A PHASE 3 RANDOMIZED WITHDRAWAL, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY INVESTIGATING THE EFFICACY AND SAFETY OF PF-04965842 IN SUBJECTS AGED 12 YEARS AND OVER, WITH MODERATE TO SEVERE ATOPIC DERMATITIS WITH THE OPTION OF RESCUE TREATMENT IN FLARING SUBJECTS

Investigational Product Number:	PF-04965842
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Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 5	28 October 2019	The Columbia Suicide Severity Rating Scale (C-SSRS) will be administered to all ongoing subjects at all remaining scheduled visits in Run In and Blinded treatments, and Rescue weeks 0, 8, 12, 16, and up to and including the End of Treatment/Early Termination (EOT/ET) and/or the End of Study (EOS) visit to align with new cross-program processes. The sections of the protocol affected include Schedules of Activities and in Section 6. Endpoints were reworded for clarity. Removal of EQ-5D-5L/EQ-5D-Y, FACIT-F/Peds-FACIT-F, and SF-36, acute patient-reported outcome (PRO) endpoints from secondary objectives to align with the Statistical Analysis Plan. Administrative changes and clarifications have been made in various sections of the protocol that are not considered substantial by Pfizer because there was no impact to the safety of the trial participants, the scope of the trial, or the scientific interpretation of the study. These changes include: • Administration of the last dose of open-label run-in period study drug (200 mg QD) at the Week 12 visit (Sections 5 and 6); • Initiating administration of randomized blinded treatment on the day after the Week 12 visit (Sections 5 and 6); • Administration of the first dose of open-label Rescue treatment at the start of flare (Section 5); • Additional blood collection at the

		current PK sample time point for analysis of PF-04965842 metabolites (Sections 1, 2, and 7); • Update and clarification of washout period for CYP2C9 and CYP2C19 inducers (Appendix 3).
Amendment 4	27 November 2018	For Taiwan only: Similar to China, other countries in Asia, such as 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, Taiwan will adopt the same changes as those proposed for China in Amendment 3 to monitor the risk of hepatitis B reactivation. The following sections of the protocol are affected: Schedule of Activities, Sections 4, 6, and 7, as applicable.
Amendment 3	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) will be excluded. Subjects who are HBV DNA negative or below LLQ may enroll but will have HBV DNA testing repeated at Weeks 12, 28, 40, 52, Rescue Week 12, and early termination from study during any treatment period.

		A single HBV DNA test result above the LLQ requires immediate and permanent discontinuation from treatment. The following sections of the protocol are affected: Schedule of Activities, Sections 4, 6, and 7, as applicable.
Amendment 2	23 July 2018	Summary and Section 1: • Updated Background and Rationale text to align across the JAK1 program. Summary and Section 2: • Clarified the primary and secondary objectives and endpoints. • Addition of Key Secondary endpoint. Summary and Sections 1, 3 and/or 4: • Clarified Study design. • Clarified informed consent requirments. • For clarity, defined medicated topical therapy 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). Summary and/or Section 9: • Clarified per-protocol analysis set major deviations. • Clarified wording/group definitions and other clarification of endpoints. • Addition of Key Secondary endpoint.

		Sections 3, 5, 6, 7 and Schedule of Activities (As Applicable): • Added guidance for the temporary interruption to dosing. • Added Lymphocyte Subset to the Clinical Laboratory tests to support additional analysis. Schedule of Activities, Sections 6 and 7: • Clarifying that subjects in regions above a low risk for tuberculosis (eg, >10/100,000 prevalence) will have TB test repeated after one year of treatment exposure. • Added Asthma Questionnaire as a PRO and removed it as a safety assessment. Section 7.8 Patient Reported Outcomes: • Clarified process for collection of Patient Reported Outcome data. Sections 11.1, 11.2, 12.3 updated with new Global Data Protection Regulation language to align with requirement for inclusion of recently published European Union (EU) Data Privacy language and legislation. Appendix 3 Prohibited Concomitant Medications updated to reduce number of prohibited medications based on current understanding of metabolism, and to provide clarity around wash-out periods. Appendix 4 updated to align with new Temporary Interruption of Dosing language and clarify discontinuation criteria.
Amendment 1	20 June 2018	The following revisions were made based

