A PHASE 3 RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTI-CENTER STUDY INVESTIGATING THE EFFICACY AND SAFETY OF PF-04965842 AND DUPILUMAB IN COMPARISON WITH PLACEBO IN ADULT SUBJECTS ON BACKGROUND TOPICAL THERAPY, WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Investigational Product Number:	PF-04965842
Investigational Product Name:	Not applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2018-002573-21
Protocol Number:	B7451029
Phase:	3

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 5	29 May 2019	To address the recommendations made by the Food and Drug Administration (FDA) following review of the protocol (ordered as they first appear in the protocol): 1. Details of the randomization plan have been added in Section 4.3 Randomization Criteria to clarify that the randomization will be administered using center-based permuted blocks. 2. In Section 9.2.1, the definition of Full Analysis Set (FAS) was clarified and details were added on major protocol violations that would preclude inclusion in the Per Protocol Analysis Set (PPAS). 3. Added a summary of the proposed sensitivity analyses for the co-primary endpoints in Section 9.2.3. The protocol changes specified in Protocol Administrative Change Letter 20 December 2018 have been incorporated as follows: 1. Since atopic dermatitis has a natural history of chronic remissions and flares, subjects may be inappropriately disqualified during periods of remission, and may become eligible when re-screened during a flare episode. For subjects who are screen-failure due to not meeting the disease severity inclusion criteria, re-screening may be considered. This re-screening should only occur after discussion with Pfizer Medical Monitor (or designee). The following sections of the protocol are affected: Protocol Summary, Study Design and Section 3,

		Study Design. 2. Medical Device Incidents Reporting: Pre-filled syringes used to administer dupilumab or matching placebo are combination products and considered medical devices. For clarification, the following sections describing the medical devices used in study B7451029, medical device incidents definition and medical device incidents reporting are added in the protocol. The following sections of the protocol are affected: Section 5.6. Medical Devices, Section 8.4.5 Medical Device Incidents (Including Malfunctions) and Appendix 17: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting. The protocol changes specified in Protocol Administrative Change Letter - France 20 February 2019, which is applicable to site in France only, have been incorporated in Appendix 18, adding operational items not included in the mandatory contract format for France, which Pfizer includes in standard contract language for other countries. The information being added relates to requirements for: 1. GCP Training. 2. Investigational Product. 3. Suspected Unexpected Serious Adverse Reactions (SUSARs). 4. Collection of ethnic origin information. The protocol changes specified in Protocol Administrative Change Letter 08 March 2019 have been incorporated as follows: 1. The intent of the criterion "Subjects who have received prior treatment with

		any JAK inhibitors" is clarified to specify that only systemic JAK inhibitors are excluded. Prior treatment with topical JAK inhibitors is not exclusionary. Changes were made Section 4.2 Exclusion Criteria, Criterion 7, and Section 5.9.2 Prohibited Medications and Treatments. 2. In Section 4.2 Exclusion Criteria, Criterion 18, it is clarified that the definition of "acceptable alternative regimen" refers to acceptability as described by local standards of care. 3. In Appendix 3 Prohibited Concomitant Medications, the following medications are deleted form the CYP2C19 inhibitors list, as they are not inhibitors of CYP2C19 and were included inadvertently: Amitriptyline (Elavil), Clomipramine (Anafranil), Imipramine (Tofranil). In addition, protocol inconsistencies and clarifications have been corrected as follows (ordered as they first appear in the protocol): The number of sites was updated in the Study Design sections. Clarified in the Schedule of Activities footnote q and in Section 7.3.4 that if the results of the TB test procedure using the QuantiFERON®-TB Gold In-Tube Test are indeterminate, the test should be repeated. In Section 4.2 Exclusion Criteria 10, and in Note 2 of Appendix 3 Prohibited Concomitant Medications, the number of days included in the calculation of the washout period for CYP2C9 and CYP2C19 inducer drugs has been corrected from

		28 days to 14 days. In section 4.2 Exclusion Criterion 10 and in Appendix 3, "28 days" was corrected to "14 days": Use of CYP2C9 and CYP2C19 inducers within 5 half-lives of the inducer plus 14 days of first dose of investigational product. A note has been added in Section 4.2 Exclusion Criterion 10 and in Appendix 3 to clarify that the half-life refers to 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 investigational product. It was clarified in Section 4.4.1 Contraception, that male subjects are not required to use contraception. In Section 4.2 Exclusion Criteria, Criterion 19, the absolute lymphocyte count in the parenthesis was corrected from $<500/mm^3$ to $<750/mm^3$. A clarification to the criteria for screening ECG findings has been added in Section 7.3.5, as the intent is that the subject's screening ECG must not have clinically significant adverse findings. Additional minor edits were made in Section 9.2.4 Analysis of Secondary Endpoints to improve clarity. Section 9.6 Week 16 Analysis and End of Study Analysis was added outlining details of performing two planned analyses. The Week 16 Analysis was added to accelerate the final reporting timeline. Abbreviations were added to Appendix 1. Country/region specific changes from

		Amendments 2, 3 and 4 were incorporated into Amendment 5.
Amendment 4	24 January 2019	For Republic of Korea and Taiwan only: Similar to China, other countries in Asia, such as Republic of Korea and Taiwan, have a high prevalence of hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (HBcAb) positive, and hepatitis B surface antibody (HBsAb) positive serology. Therefore, Republic of Korea and Taiwan will adopt the same changes as those proposed for China in Amendment 2 to monitor the risk of hepatitis B reactivation. The following sections of the protocol are affected: Schedule of Activities, Sections 4.2, 6.1, 6.2.6, 6.2.9, 7.6.2, and 7.6.2.1.
Amendment 3	05 December 2018	For Japan only: Similar to China, other countries in Asia, such as Japan, have a high prevalence of hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (HBcAb) positive, and hepatitis B surface antibody (HBsAb) positive serology. Therefore, Japan will adopt similar changes as those proposed for China in Amendment 2 to monitor the risk of hepatitis B reactivation. The following sections of the protocol are affected: Schedule of Activities, Sections 4.2, 6.1, 6.2.6, 6.2.9, 7.6.2, 7.6.2.1 and Appendix 1. Based on local request, HBsAg, HBcAb and HBsAb testing will be performed concurrently at Screening for all subjects rather than performing HBsAb as a reflex test only. Based on local practices for tuberculosis testing in Japan, if QuantiFERON®- TB Gold In-Tube (QTF-G) testing is not possible, the T-SPOT®.*TB* test performed

		at a local laboratory is acceptable as the screening TB test. The following sections of the protocol are affected: Schedule of Activities, Sections 4.2, 6.1, 7.3.4, and 7.6.2.
Amendment 2	12 September 2018	The following changes, requested by an Ethics Committee in China for study B7451013, are being applied to the PF-04965842 program. These changes are in effect for China only. Subjects 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 Deoxyribonucleic Acid (HBV DNA). Subjects who have HBV DNA above the lower limit of quantification (LLQ) are excluded. Subjects who have HBV DNA negative or below LLQ may be randomized, but will have HBV DNA testing repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner. A single HBV DNA test result above the LLQ for a subject requires immediate and permanent discontinuation from treatment. The following sections of the protocol are affected: • Schedule of Activities; • Section 4.2. Exclusion Criteria; • Section 6.1. Visit 1, Screening; • Section 6.2.6. Visit 7, Day 85/Week 12 (±3 days); • Section 6.2.9. Visit 10, Day 141/Week

		20 (±3 Days) End of Treatment or Early Termination Visit; • Section 7.6.2. Laboratory Tests; • Section 7.6.2.1. Hepatitis Testing.
Amendment 1	09 August 2018	Added European Clinical Trials Database (EudraCT) Number on the cover page. Added 100% improvement in EASI total score (EASI-100) secondary efficacy endpoint in the Protocol Summary and in Section 2 to ascertain the proportion of patients achieving complete EASI clearance. CCI [redacted] [redacted] Added two secondary efficacy endpoints related to SCORing Atopic Dermatitis (SCORAD) in the Protocol Summary and in Section 2, corresponding to the respective PRO. CCI [redacted] CCI [redacted]

[redacted]

		CCI [redacted] CCI [redacted] In Section 9.2.4 Analysis of Secondary Endpoints, removed “and frequency” from the analysis, as this is no longer a secondary endpoint. CCI [redacted]

		CCI [redacted] Corrections of typographical errors and administrative edits were made.
Original Protocol	25 June 2018	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Background and 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 patients enrolled in the Pediatric Eczema Elective Registry (PEER) study, comprising a total of 22,550 person-years, it was concluded that symptoms associated with AD seem to persist well into the second decade of life and likely longer.[4] At every age, more than 80% of PEER study subjects 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 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 in December 2016 by the Food and Drug Administration (FDA) for use in patients with mild to moderate AD. 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 USA, the only approved systemic drugs are corticosteroids and dupilumab. 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 were 26% and 46%, respectively. The placebo response rate for IGA and EASI-75 was 12% and 23%, respectively.[8] 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 an oral 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. PF-04965842 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, PF-04965842 is a small molecule and there is no anticipated immunogenicity for PF-04965842, and so it is unlikely to generate antidrug antibodies.

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.[8]

PF-04965842 is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. PF-04965842 has a high degree of selectivity in vitro against other kinases: 28-fold selectivity over JAK2, >340-fold over 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-5, IL-13, IL-31 and IFN-γ. Data from a Phase 2b proof of concept (POC) study (B7451006) that evaluated subjects with moderate to severe AD have shown positive efficacy, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

Objectives and Endpoints

Primary Objective	Primary Endpoints
To compare the efficacy of 100 mg and 200 mg once daily (QD) of PF-04965842 versus placebo in adult subjects on background topical therapy with moderate to severe atopic dermatitis (AD).	The following co-primary endpoints will be tested: • Response based on achieving the Investigator's Global Assessment (IGA) of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline (pre-dose Day 1) of ≥2 points at Week 12; • Response based on achieving the Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at Week 12.
Secondary Objectives	**Secondary Endpoints**
To compare the efficacy of PF-04965842 versus dupilumab in terms of attaining a clinically significant improvement in the severity of pruritus for adult subjects on background topical therapy with moderate to severe AD.	**Key Secondary Endpoints:** • Response based on achieving at least 4 points improvement in the severity of Pruritus Numerical Rating Scale (NRS) from baseline at Week 2.
To estimate the difference in efficacy measures between two doses of PF-04965842 and dupilumab for adult subjects on background topical therapy with moderate to severe AD.	• Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16; • Response based on achieving EASI-75 (≥75% improvement from baseline) at Week 16.
To estimate the effect of PF-04965842 on additional efficacy endpoints and patient-reported outcomes over time in adult subjects on background topical therapy with moderate to severe AD.	**Secondary Efficacy Endpoints:** • Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and ≥2 point reduction from baseline at all scheduled time points except Week 12 and Week 16; • Response based on achieving a ≥75% improvement in the EASI total score (EASI-75) at all scheduled time points except Week 12 and Week 16; • Response based on achieving a ≥50%, ≥90%, and 100% improvement in the EASI total score (EASI-50, EASI-90, and EASI-100) at all scheduled time points; • Response based on achieving at least 4 points improvement in the severity of Pruritus NRS from baseline at all scheduled time points except Week 2; • Time from baseline to achieve at least 4 points improvement in the severity of Pruritus NRS scale; • Change from baseline in the percentage Body Surface Area (BSA) affected at all scheduled time points; • Change from baseline of Patient Global Assessment (PtGA) at all scheduled time points; • 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 Hospital Anxiety and Depression Scale (HADS) at all scheduled time points; • Change from baseline in Patient-Oriented Eczema Measure (POEM) at all scheduled time points; • Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at all scheduled time points; • Response based on a ≥50% and ≥75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points; • Change from baseline at all scheduled time points in SCORAD subjective assessments of itch and sleep loss; • Steroid-free days at Week 16.
Safety Objectives	**Safety Endpoints**
To compare the safety and tolerability of 100 mg and 200 mg QD of PF-04965842 and dupilumab versus placebo in adult subjects on background topical therapy with moderate to severe AD. To estimate the safety and tolerability of the two doses of PF-04965842 versus dupilumab, for adult subjects 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.
CCI [redacted]	[redacted]
[redacted]	[redacted]

AD = Atopic dermatitis; AE = Adverse Event; BSA = Body Surface Area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = Electrocardiogram; EQ-5D-5L = EuroQol Quality of Life 5-Dimension 5-Level Scale; HADS = Hospital Anxiety and Depression Scale; CCI ; IGA = Investigator's Global Assessment; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; PSAAD = Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA = Patient Global Assessment; SAE = Serious Adverse Event; SCORAD = Scoring Atopic Dermatitis; CCI

Study Design

This is a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multi-center study to assess the efficacy and safety of PF-04965842 100 mg or 200 mg QD and dupilumab (as per label) compared with placebo in adult subjects on background topical therapy, with moderate to severe AD. This study will provide a direct comparison of both doses of PF-04965842 with dupilumab in terms of pruritus relief. This study will also provide data, which will estimate the relative efficacy of both doses of PF-04965842 and dupilumab. The treatment duration is 20 weeks. A total of approximately 700 subjects will be enrolled from approximately 270 sites globally. There is a primary efficacy assessment at Week 12, and key secondary efficacy assessments at Week 2 and Week 16. Efficacy and safety endpoints will be assessed throughout the entire study.

After providing informed consent, subjects will be assessed for study eligibility at the screening visit. Subjects will undergo screening within 28 days prior to randomization. During the screening period, systemic treatments and medicated topical therapy for AD will be washed out, as applicable, according to eligibility requirements. Eligible subjects 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. Eligible subjects must meet the eligibility criteria at both screening and baseline. In addition, subjects are required to use non-medicated topical therapy (ie, emollients) at least twice daily for the last 7 days prior to Day 1 and must also be willing and able to use standardized background topical therapy, as per protocol guidelines, throughout the duration of the study. Subjects may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions. Subjects 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.

Subjects who continue to meet eligibility criteria at baseline will undergo Day 1 assessments and be randomized in a 4:4:4:1:1 ratio to receive 100 mg or 200 mg of PF-04965842 QD with dupilumab-matching placebo administered every other week, dupilumab 300 mg administered every other week (with a loading dose of 600 mg at baseline) with PF-04965842-matching placebo administered QD, or one of 2 sequences of PF-04965842-matching placebo administered QD with dupilumab-matching placebo administered every other week from Day 1, for 16 weeks followed by either 100 mg or 200 mg of PF-04965842 QD. Investigators, subjects, and the sponsor study team will be blinded as to treatment group.

The total treatment period is 20 weeks. The first part of this treatment period consists of a 16-week randomized, double-blind, placebo-controlled, double-dummy treatment period with subjects receiving both injectable and oral investigational product. The randomization and double-blind will be maintained during the final 4 weeks of the treatment period, but subjects will only receive oral investigational product. At Week 16 in the treatment period, all

subjects will cease injectable dupilumab or its matching placebo. This is to facilitate the washout of dupilumab (for a total of 6 weeks; as the final dose of dupilumab or its matching placebo is administered at Week 14) prior to eligible subjects entering the long-term extension study, in which all subjects will receive PF-04965842 active treatment. As, following Week 16, data for the primary and key secondary efficacy assessments will have already been obtained, subjects previously receiving only placebo will receive PF-04965842 100 mg or 200 mg QD as per their randomized allocation. Subjects previously receiving PF-04965842 100 mg or 200 mg QD will continue on their respective dose. Subjects previously receiving dupilumab will continue to take oral placebo. These alterations to study treatment will all be conducted while maintaining the blind when re-issuing oral investigational product to all subjects at the Week 16 time point.

Eligible subjects completing the entire 20-week treatment period of the study will have the option to enter a long-term extension (LTE) study, B7451015, in which all subjects will receive PF-04965842 active treatment. Subjects discontinuing early from treatment, or who are otherwise ineligible for the LTE study, will undergo a 4-week follow-up period in study B7451029.

Study Treatments

- Orally administered 100 mg of PF-04965842 QD with dupilumab-matching placebo administered by subcutaneous injection every other week (two injections at baseline; to dummy the loading dose) from Day 1 to Week 16, followed by orally administered 100 mg of PF-04965842 QD until Week 20.

- Orally administered 200 mg of PF-04965842 QD with dupilumab-matching placebo administered by subcutaneous injection every other week (two injections at baseline; to dummy the loading dose) from Day 1 to Week 16, followed by orally administered 200 mg of PF-04965842 QD until Week 20.

- Dupilumab 300 mg administered every other week (with a loading dose of 600 mg at baseline) with PF-04965842-matching orally administered placebo QD from Day 1 to Week 16, followed by PF-04965842-matching orally administered placebo QD until Week 20.

- PF-04965842-matching orally administered placebo QD with dupilumab-matching subcutaneously injected placebo administered every other week (two injections at baseline; to dummy the loading dose) from Day 1 to Week 16 followed by orally administered 100 mg of PF-04965842 QD until Week 20.

- PF-04965842-matching orally administered placebo QD with dupilumab-matching subcutaneously injected placebo administered every other week (two injections at baseline; to dummy the loading dose) from Day 1 to Week 16 followed by orally administered 200 mg of PF-04965842 QD until Week 20.

- Treatment duration will be 20 weeks (with the blind maintained throughout).

- Subjects who do not enroll into the long-term extension study, B7451015, will enter a 4-week follow-up post-treatment period.

