screening visit, of inadequate response to treatment with medicated topical therapy for at least 4 weeks or must have required systemic therapies for control of their disease within the previous year. Eligible participants must meet the eligibility criteria, which includes being dupilumab naïve, at baseline.

In addition, participants must be willing and able to use standardized background topical therapy, as per protocol guidelines, throughout the duration of the study. After Week 4, if medically necessary, participants with intolerable AD symptoms may receive locally-approved rescue therapy, at the investigator's discretion, pursuant to the protocol guidelines (refer to Section 6.5.2).

Participants may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions. Participants 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.

Participants who continue to meet eligibility criteria at baseline will undergo Day 1 assessments and be randomized in a 1:1 ratio to receive abrocitinib 200 mg QD with dupilumab-matching placebo administered every other week or dupilumab 300 mg administered every other week (with a loading dose of 600 mg at baseline) with abrocitinib-matching placebo administered QD. Investigators, participants, and the sponsor study team will be blinded to treatment group assignment.

The total treatment period is 26 weeks. Participants discontinuing early from treatment, or who are otherwise ineligible for the LTE study, will undergo a 4-week follow-up period (See Section 10.12.3 for UK country-specific requirements).

Disclosure Statement:
This is a Parallel Treatment study with 2 Arms that are double-blind, double-dummy.

Number of Participants:
Approximately 600 participants will be randomly assigned to study intervention.

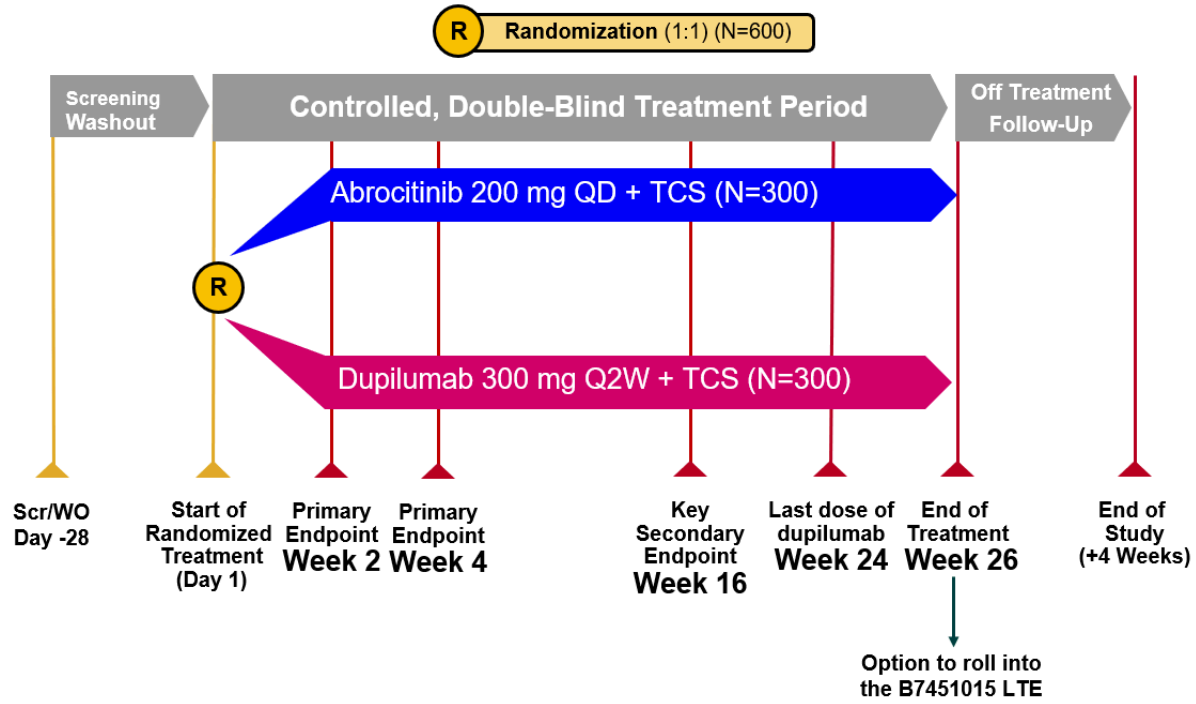
Intervention Groups and Duration:

- Abrocitinib 200 mg (2 x 100 mg tablets) administered orally QD and dupilumab-matching placebo administered by subcutaneous injection every other week (2 injections at baseline; to dummy the loading dose) from Day 1 to Week 26 (the last injection of dupilumab-matching placebo will occur at Week 24).

- Dupilumab 300 mg administered by subcutaneous injection every other week (with a loading dose of 600 mg at baseline) and abrocitinib-matching placebo administered orally QD from Day 1 to Week 26 (the last injection of dupilumab will occur at Week 24).

Data Monitoring Committee: Yes

1.2. Schema


R
Randomization (1:1) (N=600)
Screening Washout
Controlled, Double-Blind Treatment Period
Off Treatment Follow-Up
Abrocitinib 200 mg QD + TCS (N=300)
R
Dupilumab 300 mg Q2W + TCS (N=300)
Scr/WO Day -28
Start of Randomized Treatment (Day 1)
Primary Endpoint Week 2
Primary Endpoint Week 4
Key Secondary Endpoint Week 16
Last dose of dupilumab Week 24
End of Treatment Week 26
End of Study (+4 Weeks)
Option to roll into the B7451015 LTE

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the relevant noted sections 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.

Procedure	Screening	Study Intervention Period									EOT / ED Visit	EOS Follow-up Visit (4 weeks after ED/EOT)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Day		**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D183**	**D211**	
Study Week		**WK0**	**WK1 Call**	**WK2**	**WK4**	**WK8**	**WK12**	**WK16**	**WK20**	**WK24 Call**	**WK26**	**WK30**	
Visit Window (Days)	**-28**	**0**	**±1**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Enrollment													
Informed consent	X												Refer to Section 10.1.3 in Appendix 1.
Register participant in IRT system	X												
Inclusion/Exclusion Criteria	X	X											Refer to Section 5.1 and Section 5.2 for Inclusion and Exclusion Criteria, respectively.
Demographics: Medical, Tobacco, Alcohol, and Atopic Dermatitis (AD) Disease Histories	X												Any previous history of intolerance/allergy to any drug, regardless of indication. AD disease history includes collection of AD diagnosis and duration
Review Prior/Concomitant Medications & Treatments	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Screening	Study Intervention Period									EOT / ED Visit	EOS Follow-up Visit (4 weeks after ED/EOT)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Day		**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D183**	**D211**	
Study Week		**WK0**	**WK1 Call**	**WK2**	**WK4**	**WK8**	**WK12**	**WK16**	**WK20**	**WK24 Call**	**WK26**	**WK30**	
Visit Window (Days)	**-28**	**0**	**±1**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Dispense eDiary and instruct participants on use	X												
Train/check understanding of participants on protocol guidance for background medicated and non-medicated topical therapy and daily recording in eDiary		X	X	X	X	X	X	X	X	X	X		Refer to Section 6.5.1.
Collect eDiary											X	X	Collect the eDiary at Week 26/EOT for participants who rollover into the B7451015 long-term extension study. Collect the eDiary from all other participants at Week 30/EOS (or at the last visit a participant will have if ED).
Provide Participant Emergency Contact Card	X												
Medical Procedures													
Complete Physical Exam	X	X										X	Refer to Section 8.2.1
Targeted Physical Exam				X	X	X	X	X	X		X		Refer to Section 8.2.1
Vital Signs	X	X		X	X	X	X	X	X		X	X	Refer to Section 8.2.2. Temperature does not need to be recorded at the Week 8 visit.
Weight	X												Refer to Section 8.2.1
Height	X	X					X		X				Refer to Section 8.2.1
Chest X-ray	X												Refer to Section 8.2.3.

Procedure	Screening	Study Intervention Period									EOT / ED Visit	EOS Follow-up Visit (4 weeks after ED/EOT)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Day		**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D183**	**D211**	
Study Week		**WK0**	**WK1 Call**	**WK2**	**WK4**	**WK8**	**WK12**	**WK16**	**WK20**	**WK24 Call**	**WK26**	**WK30**	
Visit Window (Days)	**-28**	**0**	**±1**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
ECG (12-lead)	X	X									X	X	Refer to Section 8.2.4.
Laboratory Assessments Refer to Section 8.2.5 and Appendix 2 for more information on clinical safety laboratory assessments.													
Serum Chemistry and Hematology (including Coagulation Panel and additional sample for infection studies)	X	X		X	X	X	X	X	X		X	X	Refer to Section 8.2.6 for the infection studies and Appendix 2 for all tests
Lipid Panel		X			X	X		X	X		X	X	8-hour fast required.
High-sensitivity C-Reactive Protein (hsCRP)	X	X		X	X	X	X	X	X		X	X	This assessment will be blinded after the screening visit.
Urinalysis	X	X		X	X	X	X	X	X		X	X	
Serum FSH or Pregnancy Test	X												Serum pregnancy testing at screening is required for WOCBP. FSH test to be performed at screening to confirm postmenopausal status in female participants who have been amenorrhoeic for at least 12 months.
Urine Pregnancy Test (conducted at study site)		X		X	X	X	X	X	X		X	X	This test must be performed prior to dosing with study intervention for WOCBP.
HIV Testing	X												Will be performed for all participants; those who screen positive will be excluded from the study.
HBV and HCV Testing	X												Refer to Section 8.2.5.1
HBV DNA reflex testing	X							X			X		Refer to Appendix 2 and Section 8.2.5.1.

Procedure	Screening	Study Intervention Period									EOT / ED Visit	EOS Follow-up Visit (4 weeks after ED/EOT)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Day		**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D183**	**D211**	
Study Week		**WK0**	**WK1 Call**	**WK2**	**WK4**	**WK8**	**WK12**	**WK16**	**WK20**	**WK24 Call**	**WK26**	**WK30**	
Visit Window (Days)	**-28**	**0**	**±1**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Tuberculosis Test	X												A documented TB test performed within 12 weeks prior to Day 1 (Week 0) is acceptable. Refer to Appendix 2 and Section 8.2.5.2.
Lymphocyte Subsets		X		X	X	X	X	X	X		X	X	
Serum Sample for Baseline Infection Study		X											Refer to Section 8.2.6. and Appendix 2
Study Intervention Administration (NOTE: should occur at the end of the site visit where applicable).													
Randomization		X											
Oral Drug Dispensing		X			X	X	X	X	X				Refer to Section 6.1.1.1
Injectable Drug Dispensing		X		X	X	X	X	X	X				Refer to Section 6.1.1.2
Study Intervention Accountability				X	X	X	X	X	X		X		
Participant Injection Training		X											Refer to Section 6.1.1.2
Observed Study Intervention Administration		X		X	X	X	X	X	X				Refer to Section 6.1.1.2
Review eDiary to assess completion		X	X	X	X	X	X	X	X	X	X		
Assess eligibility for B7451015											X		Participants who complete the Week 26 visit will be assessed for eligibility for participation in the long-term extension study B7451015.
Atopic Dermatitis Clinical Assessments													
Eczema Area and Severity Index (EASI)	X	X		X	X	X	X	X	X		X	X	Refer to Section 8.1.2

Procedure	Screening	Study Intervention Period									EOT / ED Visit	EOS Follow-up Visit (4 weeks after ED/EOT)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Day		**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D183**	**D211**	
Study Week		**WK0**	**WK1 Call**	**WK2**	**WK4**	**WK8**	**WK12**	**WK16**	**WK20**	**WK24 Call**	**WK26**	**WK30**	
Visit Window (Days)	**-28**	**0**	**±1**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Body Surface Area (BSA from EASI)	X	X		X	X	X	X	X	X		X	X	Refer to Section 8.1.2.1
SCORing Atopic Dermatitis (SCORAD)	X	X		X	X	X	X	X	X		X	X	Refer to Section 8.1.3
Investigator's Global Assessment (IGA)	X	X		X	X	X	X	X	X		X	X	Refer to Section 8.1.4
Patient-reported Outcomes													
Peak Pruritus Numerical Rating Scale (PP-NRS)	X-------X	→	→	→	→	→	→	→	→	→	→	X	Refer to Section 8.1.6.1. **PROs must be completed before all other clinical assessments.**
Dermatology Life Quality Index (DLQI)		X		X			X	X	X		X	X	Refer to Section 8.1.6.2
EQ-5D-5L		X					X	X			X	X	Refer to Section 8.1.6.3
Healthcare Resource Utilization (HCRU)		X					**X**				X		Refer to Section 8.1.6.4
Patient-Oriented Eczema Measure (POEM)		X					X	X			X		Refer to Section 8.1.6.5
Hospital Anxiety and Depression Scale (HADS)		X					X	X			X		Refer to Section 8.1.6.6
Medical Outcomes Study (MOS) Sleep Scale		X					X	X			X		Refer to Section 8.1.6.7
Skin Pain NRS		X		X			X	X	X		X		Refer to Section 8.1.6.8
Asthma Control Questionnaire (ACQ)		X					X				X	X	Refer to Section 8.1.6.9. Given to all participants with a prior diagnosis of asthma.

Procedure	Screening	Study Intervention Period									EOT / ED Visit	EOS Follow-up Visit (4 weeks after ED/EOT)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Day		**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D183**	**D211**	
Study Week		**WK0**	**WK1 Call**	**WK2**	**WK4**	**WK8**	**WK12**	**WK16**	**WK20**	**WK24 Call**	**WK26**	**WK30**	
Visit Window (Days)	**-28**	**0**	**±1**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Optional Accelerometry													
Accelerometry training/retraining	X	X	X	X			X	X	X		X		Refer to Section 8.1.7
Issue/collect accelerometry devices	X	X		X			X	X	X		X		
Night Time Itch Accelerometry	X--------X	X----------X					X	X	X		X		
Hand Eczema Clinical Assessments													
History, subtype, clinical signs and extent	X												Refer to Section 8.1.8.
Investigator's global assessment (IGA)	X	X		X	X	X	X	X	X		X	X	
Safety													
C-SSRS	X	X				X	X	X	X		X	X	Refer to Section 8.2.7.1
PHQ-8	X												Refer to Section 8.2.7.2
Serious and non-serious adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Appendix 3.
Contraception Check	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Appendix 4 for contraceptive guidance.
Banked Biospecimens													
Banked Biospecimen for Genetics		X											Required to be collected for all participants (as local regulations and IRBs/ECs allow). Collect a 2 mL blood sample optimized for DNA isolation **(Prep D1.5)**. Refer to Section 8.7.2.

Procedure	Screening	Study Intervention Period									EOT / ED Visit	EOS Follow-up Visit (4 weeks after ED/EOT)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Study Day		**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**	**D183**	**D211**	
Study Week		**WK0**	**WK1 Call**	**WK2**	**WK4**	**WK8**	**WK12**	**WK16**	**WK20**	**WK24 Call**	**WK26**	**WK30**	
Visit Window (Days)	**-28**	**0**	**±1**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Banked Biospecimens for Biomarkers		X		X									Required to be collected for all participants (as local regulations and IRBs/ECs allow). Collect 4 mL blood sample optimized for biomarkers (**Prep B2.5**) and isolate serum. Collect a 2.5 mL blood sample optimized for RNA isolation (**Prep R1**). Refer to Section 8.8.4.

Abbreviations: → = completed daily; Ab = antibody; ACQ = Asthma Control Questionnaire; BSA = body surface area; C-SSRS = Columbia Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; D=Day; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EOS=End of Study; EOT = End of Treatment; ED= early discontinuation; EQ-5D-5L = EuroQol Quality of Life 5-Dimension 5-Level Scale; FSH = follicle stimulating hormone; HADS= Hospital Anxiety and Depression Scale; HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HBcAb = hepatitis B core antibody; HBV =hepatis b virus; HCRU = Healthcare Resource Utilization; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-Reactive Protein; IGA = Investigator's Global Assessment; IRT = Interactive Response Technology; LLQ = lower limit quantification; PHQ-8 = Patient Health Questionnaire 8 items; PP-NRS = Peak Pruritus Numerical Rating Scale; POEM = Patient-Oriented Eczema Measure; PRO = Patient Reported Outcome; RNA = Ribonucleic acid; SCORAD = SCORing Atopic Dermatitis; WK=Week; WOCBP = women of childbearing potential.