		on VHP feedback: Clarified in Schedule of Activities Week 52 (footnote ii) and in Section 7.3.4 that following one year of total exposure to study drug since the last tuberculosis (TB) test, all subjects in regions above a low-risk for TB (ie, >10/100,000 prevalence) will undergo TB testing. Clarified in Schedule of Activities footnote hh and in Section 4.2 Exclusion Criteria #18 that a chest X-ray is required unless previously performed and documented within 12 weeks prior to Study Day 1. Revised Protocol Summary, Schedule of Activities, Section 3 and Section 6.3.1 to indicate that non-responders at Week 12 may roll over onto Study B7451015 providing they remain eligible. Clarified in the Protocol Summary and in Section 9.1 that based on prior data, about 44% of subjects would meet the protocol-defined criteria to be a responder at Week 12, approximately 1370 subjects would need to enter the open label run-in period to ensure that 600 subjects are available for randomization. Section 3 was revised to indicate that all subjects who have started wash-out of AD treatment in the screening period will be allowed to enter the run-in and treatment periods providing all inclusion criteria and none of the exclusion criteria are met. Section 4.1 clarified Inclusion Criteria #3 and Section 7.8.1 to indicate the pruritus NRS severity score will be used on the day of baseline visit to determine moderate to severe AD (not the frequency of pruritus score). Section 4.2 revised Exclusion Criteria to add Criteria #23 - known hypersensitivity

		to PF-04965842 or any study drug excipients. Clarified Section 4.3 to indicate randomization is stratified by age category, ie <18 years and ≥18 years. Clarified in Section 5.3 that investigator is responsible for breaking the blind for safety reasons where knowledge of treatment is essential. Clarified in Section 5.9.1 that low dose acetyl salicylic acid (≤100 mg QD) is permitted for the purpose of cardiovascular prophylaxis. Section 6.1 revised to indicate that subjects not meeting enrollment criteria (screen failures) should be contacted quickly to resume/initiate AD treatments.
Original protocol	26 February 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 beyond childhood reported to be 34%.[8] 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.[3] 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 therapies 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 topical medicated treatment 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 available for moderate to severe AD, and, in the United States of America (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 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 Global Assessment (IGA) response rate and the 75% improvement response rate in the Eczema Area and Severity Index (EASI-75) were 26% and 46%, respectively. The placebo response rate for IGA and EASI-75 was 12% and 23%. 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 then 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. The longer half-life of dupilumab also means that it may take a relatively long period of time for some undesirable pharmacodynamic effects (eg, treatment-related adverse event [AE]) to subside after its discontinuation. In this respect, the benefit of a shorter half-life with agents such as PF-04965842 is that an AE may potentially resolve more rapidly than is the case with dupilumab. 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, 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.[7]

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 Janus kinase 2 (JAK2), >340-fold over Janus kinase 3 (JAK3) and 43-fold over tyrosine kinase 2 (TYK2), as well as a good selectivity profile over the broader range of human kinases. The selective inhibition of JAK1 will lead to modulation of multiple cytokine pathways involved in the pathophysiology of AD, including IL-4, IL-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. Study B7451014 will investigate the time to loss of response to PF-04965842 in subjects with moderate to severe AD following a clinical response to open-label induction treatment with PF-04965842. Subjects

who experience a loss of response denoted as flare (per protocol definition) will receive rescue treatment with PF-04965842 in combination with topical therapy per standard of care.

Objectives and Endpoints

Primary Objective:

- To evaluate and compare the maintenance of effect of two doses of PF-04965842 (200 mg and 100 mg once daily [QD]) and placebo in subjects aged 12 and above with moderate to severe atopic dermatitis who respond to an initial open-label run-in treatment of 200 mg PF-04965842 QD.

Secondary Objectives:

- To evaluate and compare the effect of PF-04965842 on additional efficacy endpoints and patient-reported outcomes over time in subjects aged 12 years and older with moderate to severe atopic dermatitis.

- To assess the efficacy of open-label rescue treatment consisting of 200 mg PF-04965842 in combination with topical therapy per standard of care in cases of flare (per protocol definition).

Safety Objective:

- To assess the safety and tolerability of PF-04965842 during open-label and double-blind treatment in subjects aged 12 and over with moderate to severe AD.