Statistical Methods

A total sample of 700 subjects, with 200 randomized to PF-04965842 200 mg QD, 200 subjects randomized to PF-04965842 100 mg QD, 200 subjects randomized to dupilumab and 50 subjects each randomized to two sequences of matching placebo for 16 weeks followed by (a) PF-04965842 100 mg QD and by (b) PF-04965842 200 mg QD (4:4:4:1:1 randomization) is planned. The two placebo sequences will be combined for purposes of analyses at all visits up to and including Week 16, which will result in a 2:2:2:1 randomization ratio. This will provide at least 96% power to detect a difference of at least 20% in IGA response rate between either dose of PF-04965842 and placebo, assuming the placebo response rate is 12% at Week 12. This will also provide at least 99% power to detect a difference of at least 30% in EASI-75 response rate between either dose of PF-04965842 and placebo, assuming the placebo response rate is 23% at Week 12.

Both co-primary endpoints must achieve statistical significance to meet the primary objective.

In addition, this sample size will also provide at least 92% power to detect a difference of at least 15% in the proportion of subjects with a ≥4 points improvement in the severity of Pruritus Numerical Rating Scale (NRS) between PF-04965842 and dupilumab, assuming the dupilumab response rate is 18% at Week 2.

The Type-I error rate is set at 5% (two-sided). The familywise Type-I error rate (for testing the co-primary and key secondary endpoints) will be strongly controlled at 5% using a closed-testing method based on a sequential, iterative Bonferroni-type approach. This is described in further detail in Section 9.2.2 of the protocol and in the statistical analysis plan (SAP).

The study has been sized to help gain sufficient safety data to be able to effectively evaluate the benefit-risk of PF-04965842 in conjunction with the other studies in the clinical development program, therefore the power for the co-primary endpoints is relatively high. This sample size will also help ensure adequate power is maintained for testing all the co-primary and key secondary endpoints for both doses of PF-04965842 via the multiple testing procedure.

For analysis of the co-primary endpoints, the (Cochran-Mantel-Haenszel) test adjusted by baseline disease severity group (moderate and severe) will be used. If a subject withdraws from the study, then this subject will be counted as a non-responder for endpoints after withdrawal.

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 subjects who receive investigational product (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.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS 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 on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 127 Week 18	Day 141 Week 20 EOT or ET Visit	Day 169 Week 24 (4 Weeks after EOT or ET) EOS, Follow-up Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days
Enrollment Procedure											
Informed consent	X										
Register subject using IRT system	X										
Inclusion/Exclusion Criteria	X	X									
Demographics, Medical History, Tobacco and Alcohol History, Atopic Dermatitis Disease History[b]	X										
Review Prior/Concomitant Medications & Treatments	X	X	X	X	X	X	X	X	X	X	X
Dispense eDiary and instruct subjects on use	X										
Train on washout of medicated topical therapy and use of non-medicated topical therapy pre-baseline and daily recording in eDiary[c]	X										
Train/check understanding of subjects on protocol guidance for background topical medication and daily recording in eDiary[d]		X	X	X	X	X	X	X	X	X	

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 127 Week 18	Day 141 Week 20 EOT or ET Visit	Day 169 Week 24 (4 Weeks after EOT or ET) EOS, Follow-up Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days
Provide Patient Emergency Contact Card	X										
Medical Procedures											
Complete Physical Exam[e]	X	X								X	X
Targeted Physical Exam[e]				X	X	X	X	X	X		
Vital Signs[f]	X	X		X	X	X	X	X	X	X	X
Weight	X	X					X			X	
Height	X										
Chest X-ray[g]	X										
ECG (12-lead)	X[h]	X		X	X	X	X	X	X	X	X
Laboratory Assessments											
Serum Chemistry and Hematology (including Coagulation Panel)[i]	X	X		X	X	X	X	X	X	X	X
Lipid Panel[i]		X			X			X		X	X
CCI [redacted]											
Urinalysis	X	X		X	X	X	X	X	X	X	X
Serum FSH (WONCBP only) or Pregnancy Test[l]	X										
Urine Pregnancy Test (conducted at study site)[m]		X		X	X	X	X	X	X	X	X
CCI [redacted]											
HIV Testing[o]	X										

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 127 Week 18	Day 141 Week 20 EOT or ET Visit	Day 169 Week 24 (4 Weeks after EOT or ET) EOS, Follow-up Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days
Hepatitis B Surface Antigen (HBsAg), Hepatitis B Surface Antibody (HBsAb), Hepatitis B Core Antibody (HBcAb), Hepatitis C Antibody (HCVAb), Hepatitis C Viral RNA (HCV RNA)[p]	X										
HBV DNA testing for China, Japan, Republic of Korea, and Taiwan only[aa]	X						X			X	
Tuberculosis Test[q]	X										
Trial Treatment											
Randomization		X									
Oral Drug Dispensing		X			X	X	X	X			
Injectable Drug Dispensing		X		X	X	X	X				
Investigational Product Accountability				X	X	X	X	X	X	X	
Subject Injection Training[r]		X									
Observed Investigational Product Administration[s]		X		X	X	X	X	X	X	X	
Reallocation to new treatment regimens								X			
Review eDiary to assess completion		X	X	X	X	X	X	X	X	X	
Assess eligibility for B7451015[t]										X	
Clinical Assessments											
Fitzpatrick Skin Type Assessment		X									
Investigator's Global Assessment (IGA)	X	X		X	X	X	X	X	X	X	X
SCORing Atopic Dermatitis (SCORAD)	X	X		X	X	X	X	X	X	X	X

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 127 Week 18	Day 141 Week 20 EOT or ET Visit	Day 169 Week 24 (4 Weeks after EOT or ET) EOS, Follow-up Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days
Eczema Area and Severity Index (EASI)	X	X		X	X	X	X	X	X	X	X
Body Surface Area (BSA from EASI)	X	X		X	X	X	X	X	X	X	X
C-SSRS[u]	X										
PHQ-8[u]	X										
Patient-reported Outcomes											
Pruritus Numerical Rating Scale (NRS)[v]	X---------X	X----------X			X	X	X	X	X	X	X
Patient Global Assessment (PtGA)		X		X	X	X	X	X	X	X	X
Dermatology Life Quality Index (DLQI)		X		X			X	X		X	X
Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)[w]	X---------X	X----------X									
EQ-5D-5L		X					X	X		X	X
CCI [redacted]											
Hospital Anxiety and Depression Scale (HADS)		X					X	X		X	
Patient-Oriented Eczema Measure (POEM)		X					X	X		X	
CCI [redacted]											

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 57 Week 8	Day 85 Week 12	Day 113 Week 16	Day 127 Week 18	Day 141 Week 20 EOT or ET Visit	Day 169 Week 24 (4 Weeks after EOT or ET) EOS, Follow-up Visit
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days	±3 Days
Safety											
Serious and non-serious adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X
Contraception Check[y]	X	X	X	X	X	X	X	X	X	X	X
Ensure subject adherence to background topical therapy requirements[d]	X	X	X	X	X	X	X	X	X	X	X
Serum Sample for Baseline Viral Screen[z]		X									

Abbreviations: BSA = body surface area; C-SSRS = Columbia Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; EOS=End of Study; EOT = End of Treatment; ET= early termination; 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 DNA = hepatitis B virus deoxyribonucleic acid; CCI [redacted] CCI [redacted]; HCVAb = hepatitis C antibody; HCV RNA = Hepatitis C Viral RNA; HIV = human immunodeficiency virus; CCI [redacted]; IGA = Investigator's Global Assessment; IRT = Interactive Response System; LLQ = lower limit quantification; NRS = numerical rating scale; PHQ-8 = Patient Health Questionnaire 8 items; POEM = Patient-Oriented Eczema Measure; PSAAD = Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA = Patient Global Assessment; RNA = Ribonucleic acid; SCORAD = SCORing Atopic Dermatitis; WONCBP = women of non-childbearing potential.

a. Day relative to start of study treatment (Day 1).
b. Any previous history of intolerance/allergy to any drug, regardless of indication. Atopic Dermatitis Disease History includes collection of details of AD: AD diagnosis and duration, the use of topical treatments, systemic treatments and other treatments for AD.
c. Train the subject on washout of medicated topical therapy (Exclusion criterion 10, Section 4.2) and use of non-medicated topical therapy pre-baseline (Inclusion criterion 4, Section 4.1) Train and explain to the subject that their daily use of non-medicated topical therapy is recorded in the e-Diary.
d. For background topical therapy guidelines see Section 5.9.1.
e. 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. 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 subject.

f. Vital Signs include sitting blood pressure, pulse rate, respiratory rate, and temperature (oral or tympanic) measured (pre-dose, if applicable) after at least 5 minutes of rest.

g. Chest X-ray or other appropriate diagnostic image (ie, CT or MRI) 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.

h. A single 12-lead ECG will be performed at screening and all other on-site visits after the subject has rested quietly for at least 10 minutes in the supine position. ECG will be interpreted by a central reader. Clinically significant or exclusionary ECG findings at the screening visits will require screen failure.

i. Serum chemistry includes: blood urea nitrogen (BUN), serum creatinine, creatine phosphokinase, glucose, Ca++, Na+, K+, Cl-, P, total CO2, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total, indirect and direct bilirubin, alkaline phosphatase, lactate dehydrogenase, uric acid, albumin and total protein. The lipid profile panel will include total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. A minimum of 8-hour fasting is required for lipid profile evaluation at Day 1, Week 4, Week 16, Week 20 and EOS visits. Hematology includes: Hemoglobin, hematocrit, red blood cell count and indices (MCH, MCHC, MCV, RBC Morphology), WBC count with differential, total neutrophils (%, absolute), lymphocytes (%, absolute), monocytes (%, absolute), eosinophils (%, absolute), basophils (%, absolute), platelets, reticulocyte count and coagulation panel. Coagulation panel includes: Activated Partial Thromboplastin Time (APTT), Prothrombin Time/International Normalized Ratio (PT/INR). Laboratory tests with abnormal results (per Section 6.1 and Section 7.6.2) may be repeated once during the screening period; the last value will be used to determine eligibility.

[redacted]

l. Serum pregnancy testing at screening is required for female subjects of childbearing potential. Follicle stimulating hormone (FSH) test to be performed at Screening to confirm postmenopausal status in female subjects who have been amenorrheic for at least 12 consecutive months.

m. Urine pregnancy test must be performed prior to dosing with the investigational product for female subjects of childbearing potential.

[redacted]

o. HIV testing will be performed for all subjects. Subjects who are positive for HIV will be screen-failed.

p. HBsAb reflex testing will be performed only if HBsAg negative but HBcAb positive. Subjects who are positive for HCVAb and HCV RNA will be screen-failed.

q. A documented TB test performed within 12 weeks prior to Day 1 is acceptable. Subjects with a history of tuberculosis may not require TB testing as per the protocol exclusion criteria in Section 4.2. Perform TB test procedure using the QuantiFERON®-TB Gold In-Tube Test (or Purified Protein Derivative). If the test results are indeterminate, the test should be repeated. A negative PPD test can be substituted for the QuantiFERON®-TB Gold In-Tube test only if the central laboratory is unable to perform the QuantiFERON®-TB Gold In-Tube test or cannot determine the results to be positive or negative and the Pfizer Medical Monitor approves it on a case-by-case basis. In addition to protocol required TB testing, a chest X-ray is required, unless previously performed and documented within 12 weeks prior to Study Day 1. See Section 7.3.3. For Japan only: While QuantiFERON® is the preferred testing method, the T-SPOT®.*TB* test is acceptable as the screening TB test. T-SPOT®.*TB* testing will be performed at the site's local laboratory. Borderline results from the T-SPOT®.*TB* test should be considered exclusionary. If the test results are indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, subjects may be screened using the Mantoux/PPD skin test with Pfizer Medical Monitor approval. See Section 7.3.4.

r. The first injection will be administered by an unblinded administrator/trainer and used to train the subject on correct injection technique. The second injection will be administered by the subject (or caregiver, if applicable) under observation of the unblinded administrator/trainer.

s. When not at the site, subjects (and caregiver, if applicable) will be encouraged to administer investigational product in the morning whenever possible; however, on study visit days, subjects (and caregiver, if applicable) are to be instructed to refrain from dosing at home, and are to administer investigational product in the clinic under observation. If any issues with injection technique are observed, the unblinded administrator/trainer must retrain the subject (or caregiver, if applicable) appropriately.

t. Subjects who complete EOT will be assessed for eligibility for participation in long-term extension study B7451015 as noted in Section 6.2.9.

u. Site staff is to administer the C-SSRS and PHQ-8 to all subjects at screening and score immediately. Subjects who have recent or active suicidal ideation or behavior or clinically significant depression will be excluded from the study or discontinued from the study per Section 4.2, Section 7.5.1, and Section 7.5.2. For subjects meeting exclusionary results on the C-SSRS or PHQ-8, it is recommended the subject's primary care physician (PCP) should be informed, and the subject referred to a mental health professional, either by the PCP or the investigator according to their usual practice.

CCI [redacted]

w. Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) will be conducted to assess the severity and frequency of pruritus, symptoms and sleep and collected daily in a subject eDiary during the screening period and from Day 1 through the End of Study visit in selected countries (See Section 7.10.8). At the Screening visit, site staff will dispense the eDiary and review instructions for completion of the subject eDiary for the PSAAD questionnaire. Subjects will be asked to record their assessment in their eDiary once a day before taking the investigational product. At every visit, the study coordinator will review the eDiary for completeness and counsel the subject on how to complete the items in the daily eDiary, if needed.

CCI [redacted]

y. The contraception check is an opportunity to confirm that contraception, if required, is used consistently and correctly.

z. A serum sample will be collected at baseline but analyzed only if the subject has a suspected viral reactivation.

aa. For China, Republic of Korea, and Taiwan only: Subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for Hepatitis B Virus (HBV) DNA. Subjects who have HBV DNA above the lower limit of quantification (LLQ) are excluded. Subjects who have HBV DNA negative or below LLQ may be randomized, but will have HBV DNA testing repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner (See Section 7.6.2.1). A single HBV DNA test result above the LLQ for a subject requires immediate and permanent discontinuation from treatment. Refer to Section 6.4. For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all subjects rather than as a reflex test. Subjects with negative results for HBsAg, HBcAb and HBsAb may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner (See Section 7.6.2.1). A single HBV DNA test result above the LLQ for a subject requires immediate and permanent discontinuation from treatment. Refer to Section 6.4.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-04965842 is a Janus kinase 1 (JAK1) inhibitor that is being investigated as a treatment for patients with Atopic Dermatitis (AD).

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

Key cytokines implicated in the pathophysiology of AD include IL-4, IL-5, IL-13, IL-31, and IFN-γ, and require 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]

IL-12 and IL-23 are dependent on TYK2 and JAK2 for transmitting their signals. Following cytokine activation, receptor-associated JAKs are phosphorylated and in turn phosphorylate specific sites on the receptor intracellular domain. Phosphorylation of specific sites on the intracellular domain of the receptor allows for the recruitment of signal transducers and activators of transcription (STATs) that can subsequently be phosphorylated by JAKs. Phosphorylated STAT molecules are released from the receptor, translocate to the nucleus where they bind to specific sites on the deoxyribonucleic acid (DNA) and regulate gene transcription.

PF-04965842 is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the ATP binding site. PF-04965842 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-5, IL-13, IL-31 and IFN-γ. Data from a Phase 2b proof of concept (POC) study (B7451006) that evaluated subjects with moderate to severe AD have shown positive efficacy, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

1.2. Background and Rationale

1.2.1. Drug Development and Rationale

PF-04965842 is being developed as an oral treatment for patients with moderate to severe AD based on its mechanism of action, and the clinical results obtained in Phase 1 and Phase 2 studies. The clinical development program for PF-04965842 includes healthy volunteers, subjects with psoriasis and subjects with AD.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB).

The SRSD for dupilumab is the United States Package Insert (USPI).

1.2.2. Atopic Dermatitis

Atopic dermatitis, also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in the 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 patients enrolled in the Pediatric Eczema Elective Registry (PEER) study, comprising a total of 22,550 person-years, it was concluded that symptoms associated with AD seem to persist well into the second decade of life and likely longer.[4] At every age, more than 80% of PEER study subjects had symptoms of AD and/or were using medication to treat their AD. In 833 AD patients 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]

The majority of studies conducted across multiple age groups suggest a continued decrease in prevalence with older age.[11] Adult-onset AD does also 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.[8,14,15] Recent research showed that a small increase of Type 1 helper T cell (TH1)-associated genes has been also detected in 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.[8,15]

Non-medicated topical therapies include emollients. Medicated topical therapies 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 terms of the duration of treatment 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 in December 2016 by the FDA for use in patients with mild to moderate AD. 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 IFN-γ, mycophenolate mofetil, methotrexate [MTX], azathioprine, intravenous immunoglobulin).[4] Of the currently available therapies, none offers a cure; therefore, the main aims of existing treatments are to reduce the occurrence of acute flares, to increase the time between relapses, reduce pruritus and the resulting sleep disturbance.[5,6]

There are a limited number of approved systemic treatments for moderate to severe AD, and in the USA, the only approved systemic drugs are corticosteroids and dupilumab. 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 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 IGA response rate and EASI-75 response rate were

26% and 46%, respectively. The placebo response rate for IGA and EASI-75 was 12% and 23%, respectively.[8] The development of potential treatments with further improvements to 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 an oral 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.

Currently available therapies for the treatment of AD have multiple limitations. The medicated topical therapies have drawbacks related to the duration of use due to the potential for local and systemic side effects (eg, corticosteroid use is limited to 2 to 4 weeks) and to the body regions of use (eg, mid-high potency corticosteroids are not approved for use on the face and/or intertriginous areas). For AD patients not responding to medicated topical therapies and phototherapy, on- and off-label use of systemic agents, which include oral corticosteroids or oral immunosuppressants, remain the last viable treatment option. Systemic therapy options are associated with potentially severe adverse effects and require careful monitoring. The risk of toxicity and side effects remain a concern when systemic agents are used. For these reasons, the use of these agents is limited to short courses or intermittent therapy.