2. INTRODUCTION

Dupilumab, an injectable human monoclonal antibody targeting IL-4 and -13, was first approved in the US and EU (European Union) in 2017 for the treatment of moderate to severe AD.

Abrocitinib (formerly known as PF-04965842) is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. Abrocitinib has a high degree of selectivity in vitro against other kinases: 28-fold selectivity over JAK2, >340-fold over JAK3 and 43-fold over TYK2, as well as a good selectivity profile over the broader range of human kinases. The selective inhibition of JAK1 will lead to modulation of multiple cytokine pathways involved in the pathophysiology of AD, including IL-4, IL-13, IL-31 and IFN-γ. Abrocitinib is being developed as an oral treatment for patients with moderate to severe AD based on the existing unmet need in AD, its novel mechanism of action, and the clinical results obtained in Phase 1 and Phase 2 studies. The clinical development program for abrocitinib includes healthy volunteers, participants with psoriasis and participants with AD.

Data from a Phase 2b POC study (B7451006) that evaluated participants with moderate to severe AD have shown positive efficacy with both 100 and 200 mg, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

2.1. Study Rationale

Atopic dermatitis (AD), also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in quality of life. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the US.[1,2] AD is one of the most common, chronic, relapsing childhood dermatoses, impacting 15-30% of all children in the US and many have disease that persists into adulthood with a lifetime prevalence of those affected in childhood reported to be 34%.[3] Earlier reports indicated that, in up to 70% of cases, the disease greatly improves or resolves by late childhood, however more recent findings suggest that disease activity remains manifest for a prolonged period of time. Based on a total of 7157 participants enrolled in the PEER study, comprising a total of 22,550 person-years, it was concluded that symptoms associated with AD seem to persist well into the second decade of life and likely longer.[4] At every age, more than 80% of PEER study participants had symptoms of AD and/or were using medication to treat their AD. In 833 AD participants who were aged 20 years or older when they visited the clinic and 45 years or older when they responded to a follow-up questionnaire, 59% responded that they had defined persistent AD at some time during the last 12 months.[10]

Of the currently available therapies, none offers a cure; therefore, the main aims of existing treatments are to improve skin lesions, to reduce the occurrence of acute flares, to increase the time between relapses, and to reduce pruritus and the resulting sleep disturbance.[5,6]

Non-medicated topical therapies include emollients. Medicated topical therapy for moderate to severe AD include TCS (eg, betamethasone, clobetasol, fluocinonide), TCI (eg,

pimecrolimus, tacrolimus), and coal tar preparations. TCS are limited in terms of the treatment duration (eg, corticosteroid use is limited to 2 to 4 weeks) and the body region of treatment, due to consistent skin toxicities, as well as having risks associated with their broad immunosuppressive actions. TCI have a limited role as a second-line treatment, due to their limitations in the duration and the body region of treatment, inhibition of tumor surveillance in the skin, and safety concerns with malignancies. Crisaborole was approved as a medicated topical therapy (PDE4 inhibitor) in December 2016 by the FDA for use in patients with mild to moderate AD and is being evaluated for approval in several other regions. Additional treatments generally reserved for severe AD include phototherapy (eg, UVA with or without psoralen, UVB narrowband or broadband) and systemic agents (eg, corticosteroids, cyclosporine, recombinant interferon gamma (IFN-γ), mycophenolate mofetil, methotrexate [MTX], azathioprine, intravenous immunoglobulin).[7]

There are a limited number of approved systemic treatments for moderate to severe AD and in the US, the only approved systemic drugs are corticosteroids and dupilumab. Per the American Academy of Dermatology (AAD) guidelines, the use of steroids should be avoided for the treatment of AD and should be exclusively reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapies.[8]

The predominant unmet medical need is for a conveniently administered therapy with an acceptable safety profile, for long-term use, which is effective for moderate to severe AD. Patients with moderate to severe AD require other systemic treatment options beyond those which are currently approved.

2.2. Background

2.2.1. Atopic Dermatitis

The majority of AD studies conducted across multiple age groups suggest decreasing prevalence with older age.[11] Adult-onset AD does occur, though it is less common. The prevalence of AD in adults is estimated to be 10%.[12] Recent studies have indicated that adults with AD are more likely to smoke cigarettes, drink alcohol, and have a sedentary lifestyle, potentially associated with increased comorbidities, such as asthma and cardiovascular disease.[13]

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

Acute AD lesions have been associated with the type 2 helper T cell (TH2) phenotype, showing dominance of IL-4, -5, -13, and -31 secretion.[9,14,15] Recent research showed that a

small increase of type 1 helper T cell (TH1) associated genes has also been detected in the acute phase.[16]

While IL-4-producing TH2 cells may drive the development of atopic skin lesions, chronic lesions show either the coexistence of both IL-4-producing TH2 and IFN-γ -producing TH1 cells or TH1 dominance.[14] This coexistence of TH2 and TH1 responses or TH1 dominance is more likely to be the underlying immunopathology in adult patients who have had AD chronically or intermittently since childhood. Recent evidence also supports IL-31's role in pruritus and inflammation in AD.[9,15]

In Europe, cyclosporine is approved for use in patients with severe AD when systemic therapy is required. Cyclosporine use is associated with several undesirable side effects and due to its narrow therapeutic index, occasional therapeutic drug monitoring is recommended. Known adverse effects include infections, renal toxicity, hepatotoxicity, skin malignancies, lymphoma and other malignancies.

2.2.2. Clinical Efficacy and Safety of Dupilumab in AD

Dupilumab, an injectable human monoclonal antibody targeting interleukin (IL) -4 and -13, was approved by the FDA in March 2017 and received marketing authorization in Europe in September 2017, for the treatment of moderate to severe AD. Treatment with systemic corticosteroids has known and well documented adverse effects.

During a 1 year, randomized, double blinded study with dupilumab, in the dupilumab 300 mg every 2 weeks (marketed maintenance dose) plus TCS group, the estimated difference from placebo of the Investigator's Global Assessment (IGA) response rate and Eczema Area and Severity Index (EASI) 75 response rate (≥75% improvement from baseline in EASI score) were 26% and 46%, respectively. The placebo response rate for IGA and EASI-75 was 12% and 23%, respectively. The dupilumab response rate for a ≥4-point improvement from baseline in PP-NRS4 at Week 2 and ≥90% improvement from baseline in EASI score (EASI-90) was 18% and 40%, respectively.[9] There is a need for therapies for those patients who do not respond to dupilumab or who after responding, fail to improve with dupilumab. The development of potential treatments with further improvements in efficacy remains desirable.

In 2 randomized, placebo-controlled, Phase 3 trials of identical design (SOLO 1 and SOLO 2), adults with moderate-to-severe atopic dermatitis whose disease was inadequately controlled by topical treatment were enrolled. Participants were randomly assigned in a 1:1:1 ratio to receive, for 16 weeks, subcutaneous dupilumab (300 mg) or placebo weekly or the same dose of dupilumab every other week alternating with placebo. The primary outcome was the proportion of participants who had both a score of 0 or 1 (clear or almost clear) on the Investigator's Global Assessment and a reduction of 2 points or more in that score from baseline at week 16. In SOLO 1 (671 participants), the primary outcome occurred in 85 participants (38%) who received dupilumab every other week and in 83 (37%) who received dupilumab weekly, as compared with 23 (10%) who received placebo ($P<0.001$ for both comparisons with placebo). The results were similar in SOLO 2 (708 participants), with the primary outcome occurring in 84 participants (36%) who received dupilumab every other week and in 87 (36%) who received dupilumab weekly, as compared with 20 (8%) who

received placebo (P<0.001 for both comparisons). In addition, in the 2 trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more participants who received each regimen of dupilumab than in participants who received placebo (P<0.001 for all comparisons). Dupilumab was also associated with improvement in other clinical end points, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life. Injection-site reactions and conjunctivitis were more frequent in the dupilumab groups than in the placebo groups.[17]

In the CAFÉ study, the efficacy and safety of dupilumab in combination TCS was evaluated in 325 adults with inadequate response to/intolerance of cyclosporin A (CsA), or for whom CsA treatment was not medically advisable. In this 16-week, double-blind, randomized, placebo-controlled, Phase 3 trial, participants were randomized 1:1:1 to subcutaneous dupilumab 300 mg weekly (QW) or every 2 weeks (Q2W) or placebo. All received concomitant medium-potency TCS from Week -2 through Week 16; dosage could be tapered if lesions cleared or could be stopped for adverse reactions to TCS. Significantly more participants in the dupilumab QW + TCS and Q2W + TCS groups achieved ≥ 75% improvement from baseline in the Eczema Area and Severity Index at Week 16 vs. the placebo + TCS group (primary endpoint) (59.1% and 62.6% vs. 29.6%, respectively; P < 0·001 vs. placebo + TCS, both doses). More participants in the dupilumab QW + TCS and Q2W + TCS groups achieved ≥ 90% improvement from baseline in the EASI at Week 16 vs. the placebo + TCS group (post-hoc outcome) (37.3% and 45.8% vs. 12.0%, respectively). Other clinical outcomes and atopic dermatitis symptoms were significantly improved in the dupilumab QW + TCS and Q2W + TCS groups, including pruritus, pain, sleep disturbance, symptoms of anxiety and depression, and quality of life (QoL). Treatment groups had similar overall rates of adverse events (QW + TCS, Q2W + TCS and placebo + TCS groups: 69.1%, 72.0% and 69.4%, respectively) and serious adverse events (1·8%, 1·9% and 1·9%, respectively). Conjunctivitis was more frequent with dupilumab + TCS; skin infections were more frequent with placebo + TCS.[18]

In the CHRONOS study, the long-term efficacy and safety of dupilumab with medium-potency topical corticosteroids versus placebo with topical corticosteroids was evaluated in 740 adults with moderate-to-severe atopic dermatitis. Participants were randomly assigned (3:1:3) to subcutaneous dupilumab 300 mg QW, dupilumab 300 mg Q2W, or placebo. At Week 16, more participants who received dupilumab plus topical corticosteroids achieved the coprimary endpoints of IGA 0/1 (39% [125 participants] who received dupilumab plus topical corticosteroids QW and 39% [41 participants] who received dupilumab Q2W plus topical corticosteroids vs 12% [39 participants] who received placebo plus topical corticosteroids; p<0·0001) and EASI-75 (64% [204] and 69% [73] vs 23% [73]; p<0·0001). Week 52 results were similar. Adverse events were reported in 261 (83%) participants who received dupilumab qw plus topical corticosteroids, 97 (88%) participants who received dupilumab Q2W, and 266 (84%) participants who received placebo, and serious adverse events in 9 (3%), 4 (4%), and 16 (5%) participants, respectively. No significant dupilumab-induced laboratory abnormalities were noted. Injection-site reactions and conjunctivitis were more common in participants treated with dupilumab plus topical corticosteroids than in participants treated with placebo plus topical corticosteroids.[9]

Treatment with systemic corticosteroids has known and well documented adverse effects. Treatment with dupilumab has the risk of injection site reactions, allergic reactions, eye and eyelid inflammation and cold sores. Another potential limitation of dupilumab is the possibility for development of antidrug antibodies, which may result in loss of efficacy over time and the development of safety concerns such as serum sickness-like reactions. Furthermore, dupilumab is delivered via subcutaneous injection, which may not be a method of administration tolerated well by all participants.[20]

2.2.3. Clinical Efficacy and Safety of Abrocitinib in AD

Abrocitinib is being developed as an oral treatment for participants with moderate to severe AD based on the existing unmet need in AD, its novel mechanism of action, and the clinical results obtained in Phase 1, Phase 2, and Phase 3 studies. The clinical development program for abrocitinib includes healthy participants, as well as participants with psoriasis and with AD.

Abrocitinib is an oral tablet, providing a more convenient route of administration compared with the subcutaneous injection required for dupilumab and so it does not have the potential risk of injection site reactions. Unlike dupilumab, abrocitinib is a small molecule and there is no anticipated immunogenicity to abrocitinib, and so it is unlikely to generate antidrug antibodies and may be used intermittently.

Key cytokines implicated in the pathophysiology of AD include IL-4, IL-5, IL-13, IL-31, and IFN-γ, and require Janus kinase 1 (JAK1) for signal transduction; this suggests 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.[9] Broader inhibition of cytokines, including those important in the pathogenesis of AD, may result in an increased proportion of responders, with an acceptable safety profile.

B7451006 was a Phase 2b POC trial in 269 adults (ages 18-75) with moderate to severe AD investigating doses of abrocitinib at doses of 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 participants 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 change from baseline (% CFB) 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. At Week 12, the proportion of participants achieving

EASI-75 response was 15.6% in the placebo group, 63.7% in the 200 mg group and 41.6% in the 100 mg group. The difference from placebo was 41.8% (P<0.0001) for the 200 mg group and 26.0% (P=0.0043) in the 100 mg group.

At Day 15, the proportion of response based on achieving at least a 4-point improvement in the severity of PP-NRS from baseline of abrocitinib 100 mg and 200 mg dose groups was greater than placebo. The estimated proportion of PP-NRS responses at Day 15 were 69.8%, 41.1% and 15.7% for 200 mg, 100 mg and placebo groups, respectively.

Abrocitinib demonstrated a rapid onset of action. In the 200 mg group, IGA and EASI scores improved until Week 4 and Week 6, respectively, and maintained their effect through 12 weeks of treatment. 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 Peak Pruritus Numerical Rating Scale (PP-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 PP-NRS score).

Abrocitinib appeared generally safe and well tolerated in this study. Overall, adverse events (AE)s and serious adverse events (SAE)s were numerically higher in participants receiving abrocitinib compared to placebo but did not appear to increase with dose. The most common AEs were in the infections and infestations, skin and subcutaneous tissue disorders and gastrointestinal disorders system organ class (SOC), and the majority of the AEs were mild. There were 2 cases of herpes zoster, 1 in the 10 mg group (not treatment related), and 1 in the 30 mg group (treatment related). There were dose-dependent decreases in platelet counts observed in the study, with a return towards baseline after Week 4.
Further details of the clinical development program can be found in the Investigator's Brochure (IB).

Abrocitinib has been in Phase 3 development since December 2017 treating participants with moderate to severe AD with or without topical treatment. The first Phase 3 studies, B7451012 and B7451013, that evaluated 100 and 200 mg QD abrocitinib in participants with moderate to severe AD, which completed in 2019, reported statistically significant improvement in efficacy endpoints in both treatment groups compared to the placebo group, with an acceptable safety profile.

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% confidence interval [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 both 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 adverse events was higher in the abrocitinib group compared with the placebo group. The proportion of participants experiencing serious adverse events (SAEs) and severe adverse events was

similar across all treatment arms. The discontinuation rates due to an adverse event were low in each treatment arm compared to placebo.

This Phase 3b study will investigate whether abrocitinib provides comparable or improved efficacy and safety compared with duplilumab in the treatment of moderate to severe AD.

2.3. Benefit/Risk Assessment

There was clinically meaningful benefit demonstrated with abrocitinib in the Phase 2b POC study in adult participants with moderate to severe AD and the completed Phase 3 studies B7451012 and B7451013. The potential risks of treatment include those that were noted in Phase 2b and Phase 3 studies and those based on the pharmacology of Janus kinase (JAK) inhibitors and include 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. In Study B7451001, 2 participants discontinued from the study due to AEs. One participant in the abrocitinib 100 mg group discontinued due to an AE of second-degree atrioventricular block, which was considered as non-treatment-related and was attributed to a pre-existing condition by the investigator. Appropriate risk evaluation and mitigation strategies have been incorporated into this protocol.