Pharmacokinetic Objective:

- To evaluate the pharmacokinetics (PK) of PF-04965842 and its metabolites in subjects aged 12 years and older with moderate to severe atopic dermatitis following 12 weeks of maintenance treatment.

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- [redacted]

Primary Endpoint

1. Loss of response requiring rescue treatment will be evaluated and compared among groups during the blinded treatment period. Loss of response is denoted as flare and is defined as a loss of at least 50% of the Eczema Area and Severity Index (EASI) response at Week 12 and an Investigator's Global Assessment (IGA) score of 2 or higher.

Key Secondary Endpoint

1. Loss of response based on an IGA score of 2 or higher.

Secondary Endpoints

Clinical Efficacy Assessments:

1. Response based on the IGA (score of 0 or 1 and a reduction of ≥2 points) at all scheduled time points.

2. Response based on EASI total score (EASI-50, EASI-75, EASI-90, and EASI-100) at all scheduled time points.

3. Response based on achieving ≥4 point improvement in the severity of pruritus Numerical Rating Scale (NRS) from baseline at all scheduled time points.

4. Percent change from baseline in percent Body Surface Area (BSA) at all scheduled time points.

5. Percent change from baseline in SCORing Atopic Dermatitis (SCORAD) subjective assessments of itch and sleep loss at all scheduled time points.

6. Response based on achieving a ≥50% and ≥75% improvement in SCORAD (SCORAD-50, SCORAD-75) from baseline at all scheduled time points.

Clinical Efficacy Assessments in Subjects Requiring Rescue Treatment:

1. Response based on the IGA at the end of rescue therapy.

2. Response based on the EASI total score at the end of rescue therapy.

3. Response based on achieving ≥4 point improvement in the severity of pruritus Numerical Rating Scale (NRS) at the end of rescue therapy relative to the start of rescue therapy baseline value.

4. Percent change in percent Body Surface Area (BSA) at the end of rescue therapy relative to the start of rescue therapy baseline value.

5. Percent change in SCORAD subjective assessments of itch and sleep loss at the end of rescue therapy relative to the start of rescue therapy baseline value.

6. Response based on achieving a ≥50% and ≥75% improvement in SCORAD (SCORAD-50, SCORAD-75) at the end of rescue therapy relative to the start of rescue therapy baseline value.

Patient-Reported Outcomes in All Subjects:

1. Response based on achieving PtGA score of clear (0) or almost clear (1); and a reduction from baseline of ≥2 points at all scheduled time points (among subjects with a score ≥2 at baseline).

2. Change from baseline in Dermatology Life Quality Index (DLQI) or Children's DLQI (CDLQI) at all scheduled time points.

3. Change from baseline in Hospital Anxiety Depression Scale (HADS) at all scheduled time points.

4. Change from baseline in Patient Oriented Eczema Measure (POEM) at all scheduled time points.

5. Change from baseline in the Pruritus and Symptoms Assessment in Atopic Dermatitis (PSAAD) at all scheduled time points.

Safety Endpoints:

1. Incidence of treatment emergent adverse events.

2. Incidence of Serious Adverse Events (SAE)s and Adverse Events (AE)s leading to discontinuation.

3. Incidence of clinical abnormalities and change from baseline in clinical laboratory values, electrocardiogram (ECG) measurements and vital signs.

Pharmacokinetic Endpoint:

1. Population PK characterization in subjects aged 12 years old and above with moderate to severe atopic dermatitis.

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Study Design

This is a randomized, responder-enriched, double-blind, placebo-controlled, Phase 3 withdrawal trial to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects aged 12 years and older with moderate to severe AD as defined per the inclusion criteria and a body weight ≥40 kg. Adolescent subjects below the legal age of majority (legal adulthood), in the subject's country can only enroll in this study if instructed by the sponsor and approved by the country's regulatory/health authority. If these approvals have not been granted, only subjects ≥ the legal age of majority (legal adulthood), in the subject's country are allowed to enroll. For subjects younger than this, their legally acceptable representative/parent(s) or legal guardian provide written consent and minor children provide assent, according to local regulations and rules regarding ability to give assent and consent. After providing informed consent, subjects are assessed for study eligibility at the screening visit. During the screening period, treatments for AD are washed out, as applicable, according to eligibility requirements. -A baseline (Day 1) visit occurs within 28 days after the screening visit.