PF-04965842 is an oral tablet, a more convenient route of administration compared with subcutaneous injection required for dupilumab and so it does not have the potential risk of injection site reactions. Unlike dupilumab, PF-04965842 is a small molecule and there is no anticipated immunogenicity for PF-04965842, and so it is unlikely to generate antidrug antibodies.

As mentioned above, a variety of pro-inflammatory cytokines such as IL-4, IL-5, IL-13, IL-31 and IFN-γ, have been suggested to have a role in the pathogenesis of AD. Many of these pathogenic cytokines use the JAK1 for signaling. Therefore, JAK1 is an attractive therapeutic target for AD.

1.2.3. Non-Clinical and Phase 1 Data

Data from nonclinical and Phase 1 programs supports the planned clinical trials with PF-04965842 and further information is in the current version of the IB.

1.2.4. Phase 2b in AD (B7451006)

B7451006 was a Phase 2b proof-of-concept trial in adults (ages 18-75) with moderate to severe AD investigating doses of 10, 30, 100, and 200 mg PF-04965842 or placebo taken once daily for up to 12 weeks. The primary endpoint in this study was the proportion of subjects 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 PF-04965842 100 mg and 200 mg dose groups were significantly greater than placebo in patients with moderate to severe AD. The IGA response rates of the 200 mg and 100 mg groups were 44.5% and 27.8%, respectively. The IGA response rate in the placebo group was 6.3% and the estimated differences from placebo in the 200 mg and 100 mg groups were 38.2% (P=0.0032) and 21.5% (P=0.0184), respectively. The percent 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 subjects 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 4 points improvement in the severity of Pruritus NRS from baseline (Pruritus NRS4) of PF-04965842 100 mg and 200 mg dose groups was greater than placebo. The estimated proportion of Pruritus NRS4 responses at Day 15 were 69.8%, 41.1% and 15.7% for 200 mg, 100 mg and placebo groups, respectively.

PF-04965842 demonstrated a rapid onset of action. In the 200 mg group, IGA and EASI scores improved until Week 4 and Week 6, respectively, and maintained their effect through 12 weeks of treatment. Response rates at Week 12 for the 10 mg and 30 mg groups were not significantly different from placebo. A key differentiating feature for the JAK1 inhibitor is rapid resolution of itch associated with AD. Significant separation from placebo was achieved for the Pruritus NRS score as early as 2 days after initiation of treatment for the 200 mg dose group.

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

PF-04965842 appeared generally safe and well tolerated in this study. Overall, adverse events (AE)s and Serious Adverse Events (SAE)s were numerically higher in subjects receiving PF-04965842 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, one in the 10 mg group (not treatment related), and one in the 30 mg group (treatment related). There were dose-dependent decreases in platelet counts observed in the study, which plateaued at Week 4. Further details of the clinical Phase 2 development program can be found in the IB.

1.3. Summary of PF-04965842 Clinical Pharmacokinetics

PF-04965842 was rapidly absorbed following single dose oral solution/suspension administration over the dose range 3 mg to 200 mg with time to maximum absorption (T_{max}) ranging between 0.55 to 0.77 hours (B7451001). Median T_{max} at doses of 400 mg and 800 mg were 1.5 and 3.9 hours, respectively, which indicated the slower absorption compared to lower doses. PF-04965842 showed a monophasic decline at dose <100 mg with biphasic profiles at doses ≥100 mg. Observed peak plasma PF-04965842 concentrations (C_{max}) following the single-dose administration generally increased in proportion to the dose from 3 mg to 800 mg. In contrast, both area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC_{inf}) and area under the plasma concentration time profile from time zero to the last quantifiable concentration (AUC_{last}) were dose proportional in the range of 3 mg to 200 mg, while a greater than proportional increase was observed at doses of 400 and 800 mg. The arithmetic mean terminal phase half-life ($t_{½}$) was 1.9 to 4.9 hours.

Following QD administration over the dose range 30 mg to 400 mg and 100 mg and 200 mg twice a day (BID) for 10 days, median T_{max} ranged between 0.50 to 0.77 hours (B7451001). After attainment of C_{max}, the disposition of PF-04965842 was consistent with that observed following single-dose administration, showing a biphasic decline following all but the lowest dose and an arithmetic mean terminal phase $t_{½}$ between 2.8 to 5.0 hours. Although C_{max} generally increased in proportion to the dose up to 100 mg given twice daily (BID), it increased more than the dose increased at 400 mg QD and 200 mg BID. The same trend was also observed for area under the plasma concentration-time curve (AUC_{tau}) over the dosing interval (tau = 12 or 24 hours). The observed accumulation ratio (R_{ac}) following 200 mg BID was 2.0 and 2.5 for AUC_{tau} and C_{max}, respectively. R_{ac} was 1.1 to 1.5 at other doses. Therefore, the results showed that drug concentration accumulation is minimal after repeated oral administration at lower doses consistent with the prediction from $t_{½}$. Urinary recovery of PF-04965842 was low, with <5% of the dose recovered unchanged in urine across all doses and regimens in all cohorts.

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

Co-administration of 400 mg (4 x 100 mg) of the tablet with food resulted in equivalent geometric mean AUC_{inf} between fasted and fed conditions and a small mean decrease (<5%) in C_{max}. The magnitude of decrease in C_{max} was not considered to be clinically important. Overall, PF-04965842 can be administered with or without food.

1.3.1. Population Pharmacokinetics

Population pharmacokinetics (PK) analysis was conducted by pooling data from two Phase 1 studies (B7451001, first-in-human study, and B7451004, relative bioavailability study) in healthy subjects and the proof-of-concept study (B7451006) in AD patients. A total of 2465 PK observations from 354 subjects were included in the analysis and the data were described using a 2 compartment model with first-order absorption. The estimates of systemic clearance/fraction of dose absorbed (CL/F) and volume of distribution/fraction absorbed (V/F) were 44.8 L/hr and 147 L with inter individual variability (IIV) values of 63% and 35% (expressed as % CV) respectively. Clearance (CL/F) of AD patients was estimated to be ~38% lower than that of healthy subjects; residual variability was estimated to be higher in AD patients compared to the value in healthy subjects (66% vs. 36% CV). Baseline body weight, race, age and sex were tested as covariates on clearance and did not appear to impact the PK of PF-04965842.

1.4. Summary of Benefits and Risks

There was clinically meaningful benefit demonstrated in the Phase 2b Proof of Concept study in adult patients with moderate to severe AD. The potential risks of treatment include those that were noted in Phase 2b and/ or those based on the pharmacology of JAK inhibitors and include viral reactivation, serious and opportunistic infections, hematopoietic effects (including reduced platelet count), and malignancy and immunoproliferative disorders Further information is available in the IB. Appropriate risk evaluation and mitigation strategies have been incorporated into this protocol.

Overall, there is a favorable benefit-risk profile to support the continued development into Phase 3 of PF-04965842 in the treatment of patients, 12 years of age and older, with AD for both the 100 mg and 200 mg dose.

1.5. Dose Selection Rationale

Dose selection for Phase 3 was based on efficacy and safety of PF-04965842 from a dose-ranging Phase 2b study, B7451006 that evaluated a 20-fold dose range (10 mg to 200 mg QD) in adult subjects 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. Additionally, a dose of 100 mg QD was selected for Phase 3 evaluation. The 100 mg dose is expected to differentiate from the higher dose in terms of efficacy, safety and systemic exposure. In this study, the efficacy and safety of the 100 mg dose will be evaluated in combination with background topical therapy. Both 100 mg and 200 mg QD doses demonstrated acceptable safety and tolerability in the Phase 2 study. Further details are available in the IB. The dosing regimen of dupilumab used in the study will be based on the approved USPI (reference).

This study will assess the efficacy and safety of PF-04965842 100 mg or 200 mg QD and dupilumab compared with placebo in adult subjects on background topical therapy, with moderate to severe AD. The data generated will also estimate the efficacy of PF-04965842 and dupilumab. This study will also provide a direct comparison of both doses of PF-04965842 with dupilumab in terms of pruritus relief.

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2. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and corresponding endpoints are provided in Table 1.

Table 1. Objectives and Endpoints:

Primary Objective	Primary Endpoints
To compare the efficacy of 100 mg and 200 mg once daily (QD) of PF-04965842 versus placebo in adult subjects on background topical therapy with moderate to severe atopic dermatitis (AD).	The following co-primary endpoints will be tested: • Response based on achieving the Investigator's Global Assessment (IGA) of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline (pre-dose Day 1) of ≥2 points at Week 12; • Response based on achieving the Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at Week 12.
Secondary Objectives	**Secondary Endpoints**
To compare the efficacy of PF-04965842 versus dupilumab in terms of attaining a clinically significant improvement in the severity of pruritus for adult subjects on background topical therapy with moderate to severe AD.	**Key Secondary Endpoints:** • Response based on achieving at least 4 points improvement in the severity of Pruritus Numerical Rating Scale (NRS) from baseline at Week 2.
To estimate the difference in efficacy measures between two doses of PF-04965842 and dupilumab for adult subjects on background topical therapy with moderate to severe AD.	• Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16; • Response based on achieving EASI-75 (≥75% improvement from baseline) at Week 16.
To estimate the effect of PF-04965842 on additional efficacy endpoints and patient-reported outcomes over time in adult subjects on background topical therapy with moderate to severe AD.	**Secondary Efficacy Endpoints:** • Response based on achieving the IGA of clear (0) or almost clear (1) (on a 5-point scale) and ≥2 point reduction from baseline at all scheduled time points except Week 12 and Week 16; • Response based on achieving a ≥75% improvement in the EASI total score (EASI-75) at all scheduled time points except Week 12 and Week 16; • Response based on achieving a ≥50%, ≥90%, and 100% improvement in the EASI total score (EASI-50, EASI-90, and EASI-100) at all scheduled time points; • Response based on achieving at least 4 points improvement in the severity of Pruritus NRS from baseline at all scheduled time points except Week 2; • Time from baseline to achieve at least 4 points improvement in the severity of Pruritus NRS scale; • Change from baseline in the percentage Body Surface Area (BSA) affected at all scheduled time points; • Change from baseline of Patient Global Assessment (PtGA) at all scheduled time points; • 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 Hospital Anxiety and Depression Scale (HADS) at all scheduled time points; • Change from baseline in Patient-Oriented Eczema Measure (POEM) at all scheduled time points; • Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at all scheduled time points; • Response based on a ≥50% and ≥75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points; • Change from baseline at all scheduled time points in SCORAD subjective assessments of itch and sleep loss; • Steroid-free days at Week 16.
Safety Objectives	**Safety Endpoints**
To compare the safety and tolerability of 100 mg and 200 mg QD of PF-04965842 and dupilumab versus placebo in adult subjects on background topical therapy with moderate to severe AD. To estimate the safety and tolerability of the two doses of PF-04965842 versus dupilumab, for adult subjects 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.

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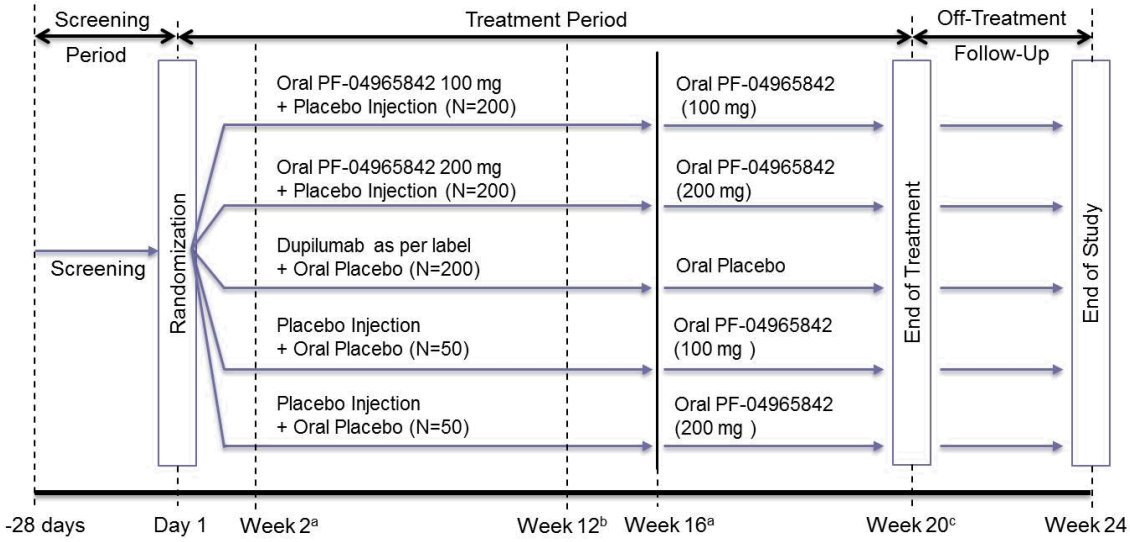
AD = Atopic dermatitis; AE = Adverse Event; BSA = Body Surface Area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = Electrocardiogram; EQ-5D-5L = EuroQol Quality of Life 5-Dimension 5-Level Scale; HADS = Hospital Anxiety and Depression Scale; CCI
IGA = Investigator's Global Assessment; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; PSAAD = Pruritus and Symptoms Assessment for Atopic Dermatitis; PtGA = Patient Global Assessment; SAE = Serious Adverse Event; SCORAD = Scoring Atopic Dermatitis; CCI .

3. STUDY DESIGN

This is a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multi-center study to assess the efficacy and safety of PF-04965842 100 mg or 200 mg QD and dupilumab (as per label) compared with placebo in adult subjects on background topical therapy, with moderate to severe AD. This study will provide a direct comparison of both doses of PF-04965842 with dupilumab in terms of pruritus relief. This study will also provide data which will estimate the relative efficacy of both doses of PF-04965842 and dupilumab. The treatment duration is 20 weeks. A total of approximately 700 subjects will be enrolled from approximately 270 sites globally. There is a primary efficacy assessment at Week 12, and key secondary efficacy assessments at Week 2 and Week 16. Efficacy and safety endpoints will be assessed throughout the entire study. A study design schematic is presented in Figure 1.

Figure 1. Study Design Schematic



[a] At Week 2 and Week 16, key secondary endpoints are measured.

[b] At Week 12, primary endpoints are measured.

[c] At Week 20, eligible subjects will enter the B7451015 long-term extension study; ineligible subjects will instead enter the 4-week off-treatment follow-up period in B7451029.

Note: Standardized background topical therapy must be used as per protocol guidelines throughout the study.

After providing informed consent, subjects will be assessed for study eligibility at the screening visit. Subjects will undergo screening within 28 days prior to randomization. During the screening period, systemic treatments and medicated topical therapy for AD will be washed out, as applicable, according to eligibility requirements. Eligible subjects 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. Eligible subjects must meet the eligibility criteria at both screening and baseline. In addition, subjects are required to use non-medicated topical therapy (ie, emollients) at least twice daily for the last 7 days prior to Day 1 and must also be

willing and able to use standardized background topical therapy, as per protocol guidelines, throughout the duration of the study. Subjects may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions. Subjects for whom screen failure is related to failing the disease severity (including extent of disease) inclusion criterion 3 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.

Subjects who continue to meet eligibility criteria at baseline will undergo Day 1 assessments and be randomized in a 4:4:4:1:1 ratio to receive 100 mg or 200 mg of PF-04965842 QD with dupilumab-matching placebo administered every other week , dupilumab 300 mg administered every other week (with a loading dose of 600 mg at baseline) with PF-04965842-matching placebo administered QD, or one of two sequences of PF-04965842-matching placebo administered QD with dupilumab-matching placebo administered every other week from Day 1, for 16 weeks followed by either 100 mg or 200 mg of PF-04965842 QD. Investigators, subjects, and the sponsor study team will be blinded as to treatment group.

The total treatment period is 20 weeks. The first part of this treatment period consists of a 16-week randomized, double-blind, placebo-controlled, double-dummy treatment period with subjects receiving both injectable and oral investigational product. The randomization and double-blind will be maintained during the final 4 weeks of the treatment period, but subjects will only receive oral investigational product. At Week 16 in the treatment period, all subjects will cease injectable dupilumab or its matching placebo. This is to facilitate the washout of dupilumab (for a total of 6 weeks; as the final dose of dupilumab or its matching placebo is administered at Week 14) prior to eligible subjects entering the long-term extension study, in which all subjects will receive PF-04965842 active treatment. As, following Week 16, data for the primary and key secondary efficacy assessments will have already been obtained, subjects previously receiving only placebo will receive PF-04965842 100 mg or 200 mg QD as per their randomized allocation. Subjects previously receiving PF-04965842 100 mg or 200 mg QD will continue on their respective dose. Subjects previously receiving dupilumab will continue to take oral placebo. These alterations to study treatment will all be conducted while maintaining the blind when re-issuing oral investigational product to all subjects at the Week 16 time point.

Eligible subjects completing the entire 20-week treatment period of the study will have the option to enter a long-term extension (LTE) study, B7451015. In which all subjects will receive PF-04965842 active treatment. Subjects discontinuing early from treatment, or who are otherwise ineligible for the LTE study, will undergo a 4-week follow-up period in study B7451029.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

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

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

2. Male or female subjects aged 18 years or older at the time of informed consent.

3. Meet all the following atopic dermatitis criteria:

   - Clinical diagnosis of chronic atopic dermatitis (also known as atopic eczema) for at least 1 year prior to Day 1 and has confirmed atopic dermatitis at the screening and baseline visits according to Hanifin and Rajka criteria for AD[17] (see Appendix 2).