It was recognized that history of venous thromboembolism (VTE) is an important potential risk. Participants with a history or family history of VTE are excluded from this study.

Overall, there is a favorable benefit-risk profile to support the continued development in Phase 3 of abrocitinib in the treatment of adult 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 adverse events (AEs) of abrocitinib may be found in the IB[19], which is the single reference safety document (SRSD) for this study. The SRSD for the comparator agent, dupilumab, is the United States Package Insert (USPI)[20].

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare the efficacy of abrocitinib 200 mg once daily (QD) versus dupilumab (as per label guidelines) in adult participants on background topical therapy with moderate to severe atopic dermatitis (AD).	• Response based on achieving at least a 4-point improvement in the severity of Peak Pruritus Numerical Rating Scale (PP-NRS4) from baseline at Week 2. • Response based on achieving the Eczema Area and Severity Index

Objectives	Endpoints
	(EASI)-90 (≥90% improvement from baseline) at Week 4.
Key Secondary	
• To compare the efficacy of abrocitinib 200 mg once daily versus dupilumab on additional efficacy endpoints in adult participants on background topical therapy with moderate to severe atopic dermatitis (AD).	• Response based on achieving the Eczema Area and Severity Index (EASI)-90 (≥90% improvement from baseline) at Week 16.
Secondary	
• To compare the efficacy of abrocitinib 200 mg once daily versus dupilumab on additional efficacy endpoints in adult participants on background topical therapy with moderate to severe atopic dermatitis (AD).	• Response based on achieving a ≥90% improvement in the EASI total score (EASI-90) at all other scheduled time points up to Week 26; • Response based on achieving a ≥75% improvement in the EASI total score (EASI-75) at all scheduled time points up to Week 26; • Response based on Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at all scheduled time points up to Week 26; • Response based on achieving at least a 4-point improvement in the severity of PP-NRS4 from baseline at all scheduled time points except Week 2; • Time from baseline to achieve at least a 4-point improvement in the severity of PP-NRS4 scale; • Percent Change from Baseline in the % Body Surface Area (BSA) affected at all scheduled time points; • Percent Change from Baseline in the SCORing Atopic Dermatitis

Objectives	Endpoints
	(SCORAD) at all scheduled timepoints; • Change from baseline in the Hospital Anxiety and Depression Scale (HADS) at all scheduled timepoints; • Change from baseline in Dermatology Life Quality Index (DLQI) at all scheduled time points; • Change from baseline in EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) at all scheduled time points; • Change from baseline in Patient-Oriented Eczema Measure (POEM) at all scheduled time points; • Change from baseline in Medical Outcomes Study – Sleep Scale (MOS-Sleep Scale) at all scheduled time points; • Change from baseline in Skin Pain NRS at all scheduled time points; • Medicated topical background therapy-free days.
Safety	
• To compare the safety and tolerability of abrocitinib 200 mg QD versus dupilumab in adult participants on background topical therapy with moderate to severe AD.	• Incidence of treatment-emergent adverse event (AE)s; • Incidence of serious adverse event (SAE)s and AEs leading to discontinuation; • Incidence of clinical abnormalities and change from baseline in clinical laboratory values, electrocardiogram (ECG) measurements, and vital signs.

Objectives	Endpoints
Tertiary/Exploratory	
• To compare the efficacy of abrocitinib 200 mg QD versus dupilumab on Healthcare Resource Utilization (HCRU) in adult participants on background topical therapy with moderate to severe AD.	• Change from baseline in the HCRU questionnaire at all scheduled time points.
• To compare the effect of abrocitinib 200 mg QD versus dupilumab on the frequency and duration of scratching during the night and sleep quantity in adult participants on background topical therapy with moderate to severe AD using wearable accelerometry devices.	• Number of scratching episodes during the evening sleep period that occur pre-treatment versus on-treatment, as derived from data analyses using wearable accelerometry monitors at scheduled time points; • Duration of scratching episodes during the evening sleep period that occur pre-treatment versus on-treatment, as derived from data analyses using wearable accelerometry monitors at scheduled time points; • Quantity of total sleep opportunity, total sleep time, percent time asleep, WASO, sleep onset latency, and number of wake bouts that occur pre-treatment versus on-treatment, as derived from data analyses using wearable accelerometry monitors at scheduled time points.
• To evaluate the efficacy of abrocitinib 200 mg QD in adult participants on background topical therapy with hand eczema.	• Response based on Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at all scheduled time points.

3.1. Estimands

The objective of the study is to demonstrate superiority of abrocitinib 200 mg once daily (QD) to dupilumab as measured by Peak Pruritus Numerical Rating Scale (PP-NRS4) response at Week 2 and EASI-90 response at Week 4. Additionally, this study is intended to

demonstrate that abrocitinib 200 mg QD is non-inferior to dupilumab and if non-inferior, to demonstrate the superiority to dupilumab as measured by EASI-90 response at Week 16.

There are two estimands for the study.

Estimand 1, composite estimand:

- Population: Participants with moderate-to-severe Atopic Dermatitis (AD) as defined by the inclusion criteria to reflect the targeted participant population;
- Variable: response based on achieving at least a 4-point improvement in the severity of PP-NRS4 from baseline at Week 2; for participants who drop out for any reason or use rescue therapy (Section 6.5.2) at any time during the treatment period, the response will be defined as "non-responsive" after that point;
- Interventional effect: Effect of randomized treatment accounting for treatment adherence, rescue therapy, and response; the intercurrent event (drop-out or use of rescue therapy) is captured through the variable definition;
- Population-level summary: differences in proportions of responders between abrocitinib and dupilumab.

Estimand 1 composite estimand is the primary estimand for the primary and key secondary endpoints: PP-NRS4 response at Week 2, EASI-90 at Week 4, and EASI-90 at Week 16. Other binary outcome measures such as response based on PP-NRS4 and EASI-90 at all other scheduled timepoints, EASI-75, and IGA will follow the same structure.

Estimand 2, hypothetical estimand:

- Population: Participants with moderate-to-severe Atopic Dermatitis (AD) as defined by the inclusion criteria to reflect the targeted participant population;
- Variable: Percent change from baseline in SCORAD at all scheduled timepoints;
- Interventional effect: Effect of randomized treatment as if all participants maintain their randomized treatment; drop-out for any reason and use of rescue therapy are the intercurrent events; data after dropout or use of rescue therapy at any time during the treatment period will be censored;
- Population-level summary: Difference in least-square means between abrocitinib and dupilumab.

Percent change from baseline or change from baseline to each specific post baseline scheduled time points in a continuous outcome measure such as HADS, POEM, DLQI, and EQ-5D-5L will follow the same structure as defined for SCORAD.

3.2. Adjudication Committee

This protocol will use an independent adjudication committee to determine whether certain investigator-reported adverse events meet the definition of disease-related safety endpoints, using predefined endpoint criteria.

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

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, double-dummy, active-controlled, multi-center study to assess the efficacy and safety of abrocitinib 200 mg (2 x 100 mg tablets) administered orally QD compared with dupilumab 300 mg administered by subcutaneous injection every other week (as per label guidelines) in adult participants on background topical therapy, with moderate to severe AD. The treatment duration is 26 weeks. A total of approximately 600 participants will be enrolled from approximately 220 sites globally. Approximately 600 participants will be randomly assigned to study intervention. There are primary efficacy assessments at Week 2 and Week 4, and a key secondary efficacy assessment at Week 16. Efficacy and safety endpoints will be assessed throughout the entire study. Exploratory endpoints related to hand eczema efficacy will be assessed throughout the study.

After providing informed consent, 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 to treatment with medicated topical therapy for at least 4 weeks or must have required systemic therapies for control of their disease within the previous year.

Eligible participants must meet the eligibility criteria at baseline. In addition, participants must be willing and able to use standardized background topical therapy, as per protocol guidelines, throughout the duration of the study.

Participants may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions. Participants 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.

Participants who continue to meet eligibility criteria at baseline will undergo Day 1 assessments and be randomized in a 1:1 ratio to receive abrocitinib 200 mg QD with dupilumab-matching placebo administered every other week or dupilumab 300 mg administered every other week (with a loading dose of 600 mg at baseline) with abrocitinib -matching placebo administered QD. Investigators, participants, and the sponsor study team will be blinded as to treatment group.

After Week 4, if medically necessary, participants with intolerable AD symptoms may receive locally-approved rescue therapy, at the investigator's discretion, pursuant to the following guidelines (refer to Section 6.5.2).

The total treatment period is 26 weeks. Participants discontinuing early from treatment, or who are otherwise ineligible for the B7451015 LTE study, will undergo a 4-week follow-up period. At Week 24 in the treatment period, all participants will cease injectable dupilumab or its matching placebo. Administration of abrocitinib 200 mg QD or its matching placebo will continue until Week 26. Efficacy and safety endpoints will be assessed throughout the entire study. Participants who complete the study through the Week 26 visit and are deemed eligible may enter the LTE Study B7451015.

See Section 10.12.3 for United Kingdom (UK) country-specific requirements.

For study estimands, refer to Section 3.1.

4.2. Scientific Rationale for Study Design

This study is part of the global Phase 3 clinical development program investigating the safety and efficacy of abrocitinib in participants with moderate to severe AD. Dupilumab is the most recent treatment available for the disease area and is expected to be a future standard of care. The comparison of dupilumab 300 mg to abrocitinib 200 mg in this study will provide efficacy and safety data for use in treating participants. In addition, medicated topical therapy is commonly used to treat moderate to severe AD. For this reason, including background medicated topicals will mimic real world medical practice. Due to the chronic nature of AD, the study will allow assessment of any difference in efficacy that may persist at month 6 of treatment. This study is designed to specifically evaluate abrocitinib and dupilumab when co-administered with background medicated topical therapy in adults with moderate to severe AD.

Participants with moderate to severe AD who also have hand eczema will undergo additional hand eczema assessments. The pathophysiology of atopic and non-atopic forms of hand eczema involve cytokines that can be affected through JAK1 inhibition, including ILγ, IL4, and IL13.[45] Therefore, this study includes exploratory endpoints related to hand eczema efficacy.

Quantitatively evaluating nighttime scratch and sleep via accelerometry using digital wearables and associated algorithms, to passively and continuously monitor participants in their "home environment," provides an opportunity to examine new and distinct endpoints. Moreover, this evaluation contributes to the understanding how scratch and sleep endpoints correlate to currently used measures of AD severity. The amount and duration of nighttime scratching and the duration and arousals from the total sleep opportunity (nighttime sleep) will be assessed using accelerometry, in selected countries.

Banked Biospecimens will be collected for pharmacogenomic/genomic/biomarker analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the study intervention's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

4.3. Justification for Dose

The original 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 as a monotherapy is expected to provide efficacy similar to that of currently approved systemic treatments (eg cyclosporine, systemic corticosteroids and dupilumab) in moderate to severe AD, based on dose-response modeling of IGA response in the Phase 2 study, and was therefore selected as the high dose for evaluation in Phase 3 studies.

The 200 mg dose demonstrated acceptable safety and tolerability in the Phase 2 study and in the completed Phase 3 studies (B7451012 and B7451013). Further details are available in the IB. The dosing regimen of dupilumab used in the study will be based on the approved USPI.[20]

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

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 Schedule of Activities for the last participant in the trial globally.

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.

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

5.1. Inclusion Criteria

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

Age

1. Participants must be 18 years of age or older inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who meet all of the following atopic dermatitis criteria:

   - Clinical diagnosis of chronic atopic dermatitis (also known as atopic eczema) for at least 6 months prior to Day 1 and has confirmed atopic dermatitis at the screening and baseline visits according to Hanifin and Rajka criteria for AD.[21] Refer to Appendix 9.

   - Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with medicated topical therapy for AD for at least 4 consecutive weeks, or who have required systemic therapies for control of their disease within the past year. NOTE: Medicated topical therapy is defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over-the-counter [OTC] or prescribed product).

   - Moderate to severe AD (BSA ≥10%, IGA ≥3, EASI ≥16, and PP-NRS severity score ≥4 on the day of the baseline visit).

Sex

3. Male or Female

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

a. Male participants:

No contraceptive measures are required.

b. Female participants:

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

- Is not a woman of childbearing potential (WOCBP) (see 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.

Informed Consent

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

5. For the treatment of AD, the participant may use low- or medium-potency medicated and non-medicated topical therapy, with response to treatment remaining inadequate at baseline. The participant must also be willing and able to comply with standardized background topical therapy, as per protocol guidelines Section 6.5.1, throughout the remainder of the study.

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

7. Participants must agree to avoid prolonged exposure to the sun and to refrain from the use of tanning booths, sun lamps, and other sources of ultraviolet light during the study.

8. If participants are receiving concomitant medications for any reason other than AD, these participants must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to Day 1. Administration of these stable regimen concomitant medications will be allowed to continue throughout the study.

5.2. Exclusion Criteria

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

Medical Conditions

1. Other acute or chronic medical condition including laboratory abnormality that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results and, in the judgement of the investigator, would make the participant inappropriate for entry into this study.

2. The participant must have a risk assessment done by a qualified mental health professional (MHP) to assess whether it is safe to participate in the trial if the participant's responses on any of the screening instruments or other screening information indicate:

   - Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia Suicide Severity Rating Scale (C-SSRS).

   - Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS.

   - Any lifetime history of serious or recurrent suicidal behavior (non-suicidal self-injurious behavior is not a trigger for a risk assessment unless in the investigator's judgement it is indicated).

   - Clinically significant depression: Patient Health Questionnaire 8 items (PHQ-8) when the total score is ≥15.

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

   - In the investigator's judgment a risk assessment or exclusion is required.

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

    - History of venous thromboembolism, or

    - First-degree relative with unprovoked venous thromboembolism (i.e. without known underlying cause such as trauma, surgery, immobilization, prolonged travel, pregnancy, hormone use, or plaster cast), that would suggest participant is at increased risk of inherited coagulation disorder (e.g. Factor V Leiden).

4. A current or past medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction.

5. Receiving anti-coagulants or medications known to cause thrombocytopenia (unless considered safe to stop and washout for the duration of the study).

6. Currently have active forms of other inflammatory skin diseases (ie, not AD) or have evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, Lupus) at the time of Day 1 that would interfere with evaluation of AD or response to treatment.

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

8. Infection history:

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

    - Have a known helminth infection;

    - Have active chronic or acute skin infection requiring treatment with systemic antimicrobials within 2 weeks prior to Day 1, or superficial skin infections within 1 week prior to Day 1;

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

        - Participants who are hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (HBcAb) positive, and hepatitis B surface antibody (HBsAb) positive at Screening will have reflex testing for hepatitis B Virus (HBV) deoxyribose nucleic acid (DNA). Participants who have HBV DNA above the lower limit of quantification (LLQ) are excluded. Participants who have HBV

DNA negative or below LLQ may be randomized but will have HBV DNA testing repeated at Week 16 and Week 26 End of Treatment (EOT) visit, or Early Discontinuation (ED) visit, whichever is sooner.

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

9. Have a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.

10. Have a history of alcohol or substance abuse within 6 months prior to Day 1 that in the opinion of the investigator will preclude participation in the study.

11. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.

12. Require treatment with prohibited concomitant medications (refer to Section 6.5) or have received a prohibited concomitant medication within the specified timeframe prior to the first dose of study intervention(s).

13. Have evidence of active, latent, or inadequately treated infection with Mycobacterium tuberculosis (TB) as evidenced by any of the following:

    - A positive QuantiFERON®-TB Gold (QFT-G) In-Tube test or positive Mantoux/Purified Protein Derivative (PPD) tuberculin skin test performed at or within the 12 weeks prior to Day 1. NOTE: The QFT-G may be repeated once if the investigator deems this to be necessary. If approved by the Pfizer clinician, other TB testing may be performed by a local lab. A negative QFT-G, Mantoux/PPD tuberculin skin test or other local lab TB test is required unless the participant has previously received a documented adequate course of therapy for latent (9 months of isoniazid in a locale where rates of primary multi-drug TB resistance are <5% or an acceptable alternative regimen per local standards of care) or active (acceptable multi-drug regimen) TB infection. If the current incidence rates of multi-drug resistant TB infection in the locale are unavailable, an adequate treatment regimen should be defined as the regimen recommended by the health ministry or expert panel in the locale.