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.

The trial consists of an open-label run-in period to determine responder status to an initial induction treatment with PF-04965842 (200 mg, QD), a randomized, placebo-controlled, double-blinded PF-04965842 maintenance treatment period, and a 4-week untreated follow-up safety period. Subjects who meet the protocol definition of flare during blinded treatment enter an open-label rescue treatment period.

Enrolled subjects initiate the 12-week, open-label run-in period to identify responders who have a positive clinical response to induction treatment with 200 mg PF-04965842 QD. **Responder criteria** are defined as a) achieving an IGA of clear (0) or almost clear (1) (on a 5-point scale), b) a reduction from IGA baseline of ≥2 points, and c) reaching an EASI-75 response compared to baseline. Baseline is defined as the IGA score and EASI score obtained prior to dosing on Day 1. Subjects meeting all of the responder criteria may be eligible for randomization.

Subjects who do not reach the response threshold required for randomization are declared non-responders after completion of the open label run-in period. Non-responders are not eligible for randomization in the B7451014 study, but may choose to enroll into the PF-04965842 Long Term Extension (LTE) study B7451015 providing they remain eligible; otherwise they are permanently discontinued from treatment and enter the 4-week untreated follow-up period in B7451014.

Subjects with a positive clinical response to PF-04965842 induction treatment at the end of the 12-week open-label run-in period enter a 40 week, double-blind, maintenance treatment period in which they are randomized into 1 of 3 treatment arms in a 1:1:1 ratio:

1. 100 mg PF-04965842 QD;
2. 200 mg PF-04965842 QD;
3. Placebo.

Randomization is stratified by age category, ie, <18 years and ≥18 years. Eligible subjects must have a documented history of inadequate response with topical AD medications or have required systemic therapies for control of their disease.

Medicated topical and/or systemic standard of care therapies are not allowed during the open-label run-in and blinded treatment periods. 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 available as an over-the-counter [OTC] or prescription only product).

Following completion of 40 weeks of blinded treatment, all subjects are assessed for eligibility to enter the PF-04965842 LTE study B7451015. If a subject discontinues prematurely or is not eligible or willing to participate in B7451015, then the subject enters the 4-week untreated follow-up period in B7451014.

During the blinded treatment period, subjects meeting the **protocol definition of flare** enter an open-label rescue period during which they receive another 12-week course of 200 mg PF-04965842 QD with topical therapy per local standard of care (SOC). In this study, flare requiring rescue treatment is defined as a loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher. For example, if a subject has a total EASI score of 40 at baseline and a score of 10 at Week 12 (achieving EASI-75 to be a responder at randomization), the EASI response is -30. To meet the definition of flare, the total EASI score for this subject would have to go up by at least 15 (50% of -30) from Week 12, which computes to a total EASI score of at least 25, this in addition to an IGA score of ≥2.

After completing the full 12-week rescue period, subjects may enter the LTE study B7451015, if eligible. Subjects discontinuing early from treatment or who are otherwise ineligible for the LTE study enter the 4 week untreated follow-up period in B7451014.

An investigator can temporarily interrupt dosing for up to a maximum of 28 consecutive days for a subject, for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary. The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the subject during this time-frame. 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.

Laboratory tests are performed throughout this study as detailed in the Schedule of Activities. Investigators follow the instructions for more frequent monitoring in Appendix 4 if the specified laboratory values reach the listed thresholds.

The total study duration if a subject does not flare is 52 weeks (12 weeks open-label induction treatment +40 weeks blinded maintenance treatment). The potential maximum study duration is 64 weeks. This would only be achieved if a subject flared on the last day of the maintenance treatment period (52 weeks + 12 weeks rescue). If subjects do not intend to enroll in the LTE study, the above durations are extended by +4 weeks of an untreated follow-up safety period.

A total of approximately 1370 subjects will be enrolled from approximately 218 sites located globally.