   - 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 weeks, or who have required systemic therapies for control of their disease.

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

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

4. During the last 7 days prior to Day 1, for the treatment of AD, the subject must have used only non-medicated topical therapy (ie, 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) at least twice daily, with response to treatment remaining inadequate at baseline. The subject must also be willing and able to comply with standardized background topical therapy, as per protocol guidelines (Section 5.9.1), throughout the remainder of the study.

5. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

6. Female subjects who are of childbearing potential must not be intending to become pregnant, currently pregnant, or lactating. The following conditions apply:

   a. Female subjects of childbearing potential must have a confirmed negative pregnancy test prior to randomization;

   b. Female subjects of childbearing potential must agree to use a highly effective method of contraception (as per Section 4.4.1) for the duration of the active treatment period and for at least 28 days after the last dose of investigational product.

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

7. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state.

   All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

8. Must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.

9. If receiving concomitant medications for any reason other than AD, must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to Day 1 and through the duration of the study.

4.2. Exclusion Criteria

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

1. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

2. Any psychiatric condition including recent or active suicidal ideation or behavior that meets any of the following criteria:

   - 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) (Appendix 15);

   - 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;

   - Clinically significant depression: patient health questionnaire – 8 items (PHQ-8) total score ≥15 (Appendix 16);

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

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

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

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

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

6. Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of investigational product, or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of investigational product.

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

8. Previous treatment with dupilumab and/or a history of hypersensitivity, intolerance, adverse event, or allergic reaction associated with prior exposure to dupilumab's excipients.

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

   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). Subjects cannot participate in studies of other investigational or experimental therapies or procedures at any time during their participation in this study.

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

    <u>Within 1 year of first dose of investigational product:</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.). Subjects 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 investigational product:</u>

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

    <u>Within 4 weeks of first dose of investigational product:</u>

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

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

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

- Use of CYP2C9 and CYP2C19 inducers within 5 half-lives of the inducer plus 14 days of first dose of investigational product. 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 investigational product.

- 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 investigational product:

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

NOTE: Non-medicated topical therapy (ie, emollients), as detailed in Section 5.9.1 are permitted.

Within 1 week of first dose of investigational product:

- Use of CYP2C9 and CYP2C19 inhibitors within 1 week of first dose of investigational product 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 3.

- Anti-platelet drugs.

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

11. 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.

12. Infection History:

    a. 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;

    b. Have a known helminth infection;

c. 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;

d. A subject known to be infected with Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C (Section 7.6.2);

For China, Republic of Korea, and Taiwan only:

Subjects 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) DNA. Subjects who have HBV DNA above the lower limit of quantification (LLQ) are excluded. Subjects who have HBV DNA negative or below LLQ may be randomized, but will have HBV DNA testing repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner.

For Japan only:

Subjects with negative results for HBsAg, HBcAb and HBsAb may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have repeat HBV DNA testing at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner.

e. 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.

13. 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.

    For Czech Republic only, exclusion criterion 13 states:

    A history of alcohol or substance abuse within 12 months prior to Day 1 that in the opinion of the investigator will preclude participation in the study.

14. A Screening 12-lead 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 (>450 milliseconds [ms]) on the screening ECG.

- A history of additional risk factors for Torsade de Pointes (TdP) (eg, heart failure, hypokalemia, family history of Long QT Syndrome).

- Use of concomitant medications that prolong the QT/QTcF interval.

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

16. 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.

17. Require treatment with prohibited concomitant medication(s) (Section 5.9.2 and Appendix 3) or have received a prohibited concomitant medication within the specified timeframe prior to the first dose of investigational product.

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

    - A positive QuantiFERON®-TB Gold (QFT-G) In-Tube test or positive Mantoux/Purified Protein Derivative (PPD) tuberculin skin test performed at or within the 12 weeks prior to Day 1.

      NOTE: A negative QFT-G, a Mantoux/PPD tuberculin skin test, or a T-SPOT®.*TB* test (Japan only) is required unless the subject has previously received a documented adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug TB resistance are <5% or an acceptable alternative regimen 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 subjects 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. See Section 7.3.4 for requirements for Mantoux/PPD tuberculin skin testing.

    - For Japan only: While QuantiFERON® is the preferred testing method, the T-SPOT®.*TB* test is also acceptable as the screening TB test. Borderline results from the T-SPOT®.*TB* test should be considered exclusionary. If the T-SPOT®.*TB* test results are indeterminate, the test should be repeated. If the

result of the repeat test is indeterminate, subjects may be screened using the Mantoux/PPD skin test with Pfizer Medical Monitor approval. See Section 7.3.4.

- Chest radiograph (or chest Computed Tomography (CT) scan, if available) taken at screening with changes suggestive of active tuberculosis (TB) infection as determined by a qualified radiologist. A chest X-ray 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 subject who is currently being treated for active TB infection is to be excluded.

19. **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 ($<500/mm^3$);

    NOTE: In the Czech Republic only an Absolute lymphocyte count of $<0.75 \times 10^9$ /L ($<750/mm^3$) is exclusionary.

    - 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; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN.

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

21. Have undergone significant trauma or major surgery within 1 month of the first dose of investigational product.

22. 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 subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have signed an informed consent document to participate in the study, have undergone all screening procedures, meet all inclusion and none of the exclusion criteria for participation in the study, and meet the randomization criterion listed above at Day 1. A computer-generated randomization schedule will be used to assign subjects to the treatment groups using an Interactive Response Technology (IRT). Randomization will be administered using center-based randomly permuted blocks. Center-based randomization was chosen based on drug management considerations. Randomization will not be stratified by baseline disease severity or age.

NOTE: the maximum screening period length is 28 days. Subjects who cannot be screened within this timeframe must be screen failed.

4.4. Lifestyle Requirements

In order to participate in the study, subjects must be aware of the following lifestyle guidelines and restrictions that apply during and after the treatment period.

- Prior to the Day 1, Week 4, Week 16, Week 20 and End of Study (EOS) visits, subjects must comply with fasting requirement for at least 8 hours prior to the visit. Water and permitted non-study medications are allowed (see Section 5.9.1).

- On study visit days, subjects must not smoke or ingest caffeine during the 30 minutes prior to blood pressure and heart rate measurements.

- On study visit days, subjects must not administer investigational product until instructed to do so by the investigator or designated study site staff.

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

- On study visit days, topical therapy (ie, non-medicated topical therapy and medicated topical therapy, if applicable as per protocol guidelines as described in Section 5.9.1) are not permitted to be applied prior to attending the study visit. Topical therapies are permitted to be applied after the visit (if applicable as per protocol guidelines as described in Section 5.9.1).

- Agree to use one highly effective method of contraception (as specified in Section 4.4.1, as applicable).

4.4.1. Contraception

Male subjects are not required to use contraception.

All female subjects of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and her partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects needs 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 subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

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

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

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

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

   NOTE: Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential (WOCBP) trial participant and that the vasectomized partner has received medical assessment of the surgical success.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

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

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

For countries in the EU:

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

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

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

3. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

   NOTE: Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

4. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

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

4.4.2. Vaccine and Exposure to Infections Guidelines

4.4.2.1. Subject Specific Recommendations

It is recommended that all subjects should be up-to-date with respect to standard of care vaccinations (as defined by their country health ministry) or AD guidelines. Vaccination of subjects with live attenuated vaccines is prohibited within the 6 weeks prior to first dose of investigational product, for the duration of the study, and for 6 weeks following completion of the study.

4.4.2.2. Guidance Regarding Household Contact Vaccine-Related Exposure

Current routine household contact with children and others who have been vaccinated with live attenuated vaccines 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 subjects 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® (intranasal flu vaccine) for 1 week following vaccination;

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

4.4.3. Surgery

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

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

4.5. 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 coordinator's manual and in the study portal.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject 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 subject'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. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

The study treatments are as follows:

- Orally administered 100 mg of PF-04965842 QD with dupilumab-matching placebo administered by subcutaneous injection every other week (two injections at baseline; to dummy the loading dose) from Day 1 to Week 16, followed by orally administered 100 mg of PF-04965842 QD until Week 20.

- Orally administered 200 mg of PF-04965842 QD with dupilumab-matching placebo administered by subcutaneous injection every other week (two injections at baseline; to dummy the loading dose) from Day 1 to Week 16, followed by orally administered 200 mg of PF-04965842 QD until Week 20.

- Dupilumab 300 mg administered every other week (with a loading dose of 600 mg at baseline) with PF-04965842-matching orally administered placebo QD from Day 1 to Week 16, followed by PF-04965842-matching orally administered placebo QD until Week 20.

- PF-04965842-matching orally administered placebo QD with dupilumab-matching subcutaneously injected placebo administered every other week (two injections at baseline; to dummy the loading dose) from Day 1 to Week 16 followed by orally administered 100 mg of PF-04965842 QD until Week 20.

- PF-04965842-matching orally administered placebo QD with dupilumab-matching subcutaneously injected placebo administered every other week (two injections at baseline; to dummy the loading dose) from Day 1 to Week 16 followed by orally administered 200 mg of PF-04965842 QD until Week 20.

- Treatment duration will be 20 weeks (with the blind maintained throughout).

- Subjects who do not enroll into the long-term extension study, B7451015, will enter a 4-week follow-up post-treatment period.

For the purposes of this study, and per International Council for Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

Allocation of subjects to treatment groups will proceed through the use of an Interactive Response Technology (IRT) system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, protocol number, the subject number and the date of birth of the subject. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when investigational product is being supplied via the IRT. The IRT system will provide a confirmation report containing the subject number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24 hour a day, 365 days a year IRT help desk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT.

NOTE: The IRT is the source of the subject number. The IRT system will provide the subject number at the end of the first IRT subject transaction.

5.2. Breaking the Blind

Investigators, subjects and the sponsor study team will be blinded as to treatment group. At each site, an unblinded administrator/trainer will administer the first dose of dupilumab or its matching placebo to train the subject (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 subject 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 subject. The method will be an electronic process. When the blind for a subject 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 subject for whom the blind has been broken will be discontinued from the study and undergo the early termination (ET) procedures.

5.3. Subject Compliance

There are viscosity differences between dupilumab and the matched placebo, and as such there is a potential for functional unblinding of the administrator/trainer; who may notice the difference in viscosity and/or may have previous experience administering dupilumab. Although no administrator/trainer will know the treatment allocation of subjects, as a risk mitigation against functional unblinding affecting study integrity this administrator/trainer will only administer injectable investigational product (IP), or observe/train subjects administering injectable IP, 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 "unblinded administrator/trainer" in order to make this clear distinction from other site personnel.

When investigational product is administered at the research facility, it will be administered under the supervision of the unblinded administrator/trainer only. From the Day 1 visit onward, subjects will be dispensed PF-04965842 or PF-04965842-matching placebo to take home with them for self-administration on non-study visit days. Subjects will be dispensed dupilumab or dupilumab-matching placebo at the Day 1, Week 2, Week 4, Week 8 and Week 12 visits for self-administration (or administration by a caregiver, if applicable) at the site. Subjects will also be dispensed dupilumab or dupilumab-matching placebo at Week 4, Week 8, and Week 12 visits to take home with them for self-administration (or administration by a caregiver, if applicable) at Week 6, Week 10, and Week 14, respectively. If the subject is unwilling/unable to self-administer the injectable investigational product or arrange for a caregiver to administer the injectable investigational product, then it is permissible for site to arrange for the subject to return to the site for administration by the unblinded trainer/administrator. Subjects will be directed to bring any used and unused syringe cartons to visits following administration at home. Study sites will provide subjects with a sharps container for disposal of used syringes. Subjects will return this sharps container to the study site at the final visit for disposal.

Subjects will be issued an electronic dosing diary (eDiary) and will be educated to record the time of their dosing, once they have taken the investigational product. Subjects 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 5.9.1, beginning at screening through the EOS visit.

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

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

Investigational product may be temporarily withheld for a maximum of 14 days at investigator's discretion due to abnormal laboratory tests or adverse event. See Appendix 4 for further guidance on temporary withholding of investigational product. 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.

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:

- Subjects interrupting oral investigational product for more than 4 consecutive days or for a total of more than 7 days between visits;
- Subjects administering >8 tablets in one day or administering ≥4 tablets/day for 4 consecutive days;
- Missed dose of injectable investigational product is not administered within 7 days of the originally scheduled dose;
- Subjects administering >1 prefilled syringe every 2 weeks, with the exception of the initial loading dose of two prefilled syringes on Day 1;
- Subjects who have an overall compliance of <80% or >120% between visits.

Compliance with background topical therapy guidelines in Section 5.9.1 will be monitored and verified by delegated site personnel through a combination of review of the electronic diary, and discussion with the subject, which will be documented in the source documents.

Any deviation from protocol specified dosing of investigational product or protocol specified guideline concerning background topical medication should be recorded as a protocol deviation and the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. In addition, if the compliance deviation reaches the thresholds defined above, it should also be recorded as a medication error (see Section 8.4.4).

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded PF-04965842 and its matched placebo will be provided as 100 mg tablets for oral administration. The 100 mg tablets and their matching placebos will be supplied in separate bottles and labeled according to local regulatory requirements. When received by the pharmacy, PF-04965842 and matching placebo will be in containers that will sufficiently blind all site staff to content within the bottles (ie, active versus placebo).

Blinded active comparator (dupilumab) will be provided as 300 mg/2 mL prefilled syringes for subcutaneous injection. Dupilumab-matching placebo will also be provided as prefilled syringes for subcutaneous injection. The dupilumab and matching placebo syringes will be labeled according to local regulatory requirements, and when received by the pharmacy will be in containers that will sufficiently blind all site staff to content within the syringes.

5.4.2. Preparation and Dispensing

The investigational product should be dispensed using a drug management system at each dispensing visit. A qualified staff member will dispense the investigational product via unique container numbers in quantities appropriate for the study visit schedule. The subject (or caregiver, if applicable) should be instructed to maintain the product in the containers provided throughout the course of dosing and return the containers to the site at the next study visit.

5.5. Administration

The treatment period is 20 weeks.

Oral investigational product, PF-04965842 or its matching placebo, will be administered for 20 weeks. Subjects will be dispensed two (2) bottles of oral investigational product at the Day 1, Week 4, Week 8, Week 12, and Week 16 visits. Subjects will be given clear dosing instructions to take one tablet from each bottle, once daily, preferably in the morning whenever possible, at approximately the same time of day. On study visit days, subjects (and caregivers, if applicable) are to be instructed to refrain from dosing at home, and are to administer investigational product in the clinic under observation.

Subjects will swallow the oral investigational product whole, and will not manipulate or chew the medication prior to swallowing. Oral investigational product may be taken with or without food, other than on study visit days where fasting is required. Injectable investigational product, dupilumab or its matching placebo, will be administered for 16 weeks with the final injection planned for Week 14. Subjects will be dispensed prefilled syringes containing injectable investigational product at the Day 1, Week 2, Week 4, Week 8,

and Week 12 visits. Injectable investigational product will be administered at the site on Day 1, Week 2, Week 4, Week 8 and Week 12 under the observation of the unblinded administrator/trainer, and at home by the subject (or caregiver, if applicable) at Week 6, Week 10, and Week 14. The unblinded administrator/trainer will instruct the subject (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 an unblinded administrator/trainer and used to train the subject (or caregiver, if applicable) on correct injection technique. The second injection will be administered by the subject (or caregiver, if applicable) immediately following the first injection, under the observation of the unblinded administrator/trainer. If any issues with technique are observed, the unblinded observer must retrain the subject appropriately. All injections should be administered in accordance with the dupilumab drug label.

The investigator should assign the responsibility of unblinded 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 functionally unblinded. Contact between the unblinded administrator/trainer and study subjects should be kept to a minimum. The unblinded administrator/trainer must not take any action that may potentially reveal treatment assignment to the subject or site staff. The investigator, site staff, and any study participants other than the unblinded administrator/trainer must not be allowed to know the investigational product assigned to any study subject and must not be allowed to see the treatment records.

At Week 16, subjects previously receiving only placebo will receive PF-04965842 100 mg QD or 200 mg QD as per randomized allocation. Subjects previously receiving PF-04965842 100 mg QD or 200 mg QD will continue on this dose. Subjects previously receiving dupilumab will continue to take oral placebo. These alterations to study treatment will all be conducted while maintaining the blind, when re-issuing oral investigational product to all subjects at the Week 16 time point.

A guidance document with detailed dosing instructions will also be provided to subjects to support at-home dosing.

5.6. Medical Devices

1. The devices manufactured for Pfizer by a third party provided for use in this study are:

    a. pre-filled syringes for subcutaneous injection of dupilumab (manufactured by Sanofi-Regeneron followed by relabeling and repackaging for Pfizer by a third party);

    b. pre-filled syringes for subcutaneous injection of matching placebo.

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

3. Pre-filled syringe medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 8.4.5).

5.7. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in their original container and in accordance with the labels. See the Investigational Product Manual (IP Manual) for storage conditions of the product.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site in the IP Manual.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.8. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. To ensure adequate records, all drug supplies will be accounted for in the drug accountability inventory forms as instructed by Pfizer and will be monitored by the accounting of unused investigational product returned by the subjects. At the end of the clinical trial, all drug supplies unallocated or unused by the subjects must be returned to Pfizer or its appointed agent, or destroyed in an approved manner unless otherwise authorized by Pfizer. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities.