    - It is recommended that participants with a history of Bacille Calmette Guérin (BCG) vaccination be tested with the QFT-G test since the Mantoux/PPD tuberculin skin test may be positive due to vaccination. Refer to Section 8.2.5.2 for requirements for Mantoux/PPD tuberculin skin testing.

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

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

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

Prior/Concomitant Therapy

14. Participants who are vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of study intervention(s), or who are expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of study intervention(s).

15. Participants who have received prior treatment with any systemic JAK inhibitors. Prior treatment with topical JAK inhibitors is not exclusionary.

16. Previous treatment with IL-4 or IL-13 antagonists, including dupilumab, lebrikizumab, or tralokinumab, or a history of hypersensitivity, intolerance, adverse event, or allergic reaction associated with prior exposure to excipients in these products.

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

<u>Within 1 year of first dose of study intervention(s):</u>

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

<u>Within 12 weeks of first dose of study intervention(s):</u>

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

Within 4 weeks of first dose of study intervention(s):

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

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

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

- Use of CYP2C9 and CYP2C19 inducers (refer to Appendix 10) within 5 half-lives of the inducer plus 14 days of first dose of study intervention(s). For example, the average half-life of Carbamazepine after repeat dosing is 15 hours. The washout period is calculated as the sum of 5 half-lives (approximately 3 days) and an additional 14 days for a total of 17 days prior to the first dose of study intervention(s).

- Phototherapy narrowband UVB (NB-UVB) or broadband phototherapy.

- Regular use (more than 2 visits per week) of a tanning booth/parlor.

- Herbal medications with unknown properties or known beneficial effects for AD.

Within 1 week of first dose of study interventions:

- Use of CYP2C9 and CYP2C19 inhibitors within 1 week of first dose of study intervention(s) or within 5 half-lives (if known) of the inhibitor, whichever is longer. NOTE: Half-life refers to the half-life of the parent drug and its metabolites, which are inhibitors, as detailed in Appendix 10.

- 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.

Prior/Concurrent Clinical Study Experience

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

Diagnostic assessments

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

20. ANY of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:
    - Absolute neutrophil count of $<1.2 \times 10^9$/L ($<1200/mm^3$);
    - Hemoglobin <10.0 g/dL or hematocrit <30%;
    - Platelet count of $<150 \times 10^9$/L ($<150,000/mm^3$);
    - Absolute lymphocyte count of $<0.50 \times 10^9$ /L ($<500/mm^3$);
    - Estimated Creatinine Clearance <40 mL/min based on the age appropriate calculation, or serum creatinine >1.5 times the upper limit of normal (ULN);
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 times the ULN;
    - Total bilirubin ≥1.5 times the ULN; participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN.

21. In the opinion of the investigator or sponsor, have any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the participant's enrollment in the study.

Other Exclusions

22. Have undergone significant trauma or major surgery within 1 month of the first dose of study interventions.

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

Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

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

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

3. On study visit days, topical therapies (ie, non-medicated topical therapy and medicated topical therapy, per protocol guidelines as described in Section 6.5) are not permitted to be applied prior to attending the study visit. Topical therapies are required to be applied after the visit (per protocol guidelines as described in Section 6.5).

4. 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 Appendix 4 Section 10.4) 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). 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. Male participants are not required to use contraception.

5.3.1. Meals and Dietary Restrictions

On study visit days as per the Schedule of Activities, participants must comply with fasting requirements for at least 8 hours prior to the visit. Water and permitted non-study medications are allowed (Section 6.5.1).

If the participant experiences nausea, consideration should be given to administering the oral study intervention with food.

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). Vaccination of participants with live components is prohibited within the 6 weeks prior to first dose of study intervention.

5.3.3.2. Guidance Regarding Household Contact Vaccine-Related Exposure

Current routine household contact with children and others who have been vaccinated with live vaccine components may pose a risk during treatment and for 6 weeks following completion of the study. Some of these vaccines include varicella ("chickenpox") vaccine, oral polio vaccine, and the inhaled flu vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted. General guidelines for immunosuppressed participants suggest that exposure (through routine contact) should be avoided following vaccination (of others) with these vaccines for the stated time period:

a. Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination.

b. Oral polio vaccination for 6 weeks following vaccination.

c. Attenuated rotavirus vaccine for 10 days following vaccination.

d. FluMist® (inhaled flu vaccine) for 1 week following vaccination.

e. Measles, Mumps and Rubella vaccine for 4 weeks following vaccination.

f. Yellow fever vaccine for 4 weeks following vaccination.

Participants should avoid exposure to vaccinated or infected persons and contact the investigator promptly should they develop signs or symptoms of infections.

5.3.4. Surgery

During the study, no elective surgery should occur without first consulting with the Pfizer clinician or designee. Preferably, elective surgery should occur before the study or be delayed until study participation is completed.

The Pfizer clinician or designee should be notified if a participant requires surgery (including dental surgery) during the study to determine whether the participant should discontinue from

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

5.4. Screen Failures

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

Individuals who do not meet the criterion for participation in this study (screen failure) may be rescreened once 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 criteria and who subsequently experience worsening AD, which in the investigator's judgement would make them eligible for participation, may be considered for re-screening. Such cases should be discussed with the Pfizer Medical Monitor (or designee) to determine if re-screening is appropriate.

6. STUDY INTERVENTION

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

6.1. Study Intervention(s) Administered

NOTE: Abrocitinib may be referred to as PF-04965842.

ARM Name	Abrocitinib	Dupilumab	Abrocitinib Matching Placebo	Dupilumab Matching Placebo
Intervention Name	Abrocitinib	Dupilumab	Placebo	Placebo
Type	Small molecule	Biological product	Other	Other
Dosage Form	Tablet	Injectable	Tablet	Injectable
Dose Strength	200 mg	300 mg	0 mg	0 mg
Dosage	100 mg x 2 tablets	300 mg x 1 injection (2 baseline injections)	0 mg x 2 tablets	0 mg x 1 injection (2 baseline injections)
Route of Administration	Oral	Subcutaneous	Oral	Subcutaneous
Sourcing	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.
Packaging and Labeling	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in prefilled syringes. Each prefilled syringe will be labeled as required per country requirement.	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in prefilled syringes. Each prefilled syringe will be labeled as required per country requirement.

6.1.1. Administration of Study Interventions

- Treatment duration is 26 weeks (with the blind maintained throughout).
- A guidance document with detailed dosing instructions will be provided to the participant to support at-home dosing.
- Participants who do not enroll into the long-term extension study, B7451015, will enter a 4-week follow-up post-treatment period. (See Section 10.12.3 for UK country-specific requirements).

6.1.1.1. Administration of Abrocitinib/Matching Placebo

- Orally administered study intervention, abrocitinib 200 mg, or its matching placebo, will be administered QD from Day 1 to Week 26. Participants will be dispensed 2 bottles of oral study intervention at the Day 1, Week 4, Week 8, Week 12, Week 16 visits, and 3 bottles of study intervention at the Week 20 visit.

- Participants will be given clear dosing instructions to take two tablets of study intervention once daily by mouth, 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. Oral study intervention may be taken with or without food, other than on study visit days where fasting is required. If the participant experiences nausea, consideration should be given to administering the oral study intervention with food.

6.1.1.2. Administration of Dupilumab/Matching Placebo

- Injectable study intervention, dupilumab 300 mg (with a loading dose of 600 mg at baseline) or its matching placebo (two injections at baseline; to dummy the loading dose), will be administered at the site on Day 1, Week 2, Week 4, Week 8, Week 12, Week 16, and Week 20 under the observation of the injection administrator/trainer at the end of the study visit, and at home by the participant (or caregiver, if applicable) at Week 6, Week 10, Week 14, Week 18, Week 22, and Week 24.

- Participants will be dispensed prefilled syringes containing injectable study intervention at the Day 1 (2 syringes dispensed and administered), Week 2 (1 syringe dispensed and administered), Week 4, Week 8, Week 12, and Week 16 visits (2 syringes dispensed per visit; 1 syringe administered every 2 weeks). Participants will be dispensed 3 prefilled syringes at the Week 20 visit (1 syringe administered every 2 weeks).

    - The injection administrator/trainer will instruct the participant (or caregiver, if applicable) on the proper aseptic technique to administer a subcutaneous injection when using the prefilled syringes.

    - The first injection at the Day 1 visit will be administered by the injection administrator/trainer and used to train the participant (or caregiver, if applicable) on correct injection technique.

    - The second injection will be administered by the participant (or caregiver, if applicable) immediately following the first injection, under the observation of the injection administrator/trainer.

- If any issues with technique are observed, the injection administrator/trainer must retrain the participant appropriately.

- All injections should be administered in accordance with the dupilumab drug label.

- The investigator should assign the responsibility of the injection administrator/trainer to a member of the study site staff who will not participate in any other study-related activities, ensuring that all other site staff do not risk becoming accidentally unblinded. Contact between the injection administrator/trainer and study participants should be kept to a minimum. The injection administrator/trainer must not take any action that may potentially reveal treatment assignment to the participant or site staff. The investigator, site staff, and any study participants other than the injection administrator/trainer must not be allowed to know the study intervention assigned to any study participant and must not be allowed to see the treatment records.

6.1.2. Medical Devices

The medical devices (or devices manufactured by and/or for Pfizer by a third party) provided for use in this study are:

- pre-filled syringes for subcutaneous injection of dupilumab and matching placebo.

Instructions for medical device use are provided in the Investigational Product Manual (IP Manual).

Pre-filled medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (refer to Section 8.3.6 and Appendix 7).

6.2. Preparation/Handling/Storage/Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

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

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

6. Study interventions should be stored in their original containers and in accordance with the labels.

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

8. 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. It will not be considered a protocol deviation if Pfizer approves the use of study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. 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.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). 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, and all destruction must be adequately documented.

Additional details about accountability, storage, destruction, and excursion reporting can be found in the IP Manual.

6.2.1. Preparation and Dispensing

The oral study intervention will be dispensed using an interactive response technology (IRT) drug management system at the Day 1, Week 4, Week 8, Week 12, and Week 16 visits (two bottles dispensed each visit), and the Week 20 visit (three bottles dispensed this visit). A qualified staff member will dispense the study interventions via unique container numbers on the bottles provided, in quantities appropriate for the study visit schedule. The participant/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.

The injectable study intervention will be provided as prefilled syringes (PFSs) packaged and dispensed in cartons with tamper-evident seals. The study interventions will be dispensed using an IRT drug management system at the Day 1 (2 syringes dispensed and administered), Week 2 (1 syringe dispensed and administered), Week 4, Week 8, Week 12, and Week 16 visits (2 syringes dispensed per visit; 1 syringe administered every 2 weeks). Participants will be dispensed 3 prefilled syringes at the Week 20 visit (1 syringe administered every 2 weeks). A qualified staff member will dispense the study interventions via unique container numbers in the cartons provided, and in quantities appropriate so that participants will receive enough PFSs to cover the number of doses until the next scheduled clinic visit. The participant/caregiver should be instructed to maintain the product in the cartons provided, and the cartons should not be opened until the study intervention is to be administered.

Refer to the IP manual for instructions on how to prepare the study interventions for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

The dupilumab and matching placebo will be administered by qualified site personnel or by the participant/caregiver according to the IP manual. The study interventions will be administered to blinded participants.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system (interactive Web-based response [IWR]). The block randomization method will be used, and participants will be stratified by baseline disease severity (IGA = 3 vs. IGA = 4). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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

Returned study intervention must not be re-dispensed 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.

6.3.2. Breaking the Blind

Investigators, participants and the sponsor study team will be blinded as to treatment group. At each site, an injection administrator/trainer will administer the first dose of dupilumab or

its matching placebo to train the participant (or caregiver, if applicable) in proper injection technique. At all times, treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, or the sponsor's study team until following the conclusion of the study, with the exception described in this section.

At the initiation of the study, the study site will be instructed on procedures for breaking the blind. Blinding codes should only be broken in emergency situations for reasons of participant safety. The investigator is responsible for, and may break the blind for safety reasons, where the knowledge of actual treatment is essential for the further management of the participant. The method will be an electronic process. When the blind for a participant has been broken, the reason must be fully documented and entered on the case report form (CRF). Whenever possible, the investigator should contact Pfizer before breaking the blind. If the blind is broken, the investigator should promptly inform the Pfizer Clinician or Medical Monitor. The participant for whom the blind has been broken will be discontinued from the study and undergo the early discontinuation (ED) procedures.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting of syringes/tablets as applicable. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

Participants will be issued an electronic dosing diary (eDiary) and will be educated to record the date and time of their dosing and date and time of their last meal before taking the study intervention. Participants will also use the eDiary to record their daily use of standardized background topical therapy for the treatment of AD, as required and as per protocol guidelines in Section 6.5.1, beginning at Day 1 visit through the EOT visit.

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

Study intervention may be temporarily withheld for a maximum of 28 days at investigator's discretion due to abnormal laboratory tests or adverse event. Refer to Section 7.1.1 for further guidance on temporary withholding of study intervention. Doses not taken for the reasons mentioned above do not constitute protocol deviations or medication errors and should not be considered dosing errors but should be noted in the dosing log with the reason for reduced drug consumption.

Compliance with background topical therapy guidelines in Section 6.5.1 will be monitored and verified by delegated site personnel through a combination of review of the electronic diary, and discussion with the participant, which will be documented in the source documents.

Other than for the above reasons, the following compliance cases will be considered medication errors and will be discussed with the sponsor for possible withdrawal from the study:

- Participants interrupting oral study intervention for more than 4 consecutive days or for a total of more than 7 days between visits;
- Participants interrupting injectable study intervention for ≥ 2 doses between visits (≥ 4 week visit intervals);
- Participants administering >8 tablets in 1 day or administering ≥4 tablets/day for 4 consecutive days;
- Participants administering >1 prefilled syringe every 2 weeks, with the exception of the initial loading dose of 2 prefilled syringes on Day 1;
- Participants who have an overall compliance of <80% or >120% between visits for oral study intervention;

Non-compliance with background topical therapy will not be considered medication error.

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

6.4.1. Abrocitinib Compliance

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

From the Day 1 visit onward, participants will be dispensed abrocitinib or abrocitinib-matching placebo to take home with them for self-administration on non-study visit days.

6.4.2. Dupilumab Compliance

There are viscosity differences between dupilumab and the matched placebo, and as such there is a potential for the administrator/trainer who may have previous experience administering dupilumab to notice this difference in viscosity. Although no injection administrator/trainer will know the treatment allocation of participants, as a risk mitigation against accidental unblinding affecting study integrity this injection administrator/trainer will only administer injectable study intervention, or observe/train participants administering injectable study intervention, and will account/reconcile any unused syringes returned by participants, will be isolated from all other study activities, and will be treated as if unblind. Throughout the protocol, these individuals will be referred to as "injection administrator/trainer" in order to make this clear distinction from other site personnel.

When injectable study intervention is administered at the research facility, it will be administered under the supervision of the injection administrator/trainer only.

If the participant is unwilling/unable to self-administer the injectable study intervention or arrange for a caregiver to administer the injectable study intervention, then it is permissible for the site to arrange for the participant to return to the site for administration by the injection administrator/trainer.

Participants will be directed to bring any used and unused syringe cartons to visits following administration at home. Study sites will provide participants with a sharps container for disposal of used syringes. Participants will return this sharps container to the study site at the final visit for disposal.