Study Treatments

All enrolled subjects receive 12 weeks of 200 mg PF-04965842 QD during the open-label run-in induction period. At the end of the 12 weeks, subjects responding to treatment as described above are randomized to receive double-blind maintenance treatment with 100 mg PF-04965842 QD, 200 mg PF-04965842 QD, or placebo (1:1:1 randomization ratio) for 40-weeks. In the event of flare during blinded treatment, subjects enter a 12-week open-label rescue period and receive 200 mg PF-04965842 QD with concomitant topical therapy per SOC.

Statistical Methods

The statistical objective of the study is to characterize the loss of response with each randomized group after achieving response at Week 12 following open-label treatment with 200 mg PF-04965842 QD.

A total of 600 subjects with 200 receiving 100 mg PF-04965842 QD, 200 receiving 200 mg PF-04965842 QD, and 200 receiving placebo (1:1:1 randomization ratio) will provide 94% power to detect a ratio of median time to flare of at least 1.5 times between either dose of PF-04965842 (100 mg or 200 mg) and placebo. The Type I error rate is assumed to be 5% (2-sided). Assuming based on prior data, that about 44% of subjects would meet the protocol-defined criteria to be a responder at Week 12, approximately 1370 subjects would need to enter the open label run-in period of the study to ensure that 600 subjects are available for randomization.

There are six key hypotheses to be tested for each pairwise comparison between two PF-04965842 doses (200 mg QD and 100 mg QD) and placebo, for the primary and key secondary endpoints. For these hypotheses, the familywise Type-I error rate will be strongly controlled at 5% using a sequential, gatekeeping procedure.

For analysis of the primary and key secondary endpoints, a combination of graphical and analytical methods will be used. The time (in weeks) to protocol-defined flare will be used to evaluate the primary endpoint while the time (in weeks) to achieve an IGA score of ≥2 will be used for the key secondary endpoint. Subjects who do not report an event (protocol-defined flare or IGA ≥2) or discontinue the study during the double-blind randomized period will have their time to event censored at their last known visit in this period. Kaplan-Meier curves will be used to display the time to event and report the median time to event among the three randomized treatment groups. The log-rank test will be used to compare these curves. Proportions of subjects with an event and confidence intervals will also be reported by randomized treatment group.

In general, binary endpoints will be analyzed using the (Cochran-Mantel-Haenszel) test adjusted by randomization strata (age groups) and baseline disease severity. The difference between treatment groups in the proportion of subjects achieving a response along with its 95% confidence interval (using the normal approximation for the difference in binomial proportions) will be reported.

In general, 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, randomization strata (age groups) and baseline disease severity, visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, differences between groups will be tested using estimates 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 FOR RUN-IN AND BLINDED TREATMENTS

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	Day -28[a] Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 Week 12 Randomize Responders	Day 113[b] Week 16	Day 197[b] Week 28	Day 281[b] Week 40	Day 365[b] Week 52 EOT/ET	EOS, Follow-up Week 56/ 4 Weeks post ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±7 Days	±7 Days	±3 Days	±3 Days
Enrollment Procedure													
Informed consent[c]	X												
Register subject using IRT system	X												
Inclusion/Exclusion Criteria	X	X						X					
C-SSRS[d]	X	X					X	X	X	X	X	X	X
SBQ-R[d]	X												
PHQ-8[d]	X												
Demographics, Medical History, Tobacco and Alcohol History, Atopic Dermatitis Disease History[e]	X												
Review Prior/Concomitant Medications & Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense e-Diary and instruct subjects on use	X												
Provide Patient Emergency Contact Card	X												
Medical Procedures													
Complete Physical Exam[f]	X	X						X				X	
Targeted Physical Exam[f]				X	X		X		X	X	X		X
Vital Signs[g]	X	X		X	X		X	X	X	X	X	X	X
Weight/Height[dd]	X	X						X				X	