All bottles of oral investigational product must be brought back to the site at every visit for inspection by the site staff and all bottles/unused oral investigational product must be returned to the investigator by the subject at the relevant visit(s).

Subjects will be directed to bring any used and unused syringe cartons to all visits for inspection by the site staff. Study sites will provide subjects with a sharps container for disposal of used syringes. Subjects will return this sharps container to the study site at the final visit for disposal.

5.8.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (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.

5.9. Concomitant Treatment(s)

Subjects will abstain from all concomitant medications as described in Section 4.2 and Appendix 3 of the protocol. Medications that are taken in the Screening/Washout period (after informed consent is obtained and before the first dose of investigational product) will be documented as prior medications. Medications taken after the first dose of investigational product 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 atopic dermatitis), reference to any associated adverse event, dose, and start and stop dates of administration. Subjects 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.

5.9.1. Permitted Concomitant Medications

Background Topical Therapy

Subjects must comply with standardized background topical therapy guidance throughout the study. Background topical therapy will not be provided by the sponsor. Standardized background topical therapy refers to the 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, throughout at least the final 7 days prior to Day 1 and throughout the remainder of the study.

Medicated Topical Therapy

- Topical Corticosteroids (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. Subjects must be clinically monitored for toxicity to topical steroids 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.
    - 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. Subjects must be clinically monitored for toxicity to topical steroids 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.

- Topical calcineurin inhibitors (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 instead should be applied after the visit, on study visit days.

Other Concomitant AD Therapies

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 subjects receiving a stable dose;
- Ophthalmic corticosteroids are permissible for subjects 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;
- Vitamin and mineral supplements of standard potency are allowed in amounts not known to be associated with adverse effects (such as hyper-vitaminosis).

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

Unless a prohibited medication or treatment, subjects may be administered any other medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician. Following Day 1, addition of concomitant medications or any change in the dosage should be limited to those considered medically essential.

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

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

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

5.9.2. Prohibited Medications and Treatments

Subjects are required to discontinue and avoid using certain medications and treatments (see Inclusion Criteria and Exclusion Criteria, and Appendix 3). Subjects 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 atopic dermatitis must be discontinued except oral antihistamines. Medicated topical therapy for AD must be washed out one week prior to Day 1 (Baseline). Starting on Day 1, standardized background topical therapy will be used as per protocol guidance in Section 5.9.1.

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

Subjects 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 investigational product.

Restrictions on certain vaccinations are described in Section 4.2.

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

6. STUDY PROCEDURES

Refer to the Schedule of Activities for a detailed list of study procedures, as they should be conducted at each respective visit.

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

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

Subjects are required to fast for at least 8 hours prior to all visits that include lipid profile panel testing (Day 1, Week 4, Week 16, Week 20 and EOS). During the fasting period, subjects 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.

Urine pregnancy test must be performed prior to dosing with the investigational product for female subjects of childbearing potential through to the EOS visit.

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

Refer to Appendix 4 for guidelines on subject safety monitoring and discontinuation.

6.1. Visit 1, Screening

Subjects will be screened (Visit 1) within 28 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in Subject Information and Consent in Section 12.3.

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

Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results; the last value will be used to determine eligibility. If results return to normal within the 4-week screening period, the subject may enter the study.

The following procedures will be completed:

- Obtain written informed consent;
- Register subject using the IRT system;
- Collect demography;
- Administer C-SSRS and PHQ-8. Subjects meeting any of the criteria specified in Exclusion Criterion 2 as described in Section 4.2 on the C-SSRS or PHQ-8 should be excluded from participation; it is recommended the subject's primary care physician (PCP) should be informed, and the subject referred to a mental health professional, either by the PCP or the investigator according to their usual practice;
- Obtain weight;
- Obtain height;

- Obtain vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);

- Complete medical history, including history of alcohol and tobacco use. Smoking status and average weekly alcohol consumption (units/week) will also 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 (45% alcohol by volume) of spirits;

- Obtain 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 drug treatments for AD including the use of topical treatments and other treatments (excluding systemic);

  - 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 AD disease history includes collection of details of AD: AD diagnosis and duration, the use of topical treatments, systemic treatments and other treatments for AD;

- Train subject on protocol guidance for the use of background topical therapy as described in Section 5.9.1;

- Conduct complete physical examination;

- Conduct clinical evaluations including IGA, SCORing Atopic Dermatitis (SCORAD), EASI and BSA (calculated in the EASI);

- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;

- Perform a single 12-lead electrocardiogram (ECG). Clinically significant or exclusionary ECG findings require screen failure;

- Review Inclusion and Exclusion criteria for subject eligibility;

- Assess for occurrence of Adverse Events: The adverse event and SAE reporting period starts with the signing of the informed consent document;

- Tuberculosis Test QuantiFERON® – TB Gold In-Tube test or locally analyzed T-SPOT®.*TB* test (Japan only) (unless performed within 12 weeks of Day 1). If Mantoux PPD tuberculin skin test is required to be performed instead, per Section 7.3.4, the subject must return between 48-72 hours post-injection for evaluation of induration (see Section 7.3.4 for further details on TB testing);

- Chest X-ray (posterior-anterior and lateral views) or other appropriate diagnostic image (ie, computerized tomography [CT] or magnetic resonance imaging [MRI]) are required. Official reading must be located and available in the source documentation. Chest X-ray may be performed up to 12 weeks prior to Day 1;

- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), CCI [redacted], urinalysis, serum FSH (female subjects of childbearing potential) or serum pregnancy test (female subjects of childbearing potential), HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb), hepatitis C viral antibody (HCV Ab), hepatitis C viral ribonucleic acid (HCV RNA) (see Section 7.6.2.1);

- For China, Republic of Korea, and Taiwan only: Collect sample for HBV DNA reflex test (see Section 7.6.2.1);

- For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all subjects rather than as a reflex test. Subjects with negative results for HBsAg, HBcAb and HBsAb may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner;

- Dispense eDiary and instruct subject in how to use the device. Instruct the subject to begin daily completion of the Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) (in selected countries), Pruritus NRS, CCI [redacted];

  - Pruritus NRS CCI [redacted] will be collected daily in a subject eDiary during the screening period and from Day 1 to 15 and then on study visit days;

  - PSAAD will be collected daily in a subject eDiary during the screening period and from Day 1 through the End of Study visit, in selected countries;

- Instruct the subject to keep a daily record of use of standardized background topical therapy. Standardized background topical therapy use and adherence with guidelines will be recorded daily in the subject eDiary during the screening period and through the End of Study visit;
- CCI [redacted]

[redacted]

- If the subject is eligible for continued participation, provide subject with emergency contact card.

6.2. Treatment Period

6.2.1. Visit 2, Day 1/Week 0 (Baseline)

- Administer patient-reported outcomes (PROs) including Patient Global Assessment (PtGA), Dermatology Life Quality Index (DLQI), EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L), CCI [redacted] Hospital Anxiety and Depression Scale (HADS), and Patient-Oriented Eczema Measure (POEM);
- Obtain weight;
- Obtain pre-dose vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Review eDiary Pruritus NRS, CCI [redacted], and PSAAD completion (in selected countries) and review eDiary procedures with subject as necessary;
- Review any changes in the subject's prior and concomitant medications and treatment information;
- Check subject's understanding of protocol guidance for the use of background topical therapy as described in Section 5.9.1, ensure subject adherence to background topical therapy requirements and re-educate as required;
- Conduct complete physical examination;

- Conduct clinical evaluations including Fitzpatrick Skin Type Assessment, IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Perform a single 12-lead electrocardiogram (ECG). Clinically significant or exclusionary ECG findings require screen failure;
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), lipid profile (fasting), CCI , and urinalysis;
- CCI
- CCI
- Collect sample for viral surveillance: Herpes simplex virus (eg, Herpes simplex virus (HSV) HSV-1, HSV-2 and varicella zoster virus (VZV), etc);
- Urine pregnancy test (female subjects of childbearing potential). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- Review of Inclusion/Exclusion Criteria;
- If subject continues to meet all Inclusion/Exclusion criteria, officially randomize subject into the study;
- Dispense oral investigational product to the subject;
- Administer oral investigational product and observe dosing;
- Dispense injectable investigational product to the subject;
- Unblinded administrator/trainer: administer the first dose of injectable investigational product, using this injection to train the subject and/or caregiver in the proper injection technique;
- Unblinded administrator/trainer: observe the administration of the second dose of injectable investigational product performed by the subject or his/her caregiver;
- CCI

- CCI [redacted]
- Assess and record any Adverse Events since the last visit.

6.2.2. Visit 3 (Phone call visit), Day 8/Week 1 (±1 day)

- Call subject and confirm compliance with daily completion of Pruritus NRS, CCI [redacted], and PSAAD (in selected countries);
- Verbally confirm subject has been compliant with study dosing and entry in the eDiary. Review eDiary procedures with subject as necessary;
- Review any changes in the subject's concomitant medications and treatment information;
- Check subject understanding of protocol guidance for the use of background topical therapy as described in Section 5.9.1 and re-educate as required;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- CCI [redacted]
- Assess and record any Adverse Events since the last visit.

6.2.3. Visit 4, Day 15/Week 2 (±1 day)

- Administer PROs including PtGA and DLQI;
- Obtain pre-dose vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Review Pruritus NRS, CCI [redacted], and PSAAD completion (in selected countries) and review eDiary procedures with subject as necessary. Instruct subject that Pruritus NRS and CCI [redacted] will now be completed only at visits on site and in the eDiary and will no longer be completed on a daily basis at home;
- Review any changes in the subject's concomitant medications and treatments information;

- Check subject understanding of protocol guidance for the use of background topical therapy as described in Section 5.9.1, ensure subject adherence to background topical therapy requirements and re-educate as required;
- Conduct targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Perform a single 12-lead electrocardiogram (ECG);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), CCI and urinalysis;
- CCI [redacted]
- Urine pregnancy test (female subjects of childbearing potential). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Dispense injectable investigational product to the subject;
- Unblinded administrator/trainer: observe the administration of injectable investigational product performed by the subject or his/her caregiver;
- Administer oral investigational product and observe dosing;
- CCI [redacted]
- Assess and record any Adverse Events since the last visit.

6.2.4. Visit 5, Day 29/Week 4 (±2 days)

- Administer PROs including PtGA;
- Review any changes in the subject's concomitant medications and treatments information;

- Obtain pre-dose vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Review PSAAD daily completion (in selected countries), CCI [redacted], and Pruritus NRS completion for this visit in the eDiary;
- Check subject understanding of protocol guidance for the use of background topical therapy as described in Section 5.9.1, ensure subject adherence to background topical therapy requirements and re-educate as required;
- Conduct targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Perform a single 12-lead electrocardiogram (ECG);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), lipid profile (fasting), CCI [redacted] and urinalysis;
- Urine pregnancy test (female subjects of childbearing potential). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Dispense oral investigational product to the subject;
- Administer oral investigational product and observe dosing;
- Dispense injectable investigational product to the subject;
- Unblinded administrator/trainer: observe the administration of injectable investigational product performed by the subject or his/her caregiver;
- Assess and record any Adverse Events since the last visit.

6.2.5. Visit 6, Day 57/Week 8 (±3 days)

- Administer PROs including PtGA;

- Obtain pre-dose vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Review PSAAD daily completion (in selected countries), CCI [redacted], and Pruritus NRS completion for this visit in the eDiary;
- Review any changes in the subject's concomitant medications and treatment information;
- Check subject understanding of protocol guidance for the use of background topical therapy as described in Section 5.9.1, ensure subject adherence to background topical therapy requirements and re-educate as required;
- Conduct targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Perform a single 12-lead electrocardiogram (ECG);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), CCI [redacted], and urinalysis;
- Urine pregnancy test (female subjects of childbearing potential). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Dispense oral investigational product to the subject;
- Administer oral investigational product and observe dosing;
- Dispense injectable investigational product to the subject;
- Unblinded administrator/trainer: observe the administration of injectable investigational product performed by the subject or his/her caregiver;
- Assess and record any Adverse Events since the last visit.

6.2.6. Visit 7, Day 85/Week 12 (±3 days)

- Administer PROs including PtGA, DLQI, EQ-5D-5L, HADS, and POEM;
- Obtain weight;
- Obtain pre-dose vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Review PSAAD daily completion (in selected countries), CCI [redacted], and Pruritus NRS completion for this visit in the eDiary;
- Review any changes in the subject's concomitant medications and treatments information;
- Check subject understanding of protocol guidance for the use of background topical therapy as described in Section 5.9.1, ensure subject adherence to background topical therapy requirements and re-educate as required;
- Conduct targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Perform a single 12-lead electrocardiogram (ECG);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), CCI [redacted], and urinalysis;
- C [redacted]
- For China, Republic of Korea, Taiwan, and Japan only: For subjects who had HBV DNA testing at Screening, collect blood sample for repeat HBV DNA testing, as appropriate;
- Urine pregnancy test (female subjects of childbearing potential). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Dispense oral investigational product to the subject;

- Administer oral investigational product and observe dosing;
- Dispense injectable investigational product to the subject;
- Unblinded administrator/trainer: observe the administration of injectable investigational product performed by the subject or his/her caregiver;
- Assess and record any Adverse Events since the last visit.

6.2.7. Visit 8, Day 113/Week 16 (±3 days)

- Administer PROs including PtGA, DLQI, EQ-5D-5L, CCI HADS, and POEM;
- Obtain pre-dose vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Review PSAAD daily completion (in selected countries), CCI , and Pruritus NRS completion for this visit in the eDiary;
- Review any changes in the subject's concomitant medication and treatments information;
- Check subject understanding of protocol guidance for the use of background topical therapy as described in Section 5.9.1, ensure subject adherence to background topical therapy requirements and re-educate as required;
- Conduct targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Perform a single 12-lead electrocardiogram (ECG);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), lipid profile (fasting), CCI , and urinalysis;
- Urine pregnancy test (female subjects of childbearing potential). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- Review eDiary to assess completion;
- Perform drug accountability procedures;

- Reallocate subject to new treatment regimen;
- Dispense oral investigational product to the subject;
- Administer oral investigational product and observe dosing;
- Assess and record any Adverse Events since the last visit.

6.2.8. Visit 9, Day 127/Week 18 (±3 Days)

- Administer PROs including PtGA;
- Obtain pre-dose vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Review PSAAD daily completion (in selected countries), CCI [redacted], and Pruritus NRS completion for this visit in the eDiary;
- Review any changes in the subject's concomitant medication and treatments information;
- Check subject understanding of protocol guidance for the use of background topical therapy as described in Section 5.9.1, ensure subject adherence to background topical therapy requirements and re-educate as required;
- Conduct targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Perform a single 12-lead electrocardiogram (ECG);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), CCI [redacted] and urinalysis;
- Urine pregnancy test (female subjects of childbearing potential). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Administer oral investigational product and observe dosing;

- Assess and record any Adverse Events since the last visit.

6.2.9. Visit 10, Day 141/Week 20 (±3 Days) End of Treatment or Early Termination Visit

- Administer PROs including PtGA, DLQI, EQ-5D-5L, HADS, and POEM;
- Obtain weight;
- Obtain pre-dose vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Review eDiary Pruritus NRS, CCI [redacted], and PSAAD completion (in selected countries) and review eDiary procedures with subject as necessary;
- Review any changes in the subject's prior and concomitant medications and treatment information;
- Check subject understanding of protocol guidance for the use of background topical therapy as described in Section 5.9.1, ensure subject adherence to background topical therapy requirements and re-educate as required;
- Conduct complete physical examination;
- Conduct clinical evaluations including, IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Perform a single 12-lead electrocardiogram (ECG);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), lipid profile (fasting), CCI [redacted], and urinalysis;
- C [redacted]
- For China, Republic of Korea, Taiwan, and Japan only: For subjects who had HBV DNA testing at Screening, collect blood sample for repeat HBV DNA testing, as appropriate;
- Urine pregnancy test (female subjects of childbearing potential). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- Review eDiary to assess completion;

- Perform drug accountability procedures;
- Administer oral investigational product and observe dosing;
- Assess and record any Adverse Events since the last visit;
- Subjects who complete the trial to this visit will be assessed for eligibility for participation in long-term extension study B7451015. Subjects who are not eligible or are not interested are to continue to Visit 11 (see Section 6.3.1).

6.3. Follow-up Visits

6.3.1. Visit 11, Day 169/Week 24 (±3 Days)

- Administer PROs including: PtGA, DLQI, and EQ-5D-5L;
- Review eDiary Pruritus NRS, CCI [redacted], and PSAAD completion (in selected countries) and review eDiary procedures with subject as necessary;
- Obtain vital signs including pulse rate, sitting blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Review any changes in the subject's prior and concomitant medications and treatment information;
- Review subject use of background topical therapy as described in Section 5.9.1;
- Conduct complete physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Perform a single 12-lead electrocardiogram (ECG);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), lipid profile (fasting), CCI [redacted], and urinalysis;
- Urine pregnancy test (female subjects of childbearing potential). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Assess need for contraception and adherence to applicable lifestyle requirements (Section 4.4). Establish willingness and ability to comply with lifestyle requirements going forward in the study;
- Assess and record any Adverse Events since the last visit.

6.4. Subject Withdrawal

Ongoing safety concern at the time of subject withdrawal from the study:

If a subject 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. Refer to Appendix 4 for Guidelines for Monitoring and Discontinuation.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study. If this request occurs at a scheduled visit, an end of treatment visit should be performed and the subject should enter into the follow-up period, with an end of study visit scheduled for 4 weeks after the end of treatment visit. If the request occurs outside of a scheduled visit (eg, via telephone contact) the subject should be scheduled to return to site for an end of treatment visit within one week, and the subject should enter into the follow-up period, with an end of study visit scheduled for 4 weeks after the end of treatment visit.