If an injectable dose is missed, participants (or caregivers, if applicable) should be instructed to administer the injection within 7 days from the missed dose and then resume the participant's original schedule. If the missed dose is not administered within 7 days, participants (or caregivers, if applicable) should be instructed to wait until the next dose on the original schedule.

6.5. Concomitant Therapy

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

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

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

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit (refer to Appendix 10 for washout periods for CYP2C9 inhibitors and inducers), unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Participants will abstain from all prohibited concomitant medications as described in Section 6.5.3 and Appendix 10 of the protocol. Medications that are taken in the Screening/Washout period (after informed consent is obtained and before the first dose of study intervention) will be documented as prior medications. Medications taken after the first dose of study intervention has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in study records with indication (if AD), reference to any associated adverse event, dose, and start and

stop dates of administration. Participants will be queried about concomitant medication (including topical medications and treatments, over-the-counter and prescription medications and treatments, and vaccinations) at each study visit. Any new concomitant medications or dose changes to current concomitant medications should be evaluated for potential new or worsening adverse events.

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.

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

The concomitant medication for any reason must be a locally-approved medication and dose. Participants are not allowed any other investigational drugs or treatments during the study.

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.

6.5.1. Permitted Concomitant Treatments

Background Topical Therapy

Participants must comply with standardized background topical therapy guidance throughout the study. Medicated and non-medicated background topical therapy will not be provided directly by the sponsor. Standardized background topical therapy begins on Day 1 but topical therapies can be taken during the screening period since washout of topical therapies for AD is not required. Standardized background topical therapy refers to the guidance below, in accordance with the local standard of care and according to the Investigator's usual practice:

Non-medicated Topical Therapy

- Non-medicated topical emollient without other active ingredients indicated to treat AD, or other additives which could affect AD (eg, hyaluronic acid, urea, ceramide or filaggrin degradation products) must be applied at least twice daily to all body areas affected with AD starting on Day 1 and throughout the remainder of the study.

Medicated Topical Therapy

- TCS must be applied once daily to areas with active lesions, starting on Day 1 (Baseline) and throughout the study, according to the guidance below:
    - Medium potency TCS (eg, Triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment) must be applied to body areas with active lesions that

are suitable for the use of medium potency TCS. Participants must be clinically monitored for toxicity to TCS and stepped down as needed.

- After lesions are under control (clear or almost clear), treat once daily for a further 7 days, then stop;
- If lesions return then resume treatment with medium potency TCS, but use the approach described above upon lesion resolution.
- If the participant experiences toxicity attributable to the background TCS, the following step-down is allowed:
    - Change from medium-potency TCS to low-potency TCS once daily (if the participant has been receiving medium-potency TCS); OR
    - Change from a TCS to a topical calcineurin inhibitor or a phosphodiesterase type 4 inhibitor; OR
    - Discontinue background medicated topical treatment, if there is documented evidence that the participant did not tolerate any of the background medicated topical treatments allowed in the protocol.
- Low potency TCS (ie, hydrocortisone 1% cream) must be applied to body areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) with active lesions instead of medium potency TCS or to body areas where continued treatment with medium potency TCS is considered unsafe. Participants must be clinically monitored for toxicity to TCS and stepped down as needed.
    - After lesions are under control (clear or almost clear), treat once daily for a further 7 days, then stop;
    - If lesions return then resume treatment with low potency TCS, but use the approach described above upon lesion resolution.

TCI (eg, tacrolimus, pimecrolimus) or a PDE4 inhibitor (eg, crisaborole) may be used instead of corticosteroids in body areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) with active lesions or if continued treatment with TCS of any potency is considered unsafe, and according to locally approved label at the investigator's discretion and considering prior response or intolerance to these medications.

NOTE: Background topical therapy must not be applied prior to attending a study visit, on the day of the study visit. Background topical therapy should instead be applied after the visit, on study visit days.

Other Permitted Concomitant Treatments

The following other concomitant AD therapies are permitted during the study and will not be provided by the sponsor:

- Oral antihistamines.

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;
- Low dose acetyl salicylic acid (≤100 mg QD) is permitted, for the purpose of cardiovascular prophylaxis, at the discretion of the investigator;
- Acetaminophen/paracetamol may be used intermittently not to exceed 1 gram per day;
- 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).

Locally approved treatments for AD other than what is outlined in this section, including topical or systemic medications, are considered rescue therapy.

Reference Appendix 10 for prohibited concomitant medications.

6.5.2. Rescue Therapy for Atopic Dermatitis

The study site will not supply rescue therapy for AD. This will be obtained locally.

After Week 4, if medically necessary, participants with intolerable AD symptoms may receive locally-approved rescue therapy, at the investigator's discretion, pursuant to the following guidelines.

- Rescue therapy may include high-potency TCS for up to 2 weeks at a time or systemic corticosteroids for up to 10 days at a time according to local product label, or other systemic therapy according to local productlabel.[8,52]
- Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering rescue therapy. An unscheduled visit may be used for this purpose if necessary.

- Participants receiving systemic rescue therapy must temporarily discontinue study intervention during the time they take the systemic rescue therapy. Participants receiving systemic rescue therapy should continue study visits and assessments.

- Participants receiving topical rescue therapy may continue to receive study intervention concurrently. Participants receiving topical rescue therapy should continue study visits and assessments.

- Rescue therapy administration must be recorded.

  See Section 10.12.2 for Czech-Republic country-specific requirements.

6.5.3. 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 10). Participants should be instructed at each visit to contact the study site investigator promptly if there are any intended changes or additions to concomitant medications.

All medications and treatments that could affect AD must be discontinued except oral antihistamines and low- or medium-potency medicated topical therapy. Starting on Day 1, standardized background topical therapy will be used as per protocol guidance in Section 6.5.1. After Week 4, rescue therapy for AD with high-potency TCS or systemic corticosteroids may be used as per protocol guidance in Section 6.5.2.

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

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

Herbal medications with unknown properties or known beneficial effects for AD must be discontinued at least 4 weeks before the first dose of study intervention. 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 clinician, the investigator will make a judgement on the ongoing eligibility of any participant with prohibited medication use during the study.

6.6. Dose Modification

No dose modifications of either study intervention are allowed.

6.7. Intervention after the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In certain instances, it may be necessary for a participant to permanently discontinue study intervention. Per the study estimands, if study intervention is permanently discontinued, the participant will remain in the study to be evaluated for EOT assessments (as per the Schedule of Activities) (See Section 6.5.2).

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. Refer to Appendix 11 for discontinuation criteria.

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.

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 6 or if the investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including, but not limited to changes from baseline in Fridericia-corrected Q wave interval [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE. Refer to Appendix 8 for ECG values of potential clinical concern.

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

7.1.1. Temporary Discontinuation

An investigator can temporarily interrupt oral study intervention for up to a maximum of 28 consecutive days and up to 2 consecutive doses of injectable study intervention for a participant, for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary. In the case of study intervention(s) being withheld, all study intervention(s) that the participant is receiving should be withheld (ie, both oral and injected study intervention, as applicable). The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the participant during this timeframe. If within this timeframe the investigator judges that it is

safe to restart dosing, then the participant may restart the study intervention. If the investigator judges that it is not safe to restart dosing within this timeframe then the participant must be permanently discontinued from study intervention, have an End of Treatment visit, and enter the 4-week follow-up period (See Section 10.12.3 for UK country-specific requirements). Doses not taken for the reasons mentioned above do not constitute protocol deviations or medication errors and should not be considered dosing errors but should be noted in the dosing log with the reason for reduced drug consumption clearly described.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. See also Section 10.11.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

- The early discontinuation visit applies only to participants who are randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent (see below) 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 a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any remaining samples but data already generated from the samples will continue to be available, and may be used to, to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

- When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the clinical trial (CT) SAE Report.

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study interventions will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only

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

7.3. Lost to Follow up

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

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

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

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

All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the participant remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the participant's medical records.

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral

reasons, or the inability of the participant to comply with the protocol-required schedule of study visits or procedures at a given study site. Participants that discontinue study intervention will remain in the study and must have their end of treatment visit within 1 week after their last dose and will then enter the 4-week follow-up period. Refer to Appendix 11 for guidelines for monitoring and discontinuation.

If the participant withdraws from the study, and also withdraws consent 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.

8. STUDY ASSESSMENTS AND PROCEDURES

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 wellbeing of the participant. Guidance on the conduct of study procedures in the context of COVID-19 or other virus/infection or public health related travel restrictions or emergency is described Appendix 10.13. 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.

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the 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 (Visit 1) within approximately 28 days prior to administration of the study intervention to confirm that they meet the participant selection criteria for the study. Use of screening procedures exceeding 28 days prior to randomization should be discussed with the Pfizer medical monitor. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each participant, in accordance with the procedures described in Section 10.1.3 of Appendix 1.

- If the Mantoux PPD tuberculin skin test is given, the participant must return between 48-72 hours post-injection for induration evaluation.

- Due to the possible need for PPD testing and chest radiograph, screening procedures may be performed over more than 1 visit in the 28 days prior to the Day 1 visit.

- Visit windows are based on Day 1 visit. To assure consistency and reduce variability, all study visits should occur in the morning whenever possible. On days of study visits, participants will receive their dose at the clinic during the visit.

- Participants are required to fast for at least 8 hours prior to all visits that include lipid profile panel testing. During the fasting period, participants should refrain from all food and liquids (water and permitted non-study medications are allowed).

- ECGs will be interpreted by a central reader for all visits where it is performed.

- Urine pregnancy test must be performed prior to dosing with the study intervention for WOCBP through the EOT visit.

- Prior to attending a study visit, participants are allowed to shower and bathe but should not moisturize or apply emollient.

- Participants will be instructed about the use of standardized background topical therapy (refer to Section 6.5.1).

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

8.1.1. Rater Qualifications

Clinical evaluations of AD and hand eczema 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 and hand eczema when designated by the primary site Investigator. The clinical 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. Eczema Area and Severity Index (EASI)

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

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

Table 1. Clinical Sign Severity Scoring Criteria for the Eczema Area and Severity Index (EASI)

Score		Description
Erythema (E)		
0	Absent	None; may have residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation)
1	Mild	Light pink to light red
2	Moderate	Red
3	Severe	Deep, dark red
Induration/Papulation (I)		
0	Absent	None
1	Mild	Barely palpable to slight, but definite hard thickened skin and/or papules
2	Moderate	Easily palpable moderate hard thickened skin and/or papules
3	Severe	Severe hard thickened skin and/or papules
Excoriation (Ex)		
0	Absent	None
1	Mild	Slight, but definite linear or picked scratch marks or penetrating surface injury
2	Moderate	Moderate linear or picked scratch marks or penetrating surface injury
3	Severe	Severe linear or picked scratch marks or penetrating surface injury
Lichenification (L)		
0	Absent	None
1	Mild	Barely perceptible to slight, but definite thickened skin, fine skin markings, and lichenoid scale

Table 1. Clinical Sign Severity Scoring Criteria for the Eczema Area and Severity Index (EASI)

Score		Description
2	Moderate	Moderate thickened skin, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale

Percent BSA with Atopic Dermatitis: The number of handprints of skin afflicted with atopic dermatitis in a body region can be used to determine the extent (%) to which a body region is involved with atopic dermatitis (Table 2). When measuring, the handprint unit refers to the size of each individual participant's hand with fingers in a closed position.

Table 2. Handprint Determination of Body Surface Area (BSA)

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

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

The extent (%) to which each of the four body regions is involved with atopic dermatitis is categorized to a numerical Area Score using a non-linear scaling method according to the following BSA scoring criteria (Table 3).

Note: The BSA for a subset of body regions (scalp, palms and soles of feet) assessed in Table 2 will be entered in the eCRF.

Table 3. Eczema Area and Severity Index (EASI) Area Score Criteria

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

Table 3. Eczema Area and Severity Index (EASI) Area Score Criteria

Percent BSA with Atopic Dermatitis in a Body Region	Area Score
90 - 100%	6

Body Region Weighting: Each body region is weighted according to its approximate percentage of the whole body (Table 4**).**

Table 4. Eczema Area and Severity Index (EASI) Body Region Weighting

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

In each body region, the sum of the Clinical Signs Severity Scores for erythema, induration/papulation, excoriation, and lichenification is multiplied by the Area Score and by the Body Region Weighting to provide a body region value, which is then summed across all 4 body regions resulting in an EASI score as described in Equation 3 on the following page**.**

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

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

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

8.1.2.1. Body Surface Area – Efficacy (BSA Efficacy)

BSA Efficacy will be derived from the sum of the BSA in handprints across 4 body regions assessed as part of the EASI assessment (Table 3). Handprint refers to that of each individual participant for their own measurement. The BSA Efficacy ranges from 0 to 100%, with higher values representing greater severity of atopic dermatitis.

8.1.3. SCORing Atopic Dermatitis (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).

8.1.4. Investigator's Global Assessment (IGA) of Atopic Dermatitis

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

Table 5. Investigator's Global Assessment (IGA) of Atopic Dermatitis Score

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

8.1.5. Standardized Background Topical Therapy

Participants will be instructed to keep a daily record of use of standardized background topical therapy. At each visit, the participant's understanding of background topical therapy requirements (refer to Section 6.5.1) and adherence to the use of background topical therapy will be checked. Participants will be re-educated as required. Standardized background

topical therapy use and adherence with guidelines will be recorded daily in the participant eDiary during the treatment period, through the EOT visit:

- Non-medicated topical therapy must be applied at least twice daily to all body areas affected with AD starting on Day 1, and continued through the EOT visit;
- Refer to Section 6.5.1 for required background medicated topical therapy during treatment through the EOT visit.

8.1.6. Patient-Reported Outcomes (PROs)

Participants will complete the PROs at the clinic prior to other clinical activities and study intervention administration. The PROs should be checked for completeness by the study site staff before proceeding with other steps of the clinical visit procedures. Compliance with scheduled PROs activities will be monitored. Delegated site staff will oversee the administration of PROs at site visits to ensure protocol compliance. Participants are given a handheld device to complete the PP-NRS on a daily basis. Delegated site staff will review compliance at each visit and counsel as appropriate. If a participant has repeated non-compliance, the participant should be re-trained on the device. If a participant is unable to complete the PROs on the handheld device due to documented difficulty using the technological devices or other limitation, the participant will be permitted to enter or remain in the study (for example, if the participant doesn't have internet access, he or she can complete the PROs offline and then they can upload the PROs to the internet when they return to the site and have internet access). In the event of electronic malfunction, a replacement device will be shipped to the site.

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.

8.1.6.1. Peak Pruritus Numerical Rating Scale (PP-NRS)

The severity of itch (pruritus) due to AD will be assessed using the PP-NRS, a validated horizontal NRS.[22,23] Participants will be asked to assess their worst itching due to AD over the past 24 hours on an NRS anchored by the terms "no itch" (0) and "worst itch imaginable" (10). This item will be administered to all participants. Participants will enter the PP-NRS assessment into an eDiary on a daily basis from the Screening visit through the Week 30 visit.