Visit Identifier	Day -28[a] Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 Week 12 Randomize Responders	Day 113[b] Week 16	Day 197[b] Week 28	Day 281[b] Week 40	Day 365[b] Week 52 EOT/ET	EOS, Follow-up Week 56/ 4 Weeks post ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±7 Days	±7 Days	±3 Days	±3 Days
ECG (12-lead)[kk]	X	X		X	X		X	X	X	X	X	X	X
Laboratory Assessments[h]													
Hematology[i]	X	X		X	X		X	X	X	X	X	X	X
Coagulation Panel[j]	X	X		X	X		X	X	X	X	X	X	X
Serum chemistry[k]	X	X		X	X		X	X	X	X	X	X	X
Urinalysis[l]	X	X		X	X		X	X	X	X	X	X	X
Lipid Panel[m]		X			X			X				X	X
Serum FSH (post-menopausal) or Pregnancy Test[n]	X												
Urine Pregnancy Test (conducted at study site)[o]		X		X	X		X	X	X	X	X	X	X
[redacted]													
HIV Testing[q]	X												
Hepatitis B Surface Antigen (HBsAg), Hepatitis B Surface Antibody (HBsAb), Hepatitis B Core Antibody (HBcAb), Hepatitis C Antibody (HCV Ab), Hepatitis C Viral RNA (HCV RNA)[r]	X												
HBV DNA testing for China and Taiwan[jj]	X							X		X	X	X	
Varicella Zoster Virus (VZV IgG Ab) (adolescents only, if applicable)[s]	X												
Tuberculosis Test[t]	X											X[ii]	
Chest X-ray[hh]	X											X[ii]	

Visit Identifier	Day -28[a] Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 Week 12 Randomize Responders	Day 113[b] Week 16	Day 197[b] Week 28	Day 281[b] Week 40	Day 365[b] Week 52 EOT/ET	EOS, Follow-up Week 56/ 4 Weeks post ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±7 Days	±7 Days	±3 Days	±3 Days
Pharmacokinetic													
Pharmacokinetic Blood Sampling (Post-dose)[u]								X					
Trial Treatment													
Randomization								X					
Drug Dispensing		X			X		X	X	X	X	X		
Investigational Product Accountability				X	X		X	X	X	X	X	X	
Investigational Treatment Administration[v]		X----------										----X	
Review eDiary to assess completion			X	X	X	X	X	X	X	X	X	X	
Assess eligibility for B7451015[w]								X				X	
Clinical Assessments													
Fitzpatrick Skin Type Assessment		X											
Investigator's Global Assessment (IGA)	X	X		X	X		X	X	X	X	X	X	X
SCORing Atopic Dermatitis (SCORAD)	X	X		X	X		X	X	X	X	X	X	X
Eczema Area and Severity Index (EASI)	X	X		X	X		X	X	X	X	X	X	X
Total Body Surface Area (BSA from EASI)	X	X		X	X		X	X	X	X	X	X	X
Patient-reported Outcome													
Pruritus Numerical Rating Scale -eDiary (NRS)[x]	X---------X	X----------		----X	X		X	X	X	X	X	X	X
Patient Global Assessment (PtGA)		X		X	X		X	X	X	X	X	X	X
Dermatology Life Quality Index (DLQI or CDLQI)[y]		X		X	X		X	X	X	X	X	X	X

Visit Identifier	Day -28[a] Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 Week 12 Randomize Responders	Day 113[b] Week 16	Day 197[b] Week 28	Day 281[b] Week 40	Day 365[b] Week 52 EOT/ET	EOS, Follow-up Week 56/ 4 Weeks post ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13
Visit Window	None	None	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days	±7 Days	±7 Days	±3 Days	±3 Days
Patient-Oriented Eczema Measure (POEM)		X		X	X		X	X	X	X	X	X	X
Hospital Anxiety and Depression Scale (HADS)		X		X	X		X	X	X	X	X	X	X
Pruritus and Symptoms Assessment for Atopic Dermatitis - eDiary (PSAAD)[z]	X--------X	X----------											----------X
EQ-5D-5L (adults) or EQ-5D-Y (ages 12-17 years)[aa]		X		X	X		X	X	X	X	X	X	X
SF-36v2, Acute[bb] (adults)		X						X				X	X
FACIT-F (adults) or Peds-FACIT-F (ages 12-17 years)[cc]		X						X				X	X
Asthma Control Questionnaire (ACQ) for all subjects with a prior diagnosis of asthma		X						X				X	X
Safety													
Serious and non-serious adverse event monitoring	X →	→	→	→	→	→	→	→	→	→	→	→	→ X
Assess for presence of flare[ee]									X	X	X	X	
Contraception Check[ff]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Sample for Baseline Viral Screen[gg]		X											