The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects 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 investigational product 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 subject 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.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject 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 subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject'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 subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects 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 (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site. Subjects that discontinue study treatment 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. See Appendix 4 for Guidelines for Monitoring and Discontinuation.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject 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.

7. ASSESSMENTS

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

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

7.1. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test with a sensitivity of at least 25 mIU/mL, will be performed at screening. A urine pregnancy test with a sensitivity of at least 25 mIU/mL, will be performed at every site visit including the End of Treatment (EOT) and follow-up visits to confirm the subject has not become pregnant during the study, and at the follow-up visit.

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (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.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects 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).

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

CCI

CCI

[redacted]

7.3. Safety Assessments

Safety will be assessed by the spontaneous reporting of AEs, physical examinations, vital signs and clinical laboratory results in all subjects who receive at least one dose of the investigational product. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns. Investigators and Pfizer Clinicians (or designees) will review individual subject data throughout the conduct of the study to ensure subjects' well-being.

7.3.1. Vitals Signs

Vital signs (sitting blood pressure, pulse rate, respiratory rates and temperature) will be measured (pre-dose, if applicable) after 5 minutes of rest as indicated in the Schedule of Activities.

Body temperature will be collected using the tympanic or oral methods and the same method should be used consistently throughout the study.

Blood pressure (BP) will be measured using a standard calibrated blood pressure measuring device. A BP device that uses multiple cuff sizes based on the arm circumference is the required type of device. The appropriate cuff size for the subject 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.

Subjects 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). Subjects should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements. Measurements should begin after at least 5 minutes of rest.

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.

7.3.2. Medical History, Physical Examination, Height, and Weight

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. Height and weight will be measured without the subject wearing shoes. Height (inches or centimeters) and weight (lb or kg) will be measured and recorded in the source document at the screening

visit. Weight (lb or kg) will continue to be measured and recorded at various time points, see Schedules of Activities.

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.

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 subject.

Complete and Targeted physical examinations are performed at various time points, see Schedules of Activities.

7.3.3. Chest X-Ray

Chest radiograph (posterior-anterior and lateral views) or other appropriate diagnostic image (ie, computed tomography [CT] or magnetic resonance imaging [MRI]) with no evidence of current, active TB or previous inactive TB, taken at screening or within 12 weeks prior to Study Day 1 and read by a qualified radiologist, are required. Documentation of the official reading must be located and available in the source documentation.

7.3.4. Tuberculosis Testing

At the time of screening, all subjects will undergo tuberculosis (TB) testing unless performed within 12 weeks of Day 1. QuantiFERON®-TB Gold In-Tube Test is the preferred testing method. If the test results are indeterminate, the test should be repeated. If the QuantiFERON®-TB Gold In-Tube test cannot be performed, or if the results of the repeat test are indeterminate, then subjects may be screened using the Purified Protein Derivative (PPD) Tuberculin Skin Test (Mantoux method) with approval of the Pfizer Medical Monitor.

In addition to TB testing as specified in this clinical protocol, a chest X-ray will be performed to aid in TB status determination.

QuantiFERON®-TB Gold In-Tube is an in vitro diagnostic test using a peptide cocktail simulating ESAT-6, CFP-10 and TB 7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon-gamma by Enzyme-Linked Immunosorbent Assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. QuantiFERON®-TB Gold In-Tube is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

A blood sample (approximately 3 mL) will be collected at screening for QuantiFERON®-TB Gold In-Tube testing. Following sample processing, the sample will be shipped to the sponsor's designated reference laboratory for testing. The procedure for processing and preparing the sample for shipment is described fully in the laboratory manual, which will be provided to investigators.

A negative PPD test can be substituted for the QuantiFERON®-TB Gold In-Tube test only if the central laboratory is unable to perform the QuantiFERON®-TB Gold In-Tube test or cannot determine the results to be positive or negative and the Pfizer Medical Monitor approves it, on a case-by-case basis.

Japan only: While QuantiFERON® is the preferred testing method, the T-SPOT®.*TB* test is also acceptable as the screening TB test. Like QuantiFERON®, the T-SPOT®.*TB* test is an in vitro diagnostic test for *M. tuberculosis* infection; however, it differs in that it uses a peptide cocktail of ESAT-6 and CFP-10 proteins to stimulate peripheral blood mononuclear cells.

T-SPOT®.*TB* testing will be performed at the site's local laboratory. Borderline results from the T-SPOT®.*TB* test should be considered exclusionary. If the T-SPOT®.*TB* test results are indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, subjects may be screened using the Mantoux/PPD skin test with Pfizer Medical Monitor approval.

Purified Protein Derivative (PPD) Test

If the QuantiFERON®-TB Gold In-Tube test or the T-SPOT®.*TB* test (Japan only) cannot be performed, or if the results cannot be determined to be positive or negative, then subjects may be screened using the Purified Protein Derivative (PPD) Tuberculin Test (Mantoux method), with the approval of the Pfizer Medical Monitor.

Subjects must have the PPD test administered and evaluated by a health care professional 48 to 72 hours later in order to be eligible for the study, unless performed and documented within the last 3 months. The test should be performed according to local standards with induration of <5 mm required for inclusion.

7.3.5. Electrocardiogram

A single 12-lead ECG will be performed at screening and all other on-site visits as specified in the Schedule of Activities. ECGs reading will be interpreted by a central reader.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

A subject's screening ECG must not demonstrate clinically significant abnormalities prior to randomization.

7.3.6. Special Safety Assessment

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

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

For subjects with a past history of oral or genital HSV and a presentation consistent to prior infections, further laboratory analysis may be performed at the discretion of the investigator.

7.4. Skin Type Assessment

As part of baseline characteristics, a skin type assessment will be done at the Day 1 visit using the Fitzpatrick Skin Type assessment (Refer to Appendix 5). This is used to classify a person's skin type by their response to sun exposure (ie, burning or tanning).

7.5. Assessment of Suicidal Ideation and Behavior

Subjects meeting exclusionary results as described in Section 4.2 on the C-SSRS or PHQ-8 should be excluded from participation; it is recommended the subject's primary care physician (PCP) should be informed, and the subject referred to a mental health professional, either by the PCP or the investigator according to their usual practice.

7.5.1. 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 (Appendix 15).[18] At the screening visit, if there are "yes" answers on items 4 or 5 in the past year or on any question in the suicidal behavior section of the C-SSRS in the past 5 years, the subject will not be included in the study. Trained site staff is to administer the C-SSRS to all subjects at screening, score immediately and assess the subject's eligibility based on the answers.

7.5.2. Patient Health Questionnaire - 8 items (PHQ-8)

The Patient Health Questionnaire – 8 items (Appendix 16) is a patient-reported questionnaire consisting of 8 items to assess the subject's depression level. At Screening Visit, if PHQ-8 total score ≥15, the subject will not be included in the study.[19] Site staff is to administer the PHQ-8 to all subjects at screening and score immediately.

7.6. Clinical Laboratory Tests

7.6.1. Blood Volume

Total blood sampling volume planned for this study is approximately 166 mL. Further details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the lab manual.

7.6.2. Laboratory Tests

The following laboratory tests will be performed at time points identified in the Schedule of Activities. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns at the investigator's discretion.

Sample collection, labeling, storage, and shipping information can be found in the laboratory manual. All laboratory tests with clinically important changes from baseline identified after administration of investigational product will be followed until the value stabilizes.

Subjects must abstain from all food and drink (except water and non-study medications) for an 8-hour overnight fast prior to labs that include the lipid profile panel on Day 1, Week 4, Week 16, Week 20 and EOS. For all other lab tests, fasting is not required.

Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Other
Hemoglobin	BUN and Creatinine	pH	HIV[a]
Hematocrit	Creatine Phosphokinase	Glucose (qual)	HBsAg[a]
RBC count and indices (MCH, MCHC, MCV,	Glucose	Protein (qual)	HBcAb[a]
	Na+, K+, Cl-, Ca++, P	Blood (qual)	HBsAb[b]
RBC	Total CO2 (Bicarbonate)	Ketones	HCVAb[a]
Morphology)	AST, ALT	Nitrites	HCV RNA[b]
Reticulocyte count	GGT	Leukocyte esterase	Serum FSH (WONCBP only) or
Platelet count	Total, Indirect & Direct	Microscopy and/or	Pregnancy Test[a, c]
WBC count with	Bilirubin	culture[d]	Urine pregnancy test[c]
differential	Alkaline phosphatase		QFT-G or PPD (if applicable) or
Total neutrophils (%, Abs)	Lactate dehydrogenase		T-SPOT®.*TB* test (Japan only)[e]
Eosinophils (%, Abs)	Uric acid		Viral Screen (if applicable)
Monocytes (%, Abs)	Albumin		[redacted] CCI
Basophils (%, Abs)	Total protein		
Lymphocytes (%, Abs)	Lipid Profile Panel[f]		
Coagulation Panel	Total cholesterol		
Activated Partial Thromboplastin Time (APTT)	LDL		
	HDL		
	Triglycerides		
Prothrombin Time/International Normalized Ratio (PT/INR)			HBV DNA

a. At Screening only. HIV testing will be performed for all subjects. Subjects who are positive for HIV will be screen-failed.

b. HBsAb reflex testing only if HBsAg negative but HBcAb positive. For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all subjects rather than as a reflex test. HCV RNA is reflex testing only if HCVAb is positive. Subjects who are positive for HCVAb and HCV RNA will be screen-failed.

c. Pregnancy testing for females of childbearing potential; serum FSH for postmenopausal female subjects who have been amenorrheic for at least 12 consecutive months.

d. Microscopy with culture performed as appropriate.

e. PPD results should be read within 48 to 72 hours. For Japan only: QFT-G is preferred but T-SPOT®.*TB* test may be performed instead through the site's local laboratory.

f. Lipid Profile Panel requires at least an 8 hour fast. Lipid profile panel will be completed at Day 1, Week 4, Week 16, Week 20, and EOS, and will include total cholesterol, LDL, HDL, and triglycerides.

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h. For China, Republic of Korea and Taiwan only: Subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for Hepatitis B Virus (HBV) DNA. Subjects who have HBV DNA above the lower limit of quantification (LLQ) are excluded. Subjects who have HBV DNA negative or below LLQ may be randomized, but will have HBV DNA testing repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner. For Japan only: Subjects with negative results for HBsAg, HBcAb and HBsAb tests may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner.

Clinically significant abnormal findings should be recorded as AEs. Abnormal test results determined to be caused from laboratory error should not be reported as AEs. Clinically significant laboratory findings at the final assessment should be followed to resolution or until determined by the investigator to be stabilized. Repeat tests may be indicated to establish this. Refer to Appendix 4 for Guidelines on Monitoring and Discontinuation.

7.6.2.1. Hepatitis Testing

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

Subjects will be screened for hepatitis B virus infection. Subjects with hepatitis B surface antigen (HBsAg) negative testing but who test positive for hepatitis B core antibody (HBcAb) must have further testing for hepatitis B surface antibody (HBsAb).

Interpretation of Hepatitis B Testing Results:

- HBsAg negative and HBcAb negative: Subject is eligible for the study;
- HBsAg positive and HBcAb negative: Subject is excluded from study participation;
- HBsAg negative and HBcAb positive and HBsAb positive: Subject is eligible for study;
- HBsAg negative and HBcAb positive and HBsAb negative: Subject is excluded from study participation;
- **For China, Republic of Korea, and Taiwan only:** Subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for Hepatitis B Virus (HBV) DNA. Subjects who have HBV DNA above the lower limit of quantification (LLQ) are excluded. Subjects who have HBV DNA negative or below LLQ may be randomized, but will have HBV DNA testing repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner;
- **For Japan only:** In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all subjects rather than as a reflex test. Subjects with negative results for HBsAg, HBcAb and HBsAb may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 and Week 20 End of Treatment (EOT) visit, or Early Termination (ET) visit, whichever is sooner;

- A single HBV DNA test result above the LLQ for a subject requires immediate and permanent discontinuation from treatment, and the Medical Monitor (or designee) must be notified. The subject must be scheduled for an End of Treatment visit/Early Termination visit, enters the end of treatment follow up period, and must be scheduled for an End of Study visit. No further scheduled HBV DNA tests will be required for a subject once a result above the LLQ is established for that subject during any study in the program. Follow up by the investigator is required as detailed in Section 6.4.

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

Interpretation of Hepatitis C Testing Results:

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

7.6.2.2. Baseline Viral Screen

A serum sample will be collected at baseline but analyzed only if the subject has suspected viral reactivation. Additional sample collection instructions will be provided in the lab manual (Schedule of Activities). The retained samples will be destroyed upon subject completion of this study or the long-term extension study.

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7.8. Efficacy Assessments

7.8.1. Rater Qualifications

Clinical evaluations of atopic dermatitis 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 AD clinical trials may be permitted to perform the clinical evaluations of atopic dermatitis when designated by the primary site Investigator. The evaluator must receive and document protocol specific and applicable efficacy assessment scales training prior to performing these evaluations. **To assure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual subject 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.

7.8.2. Investigator's Global Assessment (IGA)

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

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

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

* The IGA will exclude scalp, palms, and soles from the assessment/scoring.

7.8.3. 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 subject 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).

7.8.4. Eczema Area and Severity Index (EASI)

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

adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.

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

Table 3. Clinical Sign Severity Scoring Criteria for the Eczema Area and Severity Index (EASI)

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

* The EASI will exclude scalp, palms, and soles from the assessment/scoring.

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

Table 4. Handprint Determination of Body Surface Area (BSA)

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

Handprint refers to the hand size of each individual subject.

* The number of handprints will be for the entire body region; these values will not be adjusted for exclusion of scalp, palms, and soles from the BSA assessment.

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

Table 5. Eczema Area and Severity Index (EASI) Area Score Criteria

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

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

Table 6. Eczema Area and Severity Index (EASI) Body Region Weighting

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

* No adjustment for body regions excluded for assessment.

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

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

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

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

7.8.4.1. Body Surface Area – Efficacy (BSA Efficacy)

BSA Efficacy will be derived from the sum of the BSA in handprints across 4 body regions assessed as part of the EASI assessment (Table 4). Handprint refers to that of each individual subject for their own measurement. The BSA Efficacy ranges from 0 to 100%, with higher values representing greater severity of atopic dermatitis. Since the scalp, palms, and soles will be excluded from the BSA (Efficacy) assessment, the maximum possible value will be less than 100%.

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7.10. Patient-Reported Outcomes (PROs)

In selected countries, subjects will complete the PROs at the clinic prior to other clinical activities and investigational product 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. Subjects are given a handheld device to complete the Pruritus NRS, PSAAD CCI [redacted] according to the Schedule of Activities. Delegated site staff will review compliance at each visit and counsel as appropriate. If a subject has repeated non-compliance, the subject should be re-trained on the device. If a subject is unable to complete the PROs on the handheld device due to documented difficulty using the technological devices or other limitation, the subject will be permitted to enter or remain in the study. In the event of electronic malfunction, a replacement device will be shipped to the site.

Examples of the validated paper versions of Patient Reported Outcomes instruments are included in the Appendices of this protocol. 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.

7.10.1. Pruritus Numerical Rating Scale (NRS)

Severity of Pruritus

The severity of itch (pruritus) due to atopic dermatitis will be assessed using the Pruritus Numerical Rating Scale, a validated horizontal NRS (Appendix 6).[20] Subjects will be asked to assess their worst itching due to atopic dermatitis over the past 24 hours on an NRS anchored by the terms “no itch” (0) and “worst itch imaginable” (10). Subjects will enter the Pruritus NRS assessment into an eDiary. Severity of pruritus score as it is assessed at the screening visit and on the day of the baseline visit will be included in the evaluation of Inclusion Criteria 3 (See Section 4.1).

Frequency of Pruritus

The frequency of itch (pruritus) due to atopic dermatitis will be assessed using a horizontal NRS (Appendix 6). Subjects will be asked to assess frequency of itching due to atopic dermatitis over the past 24 hours on an NRS anchored by the terms "never/no itching" (0) and "always/constant itching" (10). Subjects will enter Pruritus NRS assessment into an eDiary. Frequency of pruritus will not be included in the evaluation of Inclusion Criteria 3 (See Section 4.1).

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

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7.10.3. Patient Global Assessment (PtGA)

The PtGA asks the subject to evaluate the overall cutaneous disease at that point in time on a single-item, 5-point scale (Appendix 8). The same category labels used in the Investigator's Global Assessment will be used for the Patient Global Assessment, ie, "severe (4)", "moderate (3)", "mild (2)", "almost clear (1)", and "clear (0)". The PtGA should be completed as per Schedule of Activities.

7.10.4. EuroQol 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) (Appendix 9).[21-24] Recently, a version was developed called EQ-5D-5L with 5 response levels on each dimension compared to the 3 response levels in the EQ-5D-3L.[21,23,24-27]

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.[22,23,25,26] 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.[24,28] The EQ-5D-3L was used previously in AD studies, including the dupilumab trials, to measure utilities.[29-32]

7.10.5. Dermatology Life Quality Index (DLQI)

The DLQI is a validated general dermatology questionnaire that consists of 10 items to assess subject-reported health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment) (Appendix 10).[33] 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.[34] The DLQI should be completed as per Schedule of Activities.

7.10.6. 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 (Appendix 11). This instrument is appropriate for use by subjects aged 12 and older.[35,36] The POEM should be completed as per Schedule of Activities.