8.1.6.2. Dermatology Life Quality Index (DLQI)

The DLQI is a validated general dermatology questionnaire that consists of 10 items to assess participant-reported health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment).[24] It has been extensively used in clinical trials for AD. The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to

be responsive to change. The minimally important difference for the DLQI has been estimated as a 3 to 5-point change from baseline.[25]

8.1.6.3. EuroQuol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L)

The EQ-5D is a validated, standardized, generic instrument that is the most widely used preference-based health-related quality of life questionnaire in cost-effectiveness and health technologies assessment (HTA).[26-29] Recently, a version was developed called EQ-5D-5L with 5 response levels on each dimension compared to the 3 response levels in the Euroquol Quality of Life 5-Dimension 3-Level Scale (EQ-5D-3L).[26-32]

Measurement properties of the EQ-5D-5L demonstrated to be a valid version of the 3-level questionnaire that improved measurements by adding discriminatory power, reducing the ceiling, and establishing convergent and known-groups validity.[26,28,30,31] Both the EuroQol EQ-5D-3L and EQ-5D-5L versions are well-established instruments used to measure health states and utilities in various diseases areas and assess mobility, self-care, usual activities, pain/discomfort, anxiety/depression and health status using a VAS.[29,33] The EQ-5D-3L was used previously in AD studies, including the dupilumab trials, to measure utilities.[17,34-36]

8.1.6.4. Healthcare Resource Utilization (HCRU) Questionnaire

The HCRU is a 14-item questionnaire. This instrument is appropriate for use in participants aged 18 years and older.[37]

8.1.6.5. Patient-Oriented Eczema Measure (POEM)

The POEM is a validated 7-item PRO measure used to assess the impact of AD recalled over the past week.[38-39]

8.1.6.6. Hospital Anxiety and Depression Scale (HADS)

The HADS is a validated 14-item PRO measure used to assess states of anxiety and depression over the past week.[40]

8.1.6.7. Medical Outcomes Study (MOS) Sleep Scale

The Medical Outcomes Study Sleep Scale (MOS-Sleep) is a validated 12-item measure used to assess sleep quality in the pastweek. The instrument has been validated for use by participants 18 years and older.[41]

8.1.6.8. Skin Pain Numerical Rating Scale (SP-NRS)

The SP-NRS queries “worst skin pain” in the past 24 hours on an 11-point scale (0 [no skin pain] – 10 [worst skin pain imaginable]).[42]

8.1.6.9. Asthma Control Questionnaire (ACQ)

Asthma control for all participants with a history of asthma, regardless of whether they are receiving medication for their asthma, should be assessed at times specified in the Schedule of Activities (SoA) using the Asthma Control Questionnaire (ACQ). The ACQ measures the adequacy of asthma control and change in asthma control which occurs either spontaneously

or as a result of treatment. The ACQ has 6 questions and participants are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0 = no impairment, 6 = maximum impairment). The questions are equally weighted and the ACQ score is the mean of the 6 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). [54, 55, 56]

8.1.7. Exploratory Accelerometry

AD is often accompanied by nighttime pruritus as well as disrupted and reduced overall sleep. Pruritus can lead to scratching, which can result in a worsening of the lesions and a further perpetuation of the disease. All of these contribute to altered quality of life for the participant. Quantitatively evaluating nighttime scratch and sleep via accelerometry using digital wearables and associated algorithms, to passively and continuously monitor participants in their "home environment," provides an opportunity to examine new and distinct endpoints. Moreover, this evaluation contributes to the understanding how scratch and sleep endpoints correlate to currently used measures of AD severity.

Academic collaborative studies have shown nighttime scratch (number of scratch events and scratch duration) in AD participants correlated to the Investigator's Static Global Assessment. In addition, accelerometry data processed by Pfizer algorithms to measure nighttime scratch and sleep quantity were able to distinguish between scratch and non-scratch movements, validated by thermal videography/annotation, and were able to detect sleep quantity, correlated to polysomnography measures (Clinicaltrials.gov study NCT03490877).[53] The amount and duration of nighttime scratching and the duration and arousals from the total sleep opportunity (nighttime sleep) will be assessed using accelerometry, in selected countries. Participants will wear wrist-worn, watch-like, accelerometry devices to continuously monitor the frequency of day and night time scratching and sleep disturbance for 1 week prior to the Day 1 visit, for 2 weeks following the Day 1 visit, and for 1-week periods during the weeks after the Week 12, Week 16, Week 20, and Week 26 visits.

Participation in accelerometry assessments is voluntary. Participants may refuse or remove the devices at any time, either entirely or for activities during which the devices are uncomfortable (ie, showering), without any impact on their study participation. Participants may also wear the devices over sleeves for comfort.

The following will be measured by accelerometry and subsequent algorithm assessment:

- Scratch (during the total sleep opportunity):
  - Number of scratching episodes;
  - Duration of scratching.
- Sleep (during the evening/major rest period):
  - Duration of the total sleep opportunity;

- Total sleep time (total time and percent time asleep);
- Sleep onset latency;
- Number of wake bouts (total and per hour of sleep);
- Wake after sleep onset (WASO);
- Sleep efficiency.

Data will remain blinded during the accelerometry endpoint processing in order to reduce bias when analyzing accelerometry data.

8.1.8. Exploratory Assessments of Hand Eczema

8.1.8.1. History, Subtype, Clinical Signs, and Extent

Participants will undergo evaluation at the screening visit of the presence and chronicity of hand eczema.[46] Not all participants are expected to have hand eczema. For participants with bilateral hand eczema, the Investigator will identify the worse hand, which will be the target hand for evaluation throughout the study. Participants with hand eczema will also undergo assessments of the subtype(s) (at sites that have capacity for this), clinical signs, and extent of hand eczema.[46, 47, 48, 49, 50] They will also be examined to determine if they have eczema of the feet.[47]

8.1.8.2. Investigator's Global Assessment (IGA) of Hand Eczema

The Investigator's Global Assessment of hand eczema is scored on a 5-point scale (0-4), reflecting a global consideration of erythema, scaling, and fissuring/cracking of the target hand, selected at the screening visit.[51] The clinical evaluator of hand eczema will perform an assessment of the overall severity of hand eczema of the target hand and assign an IGA score and category as described in Table 6. The assessment will be a static evaluation without regard to the score at a previous visit.

Table 6. Investigator's Global Assessment (IGA) of Hand Eczema Score

Score	Category	Description[a]
0	Clear	No signs of hand eczema.
1	Almost Clear	Just perceptible scaling and/or erythema.
2	Mild	Mild scaling, and/or mild erythema and/or mild cracking.
3	Moderate	Moderate scaling, and/or moderate erythema and/or moderate cracking/ fissuring.
4	Severe	Severe scaling, and/or severe erythema and/or severe cracking/fissuring.

a. If the participant has bilateral hand eczema, the worse hand is assessed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Medical History and Physical Examinations

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

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

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

  - 1 year: Previous non-systemic drug treatments for AD including topical treatments;

  - Lifetime history of previous systemic treatment for AD and reason for stopping any systemic treatment for AD;

  - Lifetime history of intolerance/allergy to any drug, regardless of indication.

- Complete physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines. Complete physical examinations consist of assessments of general appearance; skin; head, eyes, ears, nose and throat (HEENT); mouth; heart; lungs; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; and lymph nodes. In addition, height (screening visit only) and weight (screening, Week 0, Week 12, and Week 20 visits) will also be recorded.

- Targeted physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines and should include skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the participant.

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

- All AEs regarding conjunctivitis should be referred for an ophthalmology exam.
- All AEs regarding conjunctivitis, herpes zoster, and acne or folliculitis should have additional details collected.

8.2.2. Vital Signs

- Temperature (oral or tympanic), pulse rate, respiratory rate, and blood pressure will be assessed (pre-dose, if applicable).
- Blood pressure and pulse measurements will be assessed with the participant in a seated position, after at least 5 minutes of rest in a quiet setting without distractions, using a standard calibrated blood pressure measuring device. A blood pressure device that uses multiple cuff sizes based on the arm circumference is the required type of device. The appropriate cuff size for the participant must be used to ensure accurate measurement. The arm circumference at the midpoint of the length of the upper arm should be measured to determine the appropriate cuff size in accordance with the specifications of the BP measuring device. The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. Participants should be seated in a chair, back supported, and arms bared (free of restrictions such as rolled up sleeves, etc.) and supported at heart level. Measurements should be taken on the same arm at each visit (preferably non-dominant). Participants should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements.
- Vital signs will be measured in a seated position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse. Heart rate should be measured at approximately the same time as BP for a minimum of 30 seconds. When the timing of BP and pulse (heart) rate measurements coincides with a blood collection or other study procedure, BP and pulse (heart) rate should be obtained first.

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. Official reading must be located and available in the source documentation.

8.2.4. Electrocardiograms

- A single 12-lead ECG will be performed at visits specified in the Schedule of Activities after the participant has rested for at least 10 minutes quietly in the supine position. ECG will be interpreted by a central reader. Clinically significant or exclusionary ECG findings at the screening visit will result in screen failure.

- A participant's screening ECG must not demonstrate clinically significant abnormalities prior to randomization.
- If a post-dose corrected Q wave interval (QTc) interval remains ≥30 msec from the baseline and is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion 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 QTc values are in the acceptable range.
- ECG values of potential clinical concern are listed in Appendix 8.

8.2.5. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. Refer to Appendix 11 for monitoring and discontinuation criteria.

- Participants must abstain from all food and drink (except water and non-study medications) for an 8-hour overnight fast prior to labs that include the lipid profile panel as per the Schedule of Activities. All other labs do not require fasting.

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

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

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention

should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5.1. Hepatitis Testing

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

- Participants who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Participants who have HBV DNA above the LLQ are excluded. Participants who have HBV DNA negative or below LLQ may be randomized but will have HBV DNA testing repeated at Week 16 and Week 26 End of Treatment (EOT) visit, or Early Discontinuation (ED) visit, whichever is sooner (refer to Section 7.1.). A single HBV DNA test result above the LLQ for a participant requires immediate and permanent discontinuation from treatment.

Interpretation of Hepatitis B Testing Results:

HBsAg negative and HBcAb negative: Participant is eligible for the study;

HBsAg positive and HBcAb negative: Participant is excluded from study participation;

HBsAg negative and HBcAb positive and HBsAb positive: Participant may be eligible for study if HBV DNA is negative or below LLQ;

HBsAg negative and HBcAb positive and HBsAb negative: Participant is excluded from study participation.

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

Interpretation of Hepatitis C Testing Results:

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

8.2.5.2. Tuberculosis Testing

A documented TB test performed within 12 weeks prior to Day 1 (Week 0) is acceptable.

- Perform TB test procedure using the QuantiFERON®-TB Gold In-Tube Test (QFT-G). The QFT-G may be repeated once if the investigator deems this to be necessary.
- A Purified Protein Derivative (PPD) test may be performed if the central laboratory is unable to determine results of QFT-G. Should the PPD test be required, the test must be administered and evaluated by a health care professional 48 to 72 hours later, unless performed and documented within the last 3 months. The test should be performed according to local standards with induration of <5 mm required for inclusion.
- Other TB testing may be performed at a local lab with approval from the Pfizer clinician.

Participants with a history of tuberculosis may not require TB testing as per the protocol exclusion criteria in Section 5.2.

In addition to protocol required TB testing, a chest X-ray (or other imaging as specified in Section 8.2.3) is required, unless previously performed and documented within 12 weeks prior to Study Day 1. Refer to Section 8.2.3.

8.2.6. Infection Studies

Blood samples will be collected per the SOA and serum isolated for infection studies; these samples will be analyzed only if the participant has suspected infection/reactivation where results are needed to assess the case. Additional sample collection instructions will be provided in the lab manual. The retained samples will be destroyed upon participant completion of this study or, if the participant enrolls in the long-term extension study, the samples will be destroyed upon participant completion of that study.

8.2.7. Suicidal Ideation and Behavior Risk Monitoring

- Site staff is to administer the C-SSRS to all participants at screening and score immediately. Based on the judgment of the investigator, the participant must either be excluded or have a risk assessment done by a qualified MHP to assess whether it is safe to participate in the trial if the participant's responses on any of the screening instruments or other screening information indicate:
  - Suicidal ideation associated with actual intent and a method or plan in the past year: “Yes” answers on items 4 or 5 of the C-SSRS.
  - Previous history of suicidal behavior in the past 5 years: “Yes” answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS.

- Any lifetime history of serious or recurrent suicidal behavior (non-suicidal self-injurous behavior is not a trigger for a risk assessment unless it is indicated according to the investigator's judgement).

- Clinically significant depression when the PHQ-8 total score ≥ 15.

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

- In the investigator's judgement a risk assessment or exclusion is required.

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

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

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

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

8.2.7.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale is a validated tool for investigative staff to use to evaluate suicidal ideation and behavior.[43] Trained site staff is to administer the C-SSRS to all participants at screening and assess the participant's eligibility based on the answers. Refer to Section 8.2.7 for information on using this tool in SIB risk monitoring. When there is a positive response to any question on the C-SSRS, the investigator must determine whether an adverse event has occurred.

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

The Patient Health Questionnaire – 8 items is a participant-reported questionnaire consisting of 8 items to assess the participant's depression level.[44] Site staff is to administer the PHQ-8 to all participants at screening and score immediately. Refer to Section 8.2.7 for information on using this tool in SIB risk monitoring.

8.2.8. Pregnancy Testing

For all WOCBP (refer to Appendix 4 for WOCBP definition), a serum pregnancy test with a sensitivity of at least 25 mIU/mL will be performed at Screening. A urine pregnancy test will be performed at every site visit including the follow-up visit (EOT) to confirm the participant has not become pregnant during the study. Serum and urine pregnancy test kits will be provided by the central laboratory with sample collection instructions provided in the package insert.

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

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

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

8.3. Adverse Events and Serious Adverse Events

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

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 7. Device deficiencies are covered in Section 10.7.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE, or that caused the participant to discontinue the study (see Section 7).

Each participant 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, and Pfizer concurs with that assessment.

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

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

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

Investigators are not obligated to actively seek 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 Non-serious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of 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 non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An exposure during pregnancy (EDP) occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.

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

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

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

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

8.3.6. Cardiovascular and Death Events

Not applicable

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

Not applicable

8.3.8. Adverse Events of Special Interest

Not applicable

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study for the purpose of subcutaneous injection of dupilumab or matching placebo. In order to fulfill regulatory reporting obligations worldwide, the injection administrator/trainer is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies or malfunctions of the device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the injection administrator/trainer learns of any device deficiency at any time after a participant has been discharged from the study, and such incident is considered

reasonably related to a medical device provided for the study, the injection administrator/trainer will promptly notify the sponsor.

The method of documenting medical device deficiencies is provided in Appendix 7.

8.3.9.2. Follow-up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The injection administrator/trainer is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.9.3. Prompt Reporting of Device Deficiencies to Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the injection administrator/trainer determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP Manual.

Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Sections 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

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

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

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(s) 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(s);
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating participant.

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

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of abrocitinib greater than 8 tablets within a 24-hour time period (+/- 2 hours) will be considered an overdose. For this study, any dose of dupilumab greater than 1 prefilled syringe every 2 weeks, with the exception of the initial loading dose of two prefilled syringes on Day 1, will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose of either study intervention.

In the event of an overdose, the investigator should:

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

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.

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

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

8.7.2. Banked Biospecimens for Genetics

A 2 mL blood sample optimized for DNA isolation (**Prep D1.5**) will be collected as local regulations and IRBs/IECs allow.

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

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

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

8.8. Biomarkers

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

8.8.1. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.4. Banked Biospecimens for Biomarkers

A 4 mL blood sample optimized for biomarkers (**Prep B2.5**) will be collected and isolate serum retained as local regulations and IRBs/IECs allow.

A 2.5 mL blood sample optimized for RNA isolation (Prep R1) will be collected as local regulations and IRBs/IECs allow.

Banked Biospecimens may be used for research related to the study intervention and AD. Genes and other analytes (eg, proteins, RNA, non-drug metabolites) may be studied using the banked samples.

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

Refer to Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the study manual.

8.9. Medical Resource Utilization and Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study with the exception of self-reported healthcare resource utilization as indicated in the Schedule of Activities.

9. STATISTICAL CONSIDERATIONS

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

There are two estimands for the study.

Estimand 1, composite estimand:

- Population: Participants with moderate-to-severe Atopic Dermatitis (AD) as defined by the inclusion criteria to reflect the targeted participant population;
- Variable: response based on achieving at least a 4-point improvement in the severity of PP-NRS from baseline (PP-NRS4) at Week 2; for participants who drop out for any reason or use rescue therapy (Section 6.5.2) at any time during the treatment period, the response will be defined as “non-responsive” after that point;

- Interventional effect: Effect of randomized treatment accounting for treatment adherence, rescue therapy, and response; the intercurrent event (drop-out or use of rescue therapy) is captured through the variable definition;

- Population-level summary: differences in proportions of responders between abrocitinib and dupilumab.

Estimand 1 composite estimand is the primary estimand for the primary and key secondary endpoints: PP-NRS4 response at Week 2, EASI-90 at Week 4, and EASI-90 at Week 16. Other binary outcome measures such as response based on PP-NRS4 and EASI-90 at all other scheduled timepoints, EASI-75, and IGA will follow the same structure.

Estimand 2, hypothetical estimand:

- Population: Participants with moderate-to-severe Atopic Dermatitis (AD) as defined by the inclusion criteria to reflect the targeted participant population;

- Variable: Percent change from baseline in SCORAD at all scheduled timepoints;

- Interventional effect: Effect of randomized treatment as if all participants maintain their randomized treatment; drop-out for any reason and use of rescue therapy are the intercurrent events; data after dropout or use of rescue therapy at any time during the treatment period will be censored;

- Population-level summary: Difference in least-square means between abrocitinib and dupilumab.

- Percent change from baseline or change from baseline to each specific post baseline scheduled time points in a continuous outcome measure such as HADS, POEM, DLQI, and EQ-5D-5L will follow the same structure as defined for SCORAD.

9.2. Sample Size Determination

This is a randomized, double-blind, double-dummy, active-controlled, multi-center study to assess the efficacy and safety of abrocitinib 200 mg QD compared with dupilumab (as per label guidelines) in adult participants on background topical therapy, with moderate to severe AD. The treatment duration is 26 weeks. A total of approximately 600 participants will be enrolled from approximately 220 sites globally. There are primary efficacy assessments at Week 2 and Week 4, and a key secondary efficacy assessment at Week 16. Efficacy and safety endpoints will be assessed throughout the entire study.

A total sample of 600 participants, with 300 participants randomized to abrocitinib, 300 participants randomized to dupilumab (1:1 randomization) is planned. The proposed sample size provides adequate power for all superiority hypotheses, as follows:

Week 2: This sample size would provide at least 99% power to detect a difference assuming a difference of at least 25% in PP-NRS4 between abrocitinib and dupilumab and assuming the dupilumab response rate is 11% at Week 2.

Week 4: This sample size will provide approximately 99% power to detect a difference assuming a difference of at least 15% in Week 4 EASI-90 between abrocitinib and dupilumab and assuming the dupilumab response rate is 12%.

Week 16: this sample size will provide at least 99% power to show the difference is no more than 10% favoring dupilumab in EASI-90 at Week 16 (non-inferiority (NI) with a 10% margin), assuming the abrocitinib response rate is 53% and the dupilumab response rate is 43% at Week 16. This sample size will also provide approximately 70% power to demonstrate superiority of abrocitinib 200 mg QD to dupilumab as measured by EASI-90 response at Week 16.

While the power to detect a difference at the early time points of 2 and 4 weeks and non-inferiority at week 16 is strong implying a decrease sample size could be used, the power to demonstrate superiority at week 16 requires the larger number of participants. Superiority at week 16 is a valuable endpoint for the scientific community and prescribers justifying the larger sample size. In addition, the study design avoids exposing participants to the use of placebo alone. While a larger number of participants are utilized, they will be guaranteed treatment on 1 of the 2 active treatment arms, which allows for potential benefit for all participants included in the study.

The 10% NI margin between abrocitinib and dupilumab was chosen for Week 16 EASI-90 based on the historical data from dupilumab in treating participants with moderate to severe atopic dermatitis described in Section 2.2.2. Difference and the associated 95% confidence intervals (CIs) between dupilumab and placebo in combination therapy was 31.2% (22.9, 39.5). The 10% NI margin preserves around two thirds of the treatment effect of dupilumab. Added advantages of convenient route of administration, early onset of pruritus relief, and unlikely development of anti-drug antibodies support that a <10% difference would not be considered clinically important.

In projecting the difference between abrocitinib and dupilumab in Week 16 EASI-90 in combination therapy, the following assumptions were made. Based on the monotherapy and combination therapy studies in the dupilumab program (Section 2.2.2), and the monotherapy studies in the abrocitinib program (Section 2.2.3), the projected difference between abrocitinib in combination with TCS and dupilumab in combination with TCS will be similar to the projected difference between abrocitinib and dupilumab under the monotherapy setting. Similar assumptions were made for Week 2 PP-NRS4 response and Week 4 EASI-90.

The familywise Type I error rate (for testing the primary and key secondary endpoints) will be strongly controlled at 5% (2-sided) using a sequential multiple testing procedure outlined in Section 9.4.2.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICD.
Randomly Assigned to Study Intervention	All participants who were randomly assigned to abrocitinib or dupilumab.
Full Analysis Set (FAS)	All randomized participants receiving at least one dose of study intervention. Participants will be analyzed according to the intervention to which they were randomized.
Per-Protocol Analysis Set (PPAS)	All randomized participants receiving at least one dose of study intervention who had no major protocol violations. This set will include participants who: • Were eligible for the study by way of meeting key inclusion criteria and none of the key exclusion criteria. • Had valid and non-missing baseline efficacy data (EASI score). • Had actual, observed EASI scores at Week 16. • Took the correct randomized treatment for at least 80% and at most 120% of the assigned amount until Week 16. • Had no other major protocol violations as determined by the clinical team prior to database lock. A major protocol violation in this context is one that is likely to affect materially the efficacy responses of the participant and will be defined by the clinical team before database is locked and any analysis is performed for this study.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

Unless otherwise specified, all observations after dropout or use of rescue therapy will be censored. For the responder analysis, data after dropout or use of rescue therapy will be defined as "non-responsive" after that point.

9.4. Statistical Analyses

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

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

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	• The primary endpoints (PP-NRS4 response at Week 2, and EASI-90 at Week 4) will be analyzed using the Cochran Mantel Haenszel (CMH) test adjusted by baseline disease severity group (moderate and severe). The difference between the abrocitinib 200 mg group and the dupilumab 300 mg group in the proportion of participants achieving the response along with its 95% confidence interval (using the normal approximation for the difference in binomial proportions) will be reported. The difference in proportions will be calculated within each randomization stratum. The final estimate of the difference in proportions will be a weighted average of these stratum specific estimates using CMH weights. This analysis is based on Estimand 1 composite estimand and on population defined set FAS. • Secondary analysis 1: CMH test on population defined set FAS. This analysis will not consider the use of rescue therapy as an intercurrent event. For participants who drop out for any reason, the response will be defined as "non-responsive" after that point. • Secondary analysis 2 utilizes the longitudinal nature of the binary endpoint. A Generalized Linear Mixed Model (GLMM) will be fit to all observed data (ie, regardless of rescue therapy and without defining missing data as "non-response"). Under the missing at random (MAR) framework, imputations will be based on the posterior predictive probability of response obtained from the posterior distribution under the mixed model. For each such completed dataset, the estimates of the proportions and CMH-

Endpoint	Statistical Analysis Methods
	weighted difference of proportions between abrocitinib and dupilumab will be obtained and Rubin's rule will be used to combine the multiple estimates and standard errors across the imputed datasets and provide p-values.
Key Secondary	• The non-inferiority test of the key secondary endpoint EASI-90 at Week 16 will be analyzed using the 95% CMH weighted confidence interval adjusted by baseline disease severity group (moderate and severe). NI will be declared if the lower bound of the confidence interval for the response difference (abrocitinib - dupilumab) is greater than -10%. This analysis is based on Estimand 1 composite estimand and on population defined set FAS. • For the superiority test of the key secondary endpoint EASI-90 at Week 16 will be analyzed using the Cochran Mantel Haenszel test adjusted by baseline disease severity group (moderate and severe) similarly to the primary endpoints. This analysis is based on Estimand 1 composite estimand and on population defined set FAS. • Secondary analysis 1: CMH test on population defined set PPAS. • Secondary analysis 2: CMH test on population defined set FAS. This analysis will not consider the use of rescue therapy as an intercurrent event. For participants who drop out for any reason, the response will be defined as "non-responsive" after that point. • Secondary analysis 3: Missing observations will be multiply imputed similarly to secondary analysis 2 of the primary endpoints.
Secondary	• The secondary endpoints which are summarized as proportions such as EASI-90 at Week 12, will be analyzed using the same method as for the primary endpoints. This would also apply to any other binary endpoint in the study, such as the proportion of response based on IGA of clear (0) or almost clear (1) and ≥2-point improvement from baseline. • For continuous endpoints, a mixed effect model with repeated measures (MMRM) will be used. This model will include the factors (fixed effects) for treatment group, disease severity group, visit, treatment by visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will

Endpoint	Statistical Analysis Methods
	be tested at Week 16, as well as at the other time points by time point specific contrasts from the MMRM model. This analysis is based on Estimand 2 hypothetical estimand and on population defined set FAS. Observations after dropout or use of rescue therapy will be censored.
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

9.4.2. Type I Error Control Procedure

The Type I error rate is set at 5% (two sided). The familywise Type I error rate (for testing the primary and key secondary endpoints) will be strongly controlled at 5% using a sequential testing approach.

The procedure will test all hypothesis sequentially. If one hypothesis is not rejected at the 5% level, then the statistical significance will be not claimed for the subsequent hypotheses testing. The procedure will first test superiority of PP-NRS4 response at Week 2 and then EASI-90 at Week 4 between abrocitinib and dupilumab by CMH test specified in the primary analysis. If both hypotheses are rejected, the procedure will continue to test the NI of EASI-90 at Week 16 between abrocitinib and dupilumab. The 95% CMH weighted confidence interval will be constructed for the response difference and NI will be declared if the lower bound of the confidence interval for the response difference (abrocitinib - dupilumab) is greater than -10%. If the non-inferiority is achieved, the procedure will continue to test superiority of EASI-90 at Week 16 between abrocitinib and dupilumab by CMH test specified in the analysis for the key secondary endpoint.

A sequential, step-down approach with the PP-NRS4 endpoint from Week 2 to earlier time points will be utilized as an additional family of hypothesis tests once statistical significance is demonstrated at Week 2. Specifically, further hypotheses of no difference in PP-NRS4 between abrocitinib and dupilumab will be assessed at Day 15, Day 14, Day 13, Day 12, …, Day 2, in that order. Any hypotheses after the last Day for which the comparison is significant will not be considered statistically significant. All hypotheses in the sequence will be assessed at the 5% level of significance. Although this will not protect the Type-I error for the family of all possible comparisons, it will provide Type-I error protection for the family of PP-NRS4 comparisons over the first 2 weeks.

9.4.3. Safety Analyses

All participants who receive study intervention (safety population) will be included in the safety analyses. All safety analyses will be performed on the Safety Population. The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be

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

- Treatment-emergent AEs and SAEs;
- Withdrawals from active treatment due to AEs;
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials or met other criteria that required the event be classified as serious;
- Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and lipid profiles);
- Vital signs;
- ECG parameters if applicable.

9.4.4. Other Analyse(s)

Informal interim analyses (IA) may be performed for study monitoring for internal decision-making, due to health technology assessment requirements. The results from the IA will not be used to make decisions for modifying the study design or for stopping the study. The conclusions with regards to the primary endpoints and the secondary endpoints will be based on the final analysis after study completion and hence the overall family wise Type 1 error for this study is maintained. Sites and participants will remain blinded to treatment assignment and interim results distribution will be limited. Details will be described in a separate unblinding plan.

9.5. Interim Analyses

No formal interim analysis will be performed for this study.

9.5.1. Data Monitoring Committee (DMC)

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. Composition of the E-DMC and processes under which the E-DMC operates will be documented in the E-DMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations, including applicable privacy laws.

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.
- In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

10.1.4. Data Protection

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.
- Participants' personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.
- To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

10.1.5. Committees Structure

External Data Monitoring Committee (E-DMC): Refer to Section 9.5.1

10.1.6. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date

(PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Participant-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 electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan and contracts.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for so long as they are maintained.
- When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.
- The investigator(s) will notify sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Clinical Monitoring Plan.

10.1.9. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the contract research organization (CRO) if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of Study Participants.

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

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

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

10.1.10. Publication Policy

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

10.1.11. Sponsor's Qualified Medical Personnel

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

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

advice on medical questions or problems that may arise during the study. For sites other than a Pfizer clinical research unit (CRU), the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- 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 8.2.8 Pregnancy Testing for screening pregnancy criteria.
  - For details of timing of recommended pregnancy testing refer to the Schedule of Activities.

Table 1. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC RBC Morphology Reticulocyte Count	White blood cell (WBC) count with Differential: Neutrophils (%, Abs) Lymphocytes (%, Abs) Monocytes (%, Abs) Eosinophils (%, Abs) Basophils (%, Abs) Coagulation Panel • Prothrombin Time/International Normalized Ratio (PT/INR)	
Clinical Chemistry[1]	Albumin Alkaline Phosphatase ALT	Calcium Chloride Creatine	GGT Glucose (non-fasting) LDH	Sodium Total CO_2 (bicarbonate) Total Protein

Table 1. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
	AST Blood urea nitrogen (BUN)	Creatinine	Phosphokinase Phosphorus Potassium	Total, indirect, and direct bilirubin Uric Acid
Lipid Profile Panel[2]	HDL	LDL	Total Cholesterol	Triglycerides
Routine Urinalysis[3]	• pH, glucose (qual), protein (qual), blood (qual), ketones, nitrites, leukocyte esterase by dipstick • Microscopic and/or culture examination (if blood or protein is abnormal)			
Other Tests	1. HIV[4] 2. HBsAg[4] 3. HBcAb[4] 4. HBsAb[4,5] 5. HBV DNA[6] 6. HCVAb[4,5] 7. HCV RNA[4,5] 8. Serum Pregnancy Test[7] 9. Urine Pregnancy Test[7] 10. QFT-G/PPD/local lab TB test (if applicable)[8] 11. Baseline infectionstudies (if applicable) 12. Additional infection studies (if applicable)[10] 13. hsCRP[9] 14. Lymphocyte Subsets (Lymphocyte Markers) • Total T-cells (CD3+) • CD4+ T-cells (CD3+CD4+) • CD8+ T-cells (CD3+CD8+) • NK cells (CD3-CD16+CD56+) • B-cells (CD3-CD19+)			

NOTES:

1 Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

2 Lipid profile panel requires at least an 8 hour fast.

3 Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Table 1. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters

4 At screening only. HIV testing will be performed for all participants.

5 HBsAb reflex testing only if HbsAg negative but HbcAb positive. HCV RNA is reflex testing only if HCVAb is positive.

6 Participants who are HbsAg negative, HbcAb positive, and HbsAb positive at Screening will have reflex testing for HBV DNA. Participants who have HBV DNA above LLQ will be excluded. Participants who are HBV DNA negative or below LLQ may be randomized and will have repeat HBV DNA testing at Week 16 and Week 26 (EOT or ED).

7 Pregnancy testing for all WOCBP; serum FSH for confirmation of post-menopausal status.

8 PPD results should be read within 48 to 72 hours. QFT-G may be repeated once and local lab TB test may be used if approved by Pfizer clinician. (reference Section 8.2.5.2)

9 Results will be blinded after the screening visit.

10 Samples will be collected at each study visit for potential SARS-CoV-2 or other emergent microbial organism testing.

Abbreviations: cAb = core antibody ;sAb = surface antibody; sAg = surface antigen; ALT = alanine aminotransferase; AST = aspartate aminotransferase; APTT = activated partial thromboplastin time; B-cell = bone marrow derived cell; BUN = blood urea nitrogen; CO_2= carbon dioxide; CRF = case report form; hsCRP = high sensitivity C-reactive protein; DNA = deoxyribonucleic acid; GGT = Gamma-glutamyl transferase; HDL = high-density lipoprotein; HBV= hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IGRA = interferon gamma release assay; INR = international normalized ratio; LDL = low-density lipoprotein; LLQ = lower limit of quantitation; RBC = red blood cell; LDH = lactate dehydrogenase; MCV = mean corpuscular volume ; MCH = mean corpuscular hemoglobin ; MCHC = mean corpuscular hemoglobin concentration ; NK = natural killer; PPD = purified protein derivative ; PT = prothrombin time; QFT-G = QuantiFERON®-TB Gold; RNA = ribonucleic acid; TB = tuberculosis; T-cell = thymus-derived cell; ULN = upper limit of normal; WBC = white blood cell; WOCBP = women of childbearing potential.