7.10.7. 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[37] (Appendix 12). The instrument has been validated for use by adolescents aged 12 and older.[37] The HADS should be completed as per Schedule of Activities.

7.10.8. Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)

The PSAAD is a daily patient reported symptom diary. The preliminary version (Appendix 13) is a 15-item questionnaire that includes 11 items developed to measure symptoms of atopic dermatitis, capturing those identified by patients to be most important, based on a 24-hour recall. Analysis of the PSAAD will be based solely on these 11 items. CCI [redacted] The PSAAD is an electronic PRO that was developed through concept elicitation and cognitive debriefing in AD patients ages 12 to 67; CCI [redacted] All technical documents describing measurement properties of the PSAAD will be submitted as required to the Regulatory Agencies upon finalization. The PSAAD should be completed by subjects as per Schedule of Activities on an eDiary.

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8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety 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 investigational product under study during pregnancy or breastfeeding, and occupational exposure.

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 investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days; except as indicated below after the last administration of the investigational product.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;

- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result 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; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;

- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample).

In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects 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:

- Subjects 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 subjects 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 subject 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, 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, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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 co-formulated 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) 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.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.3.1. Exposure During Pregnancy

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

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

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective

of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product;
- 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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. 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's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject 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.

8.4.4. Medication Errors

Other exposures to the investigational product 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

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject;
- Refer to Section 5.3 for examples of medication errors related to compliance with investigational product.

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 immediately.

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**.

8.4.5. Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes of subcutaneous injection of dupilumab or injectable placebo. In order to fulfill regulatory reporting obligations worldwide, the investigator 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 incident can be found in Appendix 17.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8 of the protocol.

8.4.5.1. Time Period for Detecting Medical Device Incidents

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

If the investigator learns of any incident 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 investigator will promptly notify the sponsor.

The method of documenting medical device incidents is provided in Appendix 17.

8.4.5.2. Follow-up of Medical Device Incidents

All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8). This applies to all participants, including those who discontinue study intervention.

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

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.5.3. Prompt Reporting of Medical Device Incidents to Sponsor

Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.

The Investigational Drug Product and Medical Device Complaint Submission Form will be completed.

8.4.5.4. Regulatory Reporting Requirements for Medical Device Incidents

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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 co-primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

A total sample of 700 subjects, with 200 subjects randomized to PF-04965842 200 mg QD, 200 subjects randomized to PF-04965842 100 mg QD, 200 subjects randomized to dupilumab and 50 subjects each randomized to two sequences of matching placebo for 16 weeks followed by (a) PF-04965842 100 mg QD and by (b) PF-04965842 200 mg QD (4:4:4:1:1 randomization) is planned. The two placebo sequences will be combined for purposes of analyses at all visits up to and including Week 16, which would essentially result in a 2:2:2:1 randomization ratio. This would provide at least 96% power to detect a difference of at least 20% in IGA response rate between either dose of PF-04965842 and placebo, assuming the placebo response rate is 12% at Week 12. This will also provide at least 99% power to detect a difference of at least 30% in EASI-75 response rate between either dose of PF-04965842 and placebo, assuming the placebo response rate is 23% at Week 12.

For a given dose (PF-04965842 200 mg QD or 100 mg QD), both co-primary endpoints must achieve statistical significance to meet the primary objective.

In addition, this sample size will also provide at least 92% power to detect a difference of at least 15% in the proportion of subjects with a ≥4 points improvement in the severity of pruritus NRS between PF-04965842 and dupilumab, assuming the dupilumab response rate is 18% at Week 2.

The Type-I error rate is set at 5% (two-sided). The familywise Type-I error rate (for testing the co-primary and key secondary endpoints) will be strongly controlled at 5% using a closed-testing method based on a sequential, iterative Bonferroni-type approach as outlined below.

The study has been sized to help gain sufficient safety data to be able to effectively evaluate the benefit-risk of PF-04965842 in conjunction with the other studies in the clinical development program, therefore the power for the co-primary endpoints is relatively high. This sample size will also help ensure adequate power is maintained for testing all the co-primary and key secondary endpoints for both doses of PF-04965842 via the multiple testing procedure.

9.2. Efficacy Analysis

9.2.1. Analysis Sets

The primary analysis population for efficacy data will be the Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of investigational product. The primary efficacy endpoint and the key secondary efficacy endpoints will also be analyzed for the Per-Protocol Analysis Set (PPAS) defined as a subset of FAS who had no major protocol violations. Major protocol violations would consist of not meeting inclusion criteria or meeting exclusion criteria or not having taken the correct randomized treatment for at least 80% of the assigned amount or not having adhered to standardized background topical therapy guidelines or having taken a protocol-prohibited concomitant medication or any other major protocol violation as determined by the clinical team or medical monitor prior to database lock. The subjects excluded from the PPAS will be determined and documented before the study is un-blinded. For all analyses, baseline value will be based on observations collected pre-dose.

It is expected that the FAS as defined here will be identical to a true intent to treat (ITT) analysis set (randomized and dispensed study medication) because the first dose is administered in-clinic. Nevertheless, any differences from ITT in terms of the number of subjects will be noted and summarized.

9.2.2. Testing Procedure for Multiple Comparisons

The familywise Type-I error rate for testing the co-primary and key secondary endpoints will be strongly controlled at 5% using a sequential, Bonferroni-based iterative multiple testing procedure.

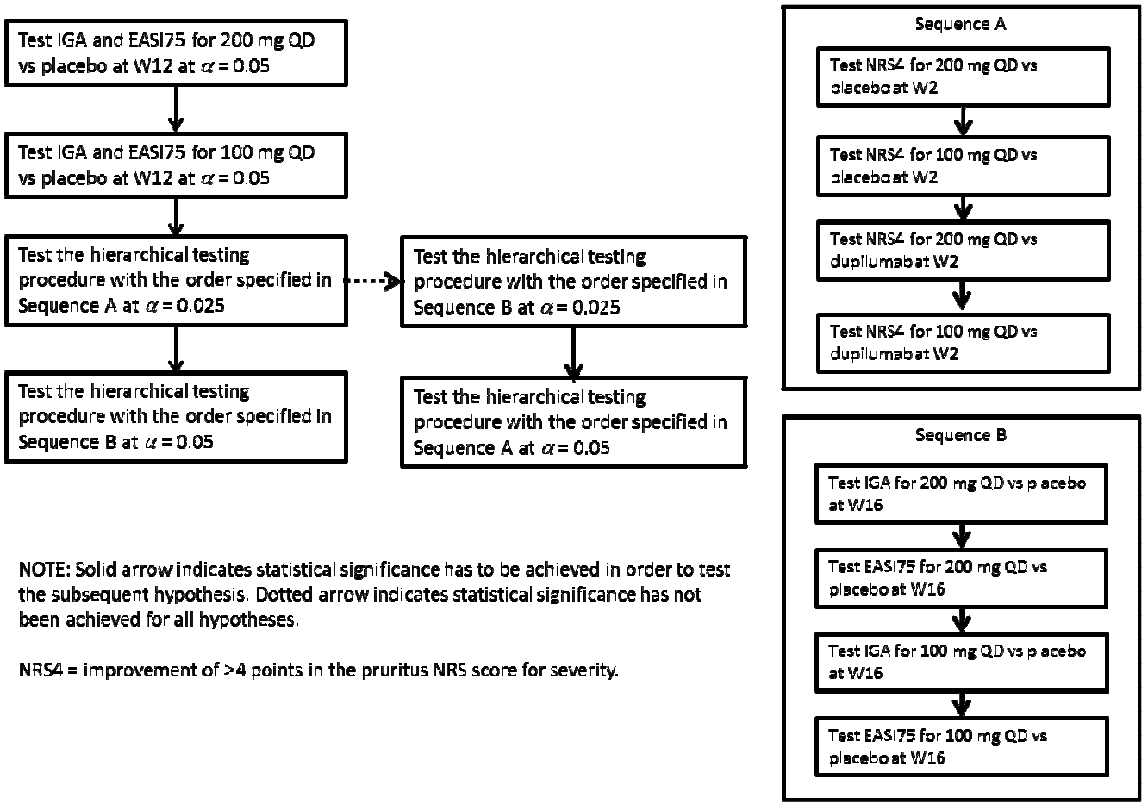
The procedure will first test the co-primary endpoints (IGA and EASI-75 at Week 12 for 200 mg QD vs placebo) at the 5% level. If this hypothesis is not rejected, then all subsequent hypotheses will not be considered statistically significant. If this hypothesis is rejected, then testing for statistical significance will continue for the co-primary endpoints (IGA and EASI-75 at Week 12) for the 100 mg QD vs placebo comparison. If this hypothesis is not rejected, then all subsequent hypotheses will not be considered statistically significant. If this hypothesis is rejected, then testing may continue as follows:

- A series of hypotheses related to the severity of pruritus at Week 2 will be tested at the 2.5% level in the order specified in Sequence A. If all hypotheses in Sequence A are rejected, then the unused alpha level of 2.5% will be passed on to the testing for the Week 16 endpoints in the order specified in Sequence B at a 5% significance level

(see figure below). All subsequent hypotheses from any point where a hypothesis cannot be rejected will not be considered statistically significant.

- If any hypothesis in Sequence A cannot be rejected at the 2.5% level, then testing for statistical significance will stop along this sequence but will continue for the hypotheses related to the Week 16 endpoints in the order specified in Sequence B at the 2.5% level. If all hypotheses in Sequence B are rejected, then the unused alpha level of 2.5% will be passed back for testing the hypotheses in Sequence A at the 5% level. All subsequent hypotheses from any point where a hypothesis cannot be rejected will not be considered statistically significant.

Figure 2. Schematic for Multiple Testing Procedure



The figure above illustrates the procedure showing the sequence of the tests.

9.2.3. Analysis of the Primary Endpoints

The co-primary endpoints will be analyzed using the (Cochran-Mantel-Haenszel) test adjusted by baseline disease severity group (moderate and severe) and for a given dose both must achieve statistical significance to meet the primary objective. The difference between each active group and the placebo group in the proportion of subjects achieving IGA response (similarly for EASI-75) along with its 95% confidence interval (using the normal approximation for the difference in binomial proportions) will be reported. If a subject withdraws from the study, then this subject will be counted as non-responder for endpoints after withdrawal.

Additional secondary analyses will utilize missing at random (MAR) and missing not at random (MNAR) approaches. Missing observations will be multiply imputed using a tipping point analysis to estimate the treatment effect under the assumption that the missing data mechanism is MAR or more generally, is MNAR. A longitudinal logit-normal mixed model will be fit using only the observed data. Under the MAR framework, imputations will be based on the posterior predictive probability of response obtained from the posterior distribution under the mixed model. Under an MNAR framework, imputations for the active treatment groups will be based on a linear combination of the posterior predictive probability of response for the active group and the placebo group. For each such completed dataset, the estimates of the proportions and Cochran-Mantel-Haenszel (CMH)-weighted difference of proportions between each active dose group and placebo 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.

9.2.4. Analysis of Secondary Endpoints

The key secondary endpoints which are summarized as proportions such as EASI-75, and the proportion of subjects achieving a 4-point improvement from baseline in the severity of Pruritus NRS measure will be analyzed using the same method as for the co-primary endpoints. This would also apply to any other binary endpoint in the study, such as the response based on subjects reported with PtGA of AD of clear (0) or almost clear (1) and ≥2 point improvement from baseline over 12 weeks.

For continuous endpoints, and change from baseline in the pruritus severity using the NRS measure at all scheduled time points, 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 be tested at the pre-specified primary time point, Week 12, as well as at the other time points by time point-specific contrasts from the MMRM model.

9.3. Safety Analysis

The safety data will be summarized in accordance with Pfizer Data Standards. All subjects who receive investigational product (safety population) will be included in the safety analyses. 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;

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

Change from baseline on laboratory data and vital signs will be additionally summarized.

9.4. External Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of the safety of subjects 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.

9.5. Safety Adjudication Committees

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

9.6. Week 16 Analysis and End of Study Analysis

There will be a total of two planned analyses conducted for the study. The Week 16 Analysis will be performed after the last subject in the study has the opportunity to complete the Week 16 visit. The Week 16 Analysis will constitute as the final analysis for the co-primary and key secondary endpoints, and the overall family-wise Type 1 error will be controlled as specified in Section 9.2.2. The conclusions with regards to the co-primary endpoints and the secondary endpoints will be based on this analysis, and hence the overall family-wise Type 1 error for this study is maintained. The results from the Week 16 Analysis will not be used to make decisions for modifying the study design or for stopping the study. Access to the database containing individual treatment group assignments will be restricted to the sponsor study team at the time of Week 16 Analysis. Study sites, investigators and subjects will not be unblinded.

The purpose of the Week 16 Analysis is to accelerate final reporting timeline. The final clinical study report (CSR) for the study will be based on the results from the Week 16 Analysis.

The End of Study Analysis will contain additional data after the final database release and the results will be reported in a supplemental CSR.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs/DCTs are securely stored at the study site in encrypted electronic and/or paper form

and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable law.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject 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 investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all countries is defined as the last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-04965842 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial 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 all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are 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 subject 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 pre-specified protocol or was terminated.

EudraCT

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has 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.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed

publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

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

Abbreviation	Term
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	Area under the curve
AUC_{inf}	area under the curve from time zero extrapolated to infinity
AUC_{last}	area under the curve from time zero to last quantifiable
AUC_{tau}	area under the curve over dosing interval tau
BBS	Biospecimen Banking System
BCG	Bacille Calmette Guérin
BID	twice a day
BP	blood pressure
BSA	body surface area
C_{max}	peak plasma concentration
CD	cluster of differentiation
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	clearance/fraction of dose absorbed
CO2	carbon dioxide
CK	creatine kinase
CMH	Cochran-Mantel-Haenszel
CNIL	French Data Protection Authority
CRF	case report form
CSA	clinical study agreement
CsA	cyclosporine A
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DCT	Data Collection Tool
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee

Abbreviation	Term
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index
EBV	Epstein Barr virus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
e-Diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
EQ-5D-5L	EuroQol Quality of Life 5-Dimension 5-Level Scale
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GM-CSF	granulocyte-macrophage colony-stimulating factor
HADS	Hospital Anxiety and Depression Scale
HADS	Hospital Anxiety and Depression Scale
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HBV DNA	hepatitis B virus deoxyribonucleic acid
CCI [redacted]	[redacted]
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
HCV RNA	hepatitis C viral ribonucleic acid
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HRQL	health-related quality of life
CCI [redacted]	[redacted]
HSV	herpes simplex virus

Abbreviation	Term
HTA	health technologies assessment
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ID	identification
IFN	interferon
IFN-α	interferon-alpha
IFN-γ	interferon-gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IgG	immunoglobulin G
IIV	inter individual variability
IL	interleukin
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
ITT	intent to treat
IUD	intrauterine device
IWR	interactive web response
JAK	Janus kinase
JAK1	Janus kinase 1
CCI	[redacted]
LDL	low-density lipoprotein
LFT	liver function test
LLQ	lower limit of quantification
LSLV	last subject last visit
LTE	long-term extension
MAA	marketing authorisation application
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMRM	mixed-effect model with repeated measures
MNAR	missing not at random
MnB	meningitidis serogroup B
MRI	magnetic resonance imaging
MTX	methotrexate
N/A	not applicable
NB-UVB	narrowband ultraviolet B light
OTC	over the counter

Abbreviation	Term
Pruritus NRS4	improvement in the severity of Pruritus NRS from baseline by at least 4 points
NRS	numerical rating scale
PCD	primary completion date
PCP	primary care physician
PD	Pharmacodynamics
PEER Study	Pediatric Eczema Elective Registry Study
PFS	prefilled syringe
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGx	Pharmacogenomics
PHQ-8	Patient Health Questionnaire - 8 items
PI	principal investigator
PK	Pharmacokinetics
POC	proof of concept
POEM	Patient-Oriented Eczema Measure
PPAS	per-protocol analysis set
PPD	purified protein derivative test
PRO	patient reported outcome
PSAAD	Pruritus and Symptoms Assessment for Atopic Dermatitis
PT	prothrombin time
PtGA	Patient Global Assessment
QD	once daily
QFT-G	QuantiFERON®-TB Gold
QT	Q wave interval
QTc	corrected Q wave interval
QTcF	Fridericia corrected Q wave interval
R_{ac}	accumulation ratio
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCORAD	SCORing atopic dermatitis
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	Half-life
TARC	thymus and activation regulated chemokine
TB	tuberculosis
TBili	total bilirubin
TCI	topical calcineurin inhibitors

Abbreviation	Term
TCS	topical corticosteroids
TdP	Torsade de Pointes
TH1	type 1 helper T cell
TH2	type 2 helper T cell
T_{max}	time to maximum absorption
TPO	Thrombopoietin
TYK2	tyrosine kinase 2
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
V/F	volume of distribution/fraction absorbed
VZV	varicella zoster virus
CCI [redacted]	[redacted]
WBC	white blood cell
WOCBP	woman of childbearing potential
WONCBP	women of non-childbearing potential

Appendix 2. Diagnostic Criteria for Atopic Dermatitis

Per Inclusion Criterion 3, a subject is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.[17]

Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

Must have three or more basic features described below:

Pruritus

Typical morphology and distribution:

- Flexural lichenification in adults
- Facial and extensor eruptions in infants and children

Chronic or chronically-relapsing dermatitis

Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Must have three or more following minor features:

Xerosis

Ichthyosis/palmar hyperlinearity, keratosis pilaris

Immediate (type 1) skin test reaction

Elevated serum IgE

Early age of onset

Tendency toward cutaneous infections (esp. staph. aureus and herpes simplex), impaired cell-mediated immunity

Tendency toward non-specific hand or foot dermatitis

Nipple eczema

Cheilitis

Recurrent conjunctivitis

Dennie-Morgan infraorbital fold

Keratoconus

Anterior subcapsular cataracts

Orbital darkening

Facial pallor, facial erythema

Pityriasis alba

Anterior neck folds

Itch when sweating

Intolerance to wool and lipid solvents

Periofollicular accentuation

Food intolerance

Course influenced by environmental and emotional factors

White dermographism, delayed blanch

Appendix 3. Prohibited Concomitant Medications

CYP2C19 Inhibitors	CYP2C19 Inducers
Fluconazole (Diflucan)	Enzalutamide (Xtandi)
Fluvoxamine (Luvox)	Rifampin
Ticlopidine (Ticlid)	
Esomeprazole (Nexium)	
Fluoxetine (Prozac)	
Moclobemide	
Omeprazole (Prilosec)	
Voriconazole (Vfend)	

CYP2C9 Inhibitors	CYP2C9 Inducers
Fluconazole (Diflucan)	Carbamazepine (Tegretol)
Amiodarone (Cordarone)	Enzalutamide (Xtandi)
Fluvoxamine (Luvox)	Rifampin
Miconazole	
Oxandrolone (Oxandrin)	
Voriconazole (Vfend)	

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

Note 2: All CYP2C9 and CYP2C19 inducers require a period of washout of at least 5 half-lives plus 14 days prior to the first dose of investigational product. 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 investigational product.