Investigators must document their review of each laboratory safety report.
Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

10.3.1. Definition of AE

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

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

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). 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 pre-existing condition including either an increase in frequency and/or intensity of the condition.
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy

assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

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

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of

events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the study interventions during pregnancy or breastfeeding, and occupational exposure.

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

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

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Pfizer Safety /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Pfizer Safety. 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** Pfizer Safety**.**
- 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" and "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 Pfizer Safety 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 health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Pfizer Safety within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes 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.

- Contacts for SAE reporting can be found in the investigator site file.

SAE Reporting to Pfizer Safety via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Pfizer Safety.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigator site file.

10.4. Appendix 4: Contraceptive 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 first dose of study intervention, additional evaluation should be considered.

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

1. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to 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.

2. Postmenopausal female:
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - high follicle stimulating hormone (FSH) level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age not using hormonal contraception or hormonal replacement therapy (HRT).
        - 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.

5. Vasectomized partner:

    - 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;
    - Injectable.

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: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to abrocitinib or study interventions of this class, treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the CSR or in a separate study summary or may be used for internal decision-making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Samples for banking (refer to Section 8.7.2 and Section 8.8.4) will be stored indefinitely or other period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Banked Biospecimens will be labelled with a code. The key between the code and the participant's personally identifying information (eg name, address) will be held at the study site and will not be provided to the sample bank.

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

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

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;
- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).
    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor. The Hepatic

Injury Council (HIC) should be informed if such a situation occurs during the study; the HIC will provide the necessary support to the study teamThe participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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

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

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

10.7. Appendix 7: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

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

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (refer to Section 6.1.2 for the list of sponsor medical devices).

10.7.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator for study participants, users, and other persons. This definition also includes events considered related to procedures for study participants only. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

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

An SAE is an AE that:
a. Led to death.
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. 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. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
SADE Definition
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.7.3. Definition of Device Deficiency

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

10.7.4. Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies

AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the injection administrator/trainer to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The injection administrator/trainer will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF.
- It is **not** acceptable for the injection administrator/trainer to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP Manual.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the product information, for marketed products, in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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.

Follow-up of AE/SAE/Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency 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 completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.7.5. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.7.6. Reporting of SADEs

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

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (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 second-degree (Wenckebach) atrioventricular (AV) block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events (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 participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 beats per minute (BPM), or with an escape rhythm that is below the AV node; In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer; Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm. • Sustained supraventricular tachycardia (rate >120 BPM) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 BPM), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >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 Serious Adverse Events

- 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.

10.9. Appendix 9: Diagnostic Criteria for Atopic Dermatitis

Per Inclusion Criterion 2, a participant is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.[21]

Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

Must have 3 or more basic features described below:
Pruritus
Typical morphology and distribution: • Flexural lichenification in adults • Facial and extensor eruptions in infants and children
Chronic or chronically-relapsing dermatitis
Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
Must have 3 or more following minor features:
Xerosis
Ichthyosis/palmar hyperlinearity, keratosis pilaris
Immediate (type 1) skin test reaction
Elevated serum Immunoglobulin E (IgE)
Early age of onset
Tendency toward cutaneous infections (esp. staph. aureus and herpes simplex), impaired cell-mediated immunity
Tendency toward non-specific hand or foot dermatitis
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor, facial erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Periofollicular accentuation
Food intolerance
Course influenced by environmental and emotional factors
White dermographism, delayed blanch

10.10. Appendix 10: Prohibited Concomitant Medications which may result in Drug-Drug Interaction (DDI)

The prohibited concomitant medications listed below should not be taken with abrocitinib for the period of time listed below.

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 study intervention 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 study intervention, 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.

Investigators should consult the dupilumab product label for information regarding medication that is prohibited for concomitant use.

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

10.11. Appendix 11: Monitoring and Discontinuation Criteria

This appendix documents the monitoring and discontinuation criteria for this study that, in rare instances, may be extenuating circumstances that might mitigate the need for discontinuation that can be discussed with the medical monitor.

Monitoring Criteria

The following laboratory abnormalities require prompt retesting:

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

Temporary Interruption to Dosing

An investigator can temporarily interrupt oral study intervention for up to a maximum of 28 consecutive days and up to 2 consecutive doses of injectable study intervention for a participant, for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary. In the case of study intervention being withheld, all study interventions that the participant is receiving should be withheld (ie, both oral and injected study interventions). The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the participant during this timeframe. If within this timeframe the investigator judges that it is safe to restart dosing, then the participant may restart study intervention. If the investigator judges that it is not safe to restart dosing within this timeframe then the participant must be permanently discontinued from treatment, have an End of Treatment visit and enter the 4-week follow-up period (See Section 10.12.3 for UK country-specific requirements). Doses not taken for the reasons mentioned above do not constitute protocol deviations or medication errors and should not be considered dosing errors but should be noted in the dosing log with the reason for reduced drug consumption clearly described.

Discontinuation Criteria

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

- Participants who have recurrent suicidal ideation and behavior (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 two 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.

- Marked prolongation of the QTcF interval to >500 ms or >60 ms change from screening ECG (refer to Appendix 8).

- Serious infection (refer to definition for Serious Adverse Events in Section 10.3.2) must result in temporary interruption of study intervention. Study intervention cannot be restarted until the serious infection has resolved, and unless 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 then the participant must be permanently discontinued.

- Any bleeding event thought to be associated with a platelet count or hemoglobin reduction per the judgement of the investigator (or, if necessary/desired, following discussion with the medical monitor).

- Adverse event, per judgment of the investigator, requiring discontinuation from treatment (or, if necessary/desired, following discussion with the medical monitor).

- Any adverse event or laboratory abnormality, that per the investigator's judgement requires withholding of oral study intervention for >28 consecutive days and > 2 consecutive doses of injectable study intervention.

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

- Two sequential platelet counts <50,000/mm^3. If the participant has a platelet count <25,000/mm^3, study intervention should be temporarily withheld pending the confirmatory retest.

- Two sequential neutrophil counts <500/mm^3.

- Two sequential lymphocyte counts <500/mm^3.

- Two sequential hemoglobin assessments <8.0 g/dL or <30% from baseline value.

- Two sequential increases in serum creatinine that are >50% over the average of screening and baseline values AND an absolute increase in serum creatinine

≥0.5 mg/dL. At the time of study completion or discontinuation, if a participant should exhibit elevations in serum creatinine ≥33% above the average of screening and baseline values, they will be re-tested every 1 to 2 weeks until the serum creatinine elevation is fully reversed to within 10% of the average of screening and baseline values or has stabilized.

- Any of the following:
  - Two sequential AST or ALT elevations >3 times the upper limit of normal with at least one Total Bilirubin value >2 times the upper limit of normal.
  - Two sequential AST or ALT elevations >3 times the upper limit of normal with an abnormal INR.
  - Two sequential AST or ALT elevations >3 times the upper limit of normal accompanied by symptoms consistent with hepatic injury.
  - Two sequential AST or ALT elevations >5 times the upper limit of normal, regardless of Total Bilirubin or accompanying symptoms.

NOTE: Any of the above LFT findings should prompt review of Appendix 6 (Liver Safety) for which additional investigations must be conducted.

Having met Discontinuation Criteria, the participant must be permanently withdrawn from treatment, have their end of treatment visit, and will then enter the 4-week follow-up period (See Section 10.12.3 for UK country-specific instructions).

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

If a participant has a clinically significant, treatment emergent, abnormality at the time of withdrawal from the study, the Pfizer 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.

10.12. Appendix 12: Country-specific Requirements

10.12.1. France Contrat Unique

1. GCP Training

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

2. Study Intervention

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

3. SUSARs.

   Pursuant to a sponsor's safety reporting obligations under 21 CFR 312.32(c)(1), Pfizer will report to the Investigator all Serious Unexpected Suspected Adverse Reactions ("SUSARs"). Investigator will receive and review SUSAR reports and report SUSARs to the responsible IRB/IEC according to institution's guidelines.

4. Collection of ethnic origin information

   Information regarding ethnic origin will be collected in this study in compliance with the French Data Protection Authority, Commission nationale de l'informatique et des libertés (CNIL): Deliberation no. 2016-262 of 21 July 2016 amending the reference methodology for the processing of personal data conducted in connection with biomedical research (MR-001), §2.2.3 Nature of the data.

   individuals participating in this study will consent that this information can be collected in the study before they enter the study.

   The electronic Case Report Form (eCRF) will be used as the source file for ethnic origin in France. This information will not be recorded in the participant's medical records.

5. Termination Rights

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

10.12.2. Czech Republic Country-specific Requirements

Participants receiving topical or systemic rescue therapy must be permanently discontinued from the study intervention, have an End of Treatment visit, and enter the 4-week follow-up period.

10.12.3. United Kingdom Country-specific Requirements

WOCBP in the UK who do not rollover into the long-term extension study (B7451015) will have a follow-up visit 4 weeks after the ED/EOT visit and have a follow-up phone call at 12 weeks after the ED/EOT visit to confirm adherence to contraception guidelines per protocol.

10.13. Appendix 13: Alternative Measures During Public Emergencies

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

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

10.13.1. Telehealth visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review eDiary for completion, including the participant's understanding of the daily completion requirements;
- Review accelerometry and arrange for return of used devices and sending of new devices, if applicable.
- Complete contraceptive check and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 regarding pregnancy tests.
- Administer the C-SSRS and follow-up as necessary per protocol Section 8.2.7.

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

10.13.2. Home health visits

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

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.

- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Physical exam and targeted physical exam
- Clinical AD assessments
- PROs
- Vital sign measurements
- Review eDiary for completion, including the participant's understanding of the daily completion requirements;
- Review accelerometry and arrange for return of used devices and sending of new devices, if applicable.
- Complete contraceptive check and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 regarding pregnancy tests.
- Administer the C-SSRS and follow-up as necessary per protocol Section 8.2.7.

10.13.3. Alternative Facilities for Safety Assessments

10.13.3.1. Laboratory testing

Protocol-specified safety laboratory tests may be performed by in-home visit (e.g. home phlebotomy service), where allowable by law or local guidance, if the study participant is unable to visit the local laboratory utilized by the study site. There must (at a minimum) be a record of verbal consent of the participant or, as applicable for minor participants, a record of verbal consent of the participant's legally authorized representative including whether they consent to provide their personal information to the 3rd party vendor for this purpose and verbal assent of the study participant.

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 IU/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. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

If the safety of a participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then potential temporary interruption or permanent discontinuation of that participant from study intervention must be discussed with the sponsor. A benefit-risk judgment by the investigator, agreed with the sponsor, will ultimately be required.

10.13.3.2. 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.

10.13.4. Study intervention

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

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

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 3rd 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.

10.13.5. Adverse events and serious adverse events

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

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

10.13.6. Efficacy assessments

The efficacy assessments may be assessed by a qualified rater and PROs administered on the tablet may be completed as part of a home health care visit but cannot be completed as part of a TeleHeath visit.

10.13.7. Data monitoring committee

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

10.14. Appendix 14: Abbreviations

Abbreviation	Term
AAD	American Academy of Dermatology
Ab	antibody
ACQ	Asthma Control Questionnaire
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AV	atrioventricular
BBS	Biospecimen Banking System
BCG	Bacille Calmette Guérin
BP	blood pressure
BPM	beats per minute
BSA	body surface area
CAFÉ	A Study to Assess the Efficacy and Safety of Dupilumab in Patients with Severe Atopic Dermatitis (AD) That Are Not Controlled with Oral Cyclosporine A (CSA) or for Those Who Cannot Take Oral CSA Because it is Not Medically Advisable
CD	cluster of differentiation
CFB	change from baseline
CFR	Code of Federal Regulations
CHRONOS	Study to Assess the Efficacy and Long-term Safety of Dupilumab (REGN668/SAR231893) in Adult Participants with Moderate-to-Severe Atopic Dermatitis
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNIL	Commission nationale de l'informatique et des libertés
CO2	carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease of 2019
CK	creatine kinase
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CsA	cyclosporine A
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
DDI	Drug-drug interaction
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index

Abbreviation	Term
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index
EBV	Epstein Barr virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
ED	early discontinuation
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EQ-5D-3L	EuroQol Quality of Life 5-Dimension 3-Level Scale
EQ-5D-5L	EuroQol Quality of Life 5-Dimension 5-Level Scale
EU	European Union
EudraCT	European Clinical Trials Database
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLMM	generalized linear mixed model
HADS	Hospital Anxiety and Depression Scale
HB	hepatitis B
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCRU	Healthcare Resource Utilization
HCV	hepatitis C virus
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
hsCRP	high-sensitivity C-reactive protein
HTA	health technologies assessment
IA	Interim Analysis
IB	Investigator’s Brochure

Abbreviation	Term
ICD	informed consent document
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	independent ethics committee
IFN	interferon
IFN-γ	interferon-gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	interleukin
INR	international normalized ratio
IP Manual	Investigational Product Manual
IRB	institutional review board
IRT	interactive response technology
IWR	interactive Web-based response
JAK	Janus kinase
JAK1	Janus kinase 1
JAK2	Janus kinase 2
JAK3	Janus kinase 3
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LLQ	lower limit of quantification
LTE	long-term extension
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MHP	mental health professional
MMRM	mixed-effect model with repeated measures
MOS	medical outcomes study
MTX	methotrexate
NB-UVB	narrowband ultraviolet B light
NI	non-inferiority
OTC	over the counter
NRS	numerical rating scale
PACL	Protocol Administrative Change Letter
PCD	primary completion date
PDE4	phosphodiesterase 4
PEER	Pediatric Eczema Elective Registry
PFS	prefilled syringe
PHQ-8	Patient Health Questionnaire - 8 items
PK	Pharmacokinetic(s)

Abbreviation	Term
PP-NRS	Peak Pruritus Numerical Rating Scale
PP-NRS	Peak Pruritis Numerical Rating Scale 4
POC	proof of concept
POEM	Patient-Oriented Eczema Measure
PPAS	per-protocol analysis set
PPD	purified protein derivative
PRO	patient reported outcome
PSAAD	Pruritus and Symptoms Assessment for Atopic Dermatitis
PT	prothrombin time
PVC(s)	premature ventricular complex(es)
QD	once daily
QFT-G	QuantiFERON®-TB Gold
QoL	quality of life
QT	Q wave interval
QTc	corrected Q wave interval
QTcF	Fridericia corrected Q wave interval
QW	weekly
Q2W	every two weeks
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCORAD	SCORing atopic dermatitis
SIB	suicidal ideation and behavior
SoA	schedule of activities
SOC	system organ class
SOLO 1	Study of Dupilumab Monotherapy Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis
SOLO 2	Study of Dupilumab Monotherapy Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis
SOP	standard operating procedure
SP-NRS	Skin Pain Numerical Rating Scale
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBili	total bilirubin
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TH1	type 1 helper T cell
TH2	type 2 helper T cell
TYK2	tyrosine kinase 2
UK	United Kingdom

Abbreviation	Term
ULN	upper limit of normal
US	United States
USPI	United States Package Insert
UVA	ultraviolet A light
UVB	ultraviolet B light
VAS	visual analog scale
VTE	venous thromboembolism
WASO	wake after sleep onset
WBC	white blood cell
WOCBP	woman of childbearing potential

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