Note 3: Half-life refers to the half-life of the parent drug and its metabolites, which are inhibitors or inducers. The longest half-life should be used to calculate the period necessary to washout a medication prior to the first dose of investigational product. 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 investigational product.

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

Appendix 4. Monitoring and Discontinuation Criteria

Monitoring Criteria

The following laboratory abnormalities require prompt retesting:

- Neutrophil counts <1000 neutrophils/mm^3; confirmed promptly by repeat testing, ideally within 3-5 days;
- Platelet counts <75,000 platelets/mm^3; confirmed promptly by repeat testing, ideally within 3-5 days;
- Any single hemoglobin value <9.0 g/dL or one that drops ≥2 g/dL below baseline; confirmed promptly by repeat testing, ideally within 3-5 days;
- Any single AST and/or ALT elevation >3 times the upper limit of normal regardless of accompanying symptoms or the total Bilirubin should prompt repeat testing. This should also prompt review of Section 8.4.2; additional investigations must be conducted.

Temporary Interruption to Dosing

An investigator can temporarily interrupt dosing for up to a maximum of 14 consecutive days for a subject, for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary. In the case of investigational product being withheld, all investigational products that the subject is receiving should be withheld (ie, both oral and injected investigational product, as applicable). The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the subject during this timeframe. If within this timeframe the investigator judges that it is safe to restart dosing, then the subject may restart investigational product. If the investigator judges that it is not safe to restart dosing within this timeframe then the subject must be permanently discontinued from treatment, have an End of Treatment visit and enter the 4-week follow-up period. 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

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

- Marked prolongation of the QTcF interval to >500 ms or >60 ms change from screening ECG.
- Serious infection (see definition for Serious Adverse Events in Section 8.2.3).

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

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

- Any adverse event or laboratory abnormality, that per the investigator's judgement requires withholding of investigational product for >14 days.

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

- Two sequential platelet counts <50,000/mm^3. If the subject has a platelet count <25,000/mm^3, investigational product 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.

- 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 findings should prompt review of "The Potential Cases of Drug-Induced Liver Injury," Section 8.4.2 for which additional investigations must be conducted.**

- Two sequential increases in serum creatinine that are >50% over the average of screening and baseline values AND an absolute increase in serum creatinine ≥0.5 mg/dL. At the time of study completion or discontinuation, if a subject should exhibit elevations in serum creatinine ≥33% above the average of screening and baseline values, they will be re-tested every 1 to 2 weeks until the serum creatinine elevation is fully reversed to within 10% of the average of screening and baseline values or has stabilized.

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

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

If a subject 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.

Appendix 5. Fitzpatrick Skin Type

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

Appendix 6. Pruritus Severity and Frequency (Pruritus NRS)

Severity of Pruritus

On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No itch										Worst itch imaginable

Frequency of Pruritus

Select the number that best describes frequency of itching due to Atopic Dermatitis over the past 24 hours (check one number only).

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Never /No itching										Always/constant itching

CCI

[redacted]

Appendix 8. Patient Global Assessment (PtGA)

Overall, how would you describe your Atopic Dermatitis right now?

Choose only ONE response.

- ☐ Severe
- ☐ Moderate
- ☐ Mild
- ☐ Almost Clear
- ☐ Clear

Appendix 9. European Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L)

EQ-5D-5L

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking	❑
I have slight problems walking	❑
I have moderate problems walking	❑
I have severe problems walking	❑
I am unable to walk	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES (eg, work, study, housework, family or leisure activities)

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN/DISCOMFORT

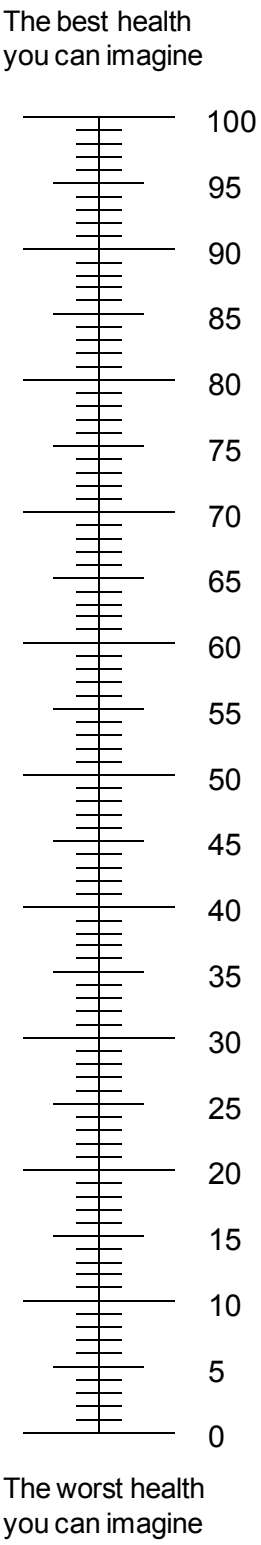
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY/DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 10. Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	□ □ □ □	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	□ □ □ □	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	□ □	Not relevant □
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	□ □ □	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	□ □ □ □	Not relevant □

Please check you have answered EVERY question. Thank you.

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Appendix 11. Patient-Oriented Eczema Measure (POEM)

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

2. Over the last week, on how many nights has your sleep been disturbed because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

3. Over the last week, on how many days has your skin been bleeding because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

5. Over the last week, on how many days has your skin been cracked because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

6. Over the last week, on how many days has your skin been flaking off because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

Total POEM Score (Maximum 28): _____

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Appendix 12. Hospital Anxiety and Depression Scale (HADS)

HOSPITAL ANXIETY AND DEPRESSION SCALE: (Page 1 of 2)

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **check the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed next to the replies.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought out-response.

1. I feel tense or 'wound up'
- ☐ 3 Most of the time
- ☐ 2 A lot of the time
- ☐ 1 From time to time, occasionally
- ☐ 0 Not at all

2. I still enjoy the things I used to enjoy
- ☐ 0 Definitely as much
- ☐ 1 Not quite so much
- ☐ 2 Only a little
- ☐ 3 Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen
- ☐ 3 Very definitely and quite badly
- ☐ 2 Yes but not too badly
- ☐ 1 A little, but it doesn't worry me
- ☐ 0 Not at all

4. I can laugh and see the funny side of things
- ☐ 0 As much as I always could
- ☐ 1 Not quite so much now
- ☐ 2 Definitely not so much now
- ☐ 3 Not at all

5. Worrying thoughts go through my mind
- ☐ 3 A great deal of the time
- ☐ 2 A lot of the time
- ☐ 1 Not too often
- ☐ 0 Very little

6. I feel cheerful
- ☐ 3 Never
- ☐ 2 Not often
- ☐ 1 Sometimes
- ☐ 0 Most of the time

7. I can sit at ease and feel relaxed
- ☐ 0 Definitely
- ☐ 1 Usually
- ☐ 2 Not often
- ☐ 3 Not at all

8. I feel as if I am slowed down
- ☐ 3 Nearly all of the time
- ☐ 2 Very often
- ☐ 1 Sometimes
- ☐ 0 Not at all

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HOSPITAL ANXIETY AND DEPRESSION SCALE: (Page 2 of 2)

9. I get a sort of frightened feeling like 'butterflies' in the stomach

- ☐ 0 Not at all
- ☐ 1 Occasionally
- ☐ 2 Quite often
- ☐ 3 Very often

10. I have lost interest in my appearance

- ☐ 3 Definitely
- ☐ 2 I don't take as much care as I should
- ☐ 1 I may not take quite as much care
- ☐ 0 I take just as much care as ever

11. I feel restless as if I have to be on the move

- ☐ 3 Very much indeed
- ☐ 2 Quite a lot
- ☐ 1 Not very much
- ☐ 0 Not at all

12. I look forward with enjoyment to things

- ☐ 0 As much as I ever did
- ☐ 1 Rather less than I used to
- ☐ 2 Definitely less than I used to
- ☐ 3 Hardly at all

13. I get sudden feelings of panic

- ☐ 3 Very often indeed
- ☐ 2 Quite often
- ☐ 1 Not very often
- ☐ 0 Not at all

14. I can enjoy a good book or radio or television program

- ☐ 0 Often
- ☐ 1 Sometimes
- ☐ 2 Not often
- ☐ 3 Very seldom

Now check that you have answered all the questions

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Appendix 13. Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) Symptom Diary

Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)

Please answer each question by thinking about your skin condition (most often called atopic eczema or atopic dermatitis) over the past 24 hours. This includes today and last night.

For each question, think about all the areas of your body affected by your skin condition and choose the number that best describes your experience.

1) How itchy was your skin over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not itchy										Extremely itchy

2) How painful was your skin over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not painful										Extremely painful

3) How dry was your skin over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not dry										Extremely dry

4) How flaky was your skin over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not flaky										Extremely flaky

5) How cracked was your skin over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not cracked										Extremely cracked

6) How bumpy was your skin over the past 24 hours?

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0	1	2	3	4	5	6	7	8	9	10
Not bumpy										Extremely bumpy

7) How red was your skin over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not red										Extremely red

8) How discolored (darker or lighter) was your skin over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not discolored										Extremely discolored

9) How much did your skin bleed over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No bleeding										Extreme bleeding

10) How much did your skin seep or ooze fluid (other than blood) over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No seeping or oozing										Extreme seeping or oozing

11) How swollen was your skin over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not swollen										Extremely swollen

Sleep & Usual Activities Questions

12) How much did your skin condition make it difficult for you to sleep over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No difficulty sleeping										Could not sleep at all

13) How much did your skin condition make it difficult for you to do your usual activities over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No difficulty doing usual activities										Could not do usual activities at all

Patient Global Impression of Severity (PGIS) & Patient Global Impression of Change Questions (PGIC) Questions

14) **Please rate the severity of your skin condition right now:**

- Not present ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Moderately Severe ☐
- Severe ☐
- Extremely Severe ☐

15) Compared to the beginning of the study, how would you describe the severity of your skin condition today?

- Much better ☐
- Better ☐
- A little better ☐
- No change ☐
- A little worse ☐
- Worse ☐
- Much worse ☐

CCI

[redacted]

ECONOMIC ASSESSMENT – Healthcare Resource Utilization – Atopic Dermatitis (Page 2 of 2)

2) In last 3 months, have you been hospitalized due to Atopic Dermatitis? ☐ No ☐ Yes

If Yes, how many times?

_ _ _ _ hospitalizations

3) In last 3 months, have you visited the emergency room due to Atopic Dermatitis? ☐ No ☐ Yes

If Yes, how many times?

_ _ _ _ ER visits

4) In last 3 months, have you received any **physical treatments**, such as physical therapy/massage, acupressure/acupuncture, or chiropractic care to manage your **Atopic Dermatitis**? ☐ No ☐ Yes

If Yes, please estimate, how much money you have spent **out-of-pocket** on **physical treatments** to manage your **Atopic Dermatitis**.

_ _ _ _ _ _ . _ _ _____

5) In last 3 months, have you used any **supplements (for example herbs, vitamins or other supplements)** to manage your **Atopic Dermatitis**? ☐ No ☐ Yes

If Yes, please estimate how much money you have spent **out-of-pocket** on these supplements to manage your **Atopic Dermatitis**.

_ _ _ _ _ _ . _ _ _____

6) In last 3 months, please estimate how much money you have spent **out-of-pocket** on **all prescription medications** to manage your **Atopic Dermatitis**?

_ _ _ _ _ _ . _ _ _____

Does **copay** influence your decision regarding choice of treatment for your **Atopic Dermatitis**? ☐ No ☐ Yes

7) In last 3 months, please estimate how much money you spent **out-of-pocket** on **non-prescription (over-the-counter)** medications to manage your **Atopic Dermatitis**.

_ _ _ _ _ _ . _ _ _____

8) In last 3 months, please estimate how much money you spent **out-of-pocket** on **professional services** to help with child care, housework, yard work or other activities of daily living that you cannot perform yourself due to your **Atopic Dermatitis**.

_ _ _ _ _ _ . _ _ _____

9) In last 3 months, how much time have other people spent **without receiving payment** to help you with child care, housework, yard work or other activities of daily living that you cannot perform yourself due to your **Atopic Dermatitis**?

_ _ _ _ hours

Appendix 15. C SSRS - Columbia Suicide Severity Rating Scale

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT
dd - MMM - yyyy

Visit: _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE - SCREENING AND BASELINE VISIT (C-SSRS) - Page 1 of 3

☐ (1) NOT DONE Language administered: ☒ (44) English for USA

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Lifetime: Time He/She Felt Most Suicidal		Past ____ Months	
	Yes	No	Yes	No
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	☐	☐	☐	☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts about killing yourself?*** If yes, describe:	☐	☐	☐	☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	☐	☐	☐	☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	☐	☐	☐	☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	☐	☐	☐	☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

	Lifetime: Most Severe	Past ____ Months: Most Severe
Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***		
Past X Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***		
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in a week (4) Daily or almost daily (5) Many times each day	____	____

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT dd - MMM - yyyy

Visit: _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE - SCREENING AND BASELINE VISIT (C-SSRS) - Page 2 of 3

Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things – anyone or anything (e.g., family religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past ____ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?***	Yes ☐ No ☐ Total # of Attempts ____	Yes ☐ No ☐ Total # of Attempts ____
Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relive stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐	Yes ☐ No ☐

Protocol ID: _____ CENTER [ ][ ][ ][ ] SUBJECT ID [ ][ ][ ][ ][ ][ ][ ][ ]

DATE OF VISIT [ ][ ] - [ ][ ][ ] - [ ][ ][ ][ ]
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COLUMBIA-SUICIDE SEVERITY RATING SCALE - SCREENING AND BASELINE VISIT (C-SSRS) - Page 3 of 3

Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted ____	Yes ☐ No ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted ____	Yes ☐ No ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempted or preparing to kill yourself (such as collection pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

Appendix 16. Patient Health Questionnaire – 8 items

Protocol ID: _____ CENTER ☐☐☐☐ SUBJECT ID ☐☐☐☐☐☐☐☐

DATE OF VISIT ☐☐ - ☐☐☐ - ☐☐☐☐
dd MMM yyyy

Visit: _____

PATIENT HEALTH QUESTIONNAIRE (PHQ-8)

☐ (1) NOT DONE Language Administered: ☒ (44) English for USA

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
1. Little interest or pleasure in doing things?	☐	☐	☐	☐
2. Feeling down, depressed, or hopeless?	☐	☐	☐	☐
3. Trouble falling or staying asleep, or sleeping too much?	☐	☐	☐	☐
4. Feeling tired or having little energy?	☐	☐	☐	☐
5. Poor appetite or overeating?	☐	☐	☐	☐
6. Feeling bad about yourself–or that you are a failure or have let yourself or your family down?	☐	☐	☐	☐
7. Trouble concentrating on things, such as reading the newspaper or watching television?	☐	☐	☐	☐
8. Moving or speaking so slowly that other people could have noticed? Or the opposite–being so fidgety or restless that you have been moving around a lot more than usual?	☐	☐	☐	☐

PHQ-8 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Kroenke at kkroenke@regenstrief.org. Use of the PHQ-8 may only be made in accordance with the Terms of Use available of http://www.pfizer.com. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.

Appendix 17. Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 5.6) for the list of sponsor medical devices).

Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel.

It is sufficient that:

- An **incident** associated with a device happened.

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness;
- Permanent impairment of body function or permanent damage to body structure;
- Condition necessitating medical or surgical intervention to prevent one of the above;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

Examples of Incidents

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documentation

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Section 8.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and 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 an incident. This includes any amendment to the device design to prevent recurrence.

Appendix 18. France Appendix

This appendix applies to study sites located in France.

1. GCP Training

   Prior to enrollment of any subjects, 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 three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product

   No subjects or third-party payers will be charged for investigational product.

3. Suspected Unexpected Serious Adverse Reactions (SUSARs)

   Pursuant to a sponsor's safety reporting obligations under 21 CFR 312.32(c)(1), Pfizer will report to the Investigator all 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 (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 patient's medical records.