Abbreviations: ACQ = Asthma Control Questionnaire; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; 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; EQ-5D-Y = EuroQol Quality of Life 5-Dimension, Youth Scale; FACIT-F = Functional Assessment of Chronic Illness Therapy Fatigue Scale; FSH = follicle stimulating hormone; GGT = gamma-glutamyl transferase; 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; HCVAb = hepatitis C antibody; HCV RNA = Hepatitis C Viral RNA; Hep B = Hepatitis B; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; HSV2 = herpes simplex virus type 2; IGA = Investigator's Global Assessment; IgE = Immunoglobulin E; IRT = Interactive Response System; LDH = Lactate dehydrogenase; LLQ = lower limit of quantification; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NK = Natural Killer; NRS = numerical rating scale; Peds-FACIT-F = Pediatric Functional Assessment of Chronic Illness Therapy Fatigue 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; RBC = Red blood cell; RNA = Ribonucleic acid; SBQ-R = Suicide Behaviors Questionnaire-Revised; SCORAD = SCORing Atopic Dermatitis; SF-36v2 = Short Form-36 Health Survey Version 2;VZV = varicella zoster virus; VZV IgG Ab = varicella zoster virus immunoglobulin G antibody.

a. Day relative to start of study treatment (Day 1).

b. From Day 86 through Day 365, if the subject flares as defined by protocol, begin rescue treatment period. See Schedule of Activities for Rescue Treatment.

c. Obtain written informed consent; for subjects aged under the legal age of majority (legal adulthood) in the subject's country, obtain written informed consent from legally acceptable representative/parent(s) orlegal guardian, and informed assent from the patient (if age appropriate according to local regulations).

d. Site staff is to administer the C-SSRS, SBQ-R 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, Section 7.5.2 and Section 7.5.3. Subjects meeting exclusionary results on the C-SSRS, SBQ-R and 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. Post-screening, if there are "yes" answers on items 4, 5 or on any behavioral question of the Since Last Visit C-SSRS a risk assessment by a qualified mental health professional (MHP) should be done to determine whether it is safe for the subject to continue to participate in the trial.

e. 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.

f. 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.

g. Vital Signs include sitting blood pressure, pulse, respiratory rate, and temperature measured after at least 5 minutes of rest.

h. 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.

i. Hematology includes: Hemoglobin, hematocrit, red blood cell count and indices (MCH, MCHC, MCV, RBC Morphology), white blood cells, neutrophils (%, absolute), lymphocytes (%, absolute), monocytes (%, absolute), eosinophils (%, absolute), basophils (%, absolute), platelets, reticulocyte count, lymphocyte subsets and markers (Total T cells [CD3+], CD4+ T cells [CD3+CD4+], CD8+ T cells [CD3+CD8+], NK cells [CD3- CD16+CD56+], B cells [CD3-CD19 +).

j. Coagulation panel includes: Activated Partial Thromboplastin Time (APTT), Prothrombin Time/International Normalized Ratio (PT/INR).

k. Serum chemistry includes: blood urea nitrogen (BUN), serum creatinine, creatine phosphokinase, glucose, Ca++, Na+, K+, Cl-, 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.

l. Urinalysis includes: pH, Glucose (qualitative), Protein (qualitative), Blood (qualitative), Ketones, Nitrites, Leukocyte esterase, Microscopy and/or culture (performed as appropriate).

m. Lipid Panel includes: 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 12, Week 52 and EOS visits.

n. Serum pregnancy testing at screening is required for women of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche. 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.

o. Urine pregnancy test must be performed at every site visit prior to dosing with the investigational product for female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche.

[redacted]

q. Subjects testing positive for HIV will be screen-failed.

r. 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.

s. VZV IgG antibody testing is required to confirm eligibility in adolescent subjects who have not received at least one dose of a varicella vaccine.

t. 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). 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, sites should follow their local standards for TB status determination, which may include chest X-ray. See Section 7.3.4.

u. A PK blood sample will be collected at 2.0 hours (±30 min) postdose of open-label study drug (200 mg) at the Week 12 visit. For Early Termination (ET) visits, if the subject discontinues before Week 4, do not collect a PK sample. If the ET visit occurs at or after Week 4 and before Week 12, collect a PK sample only if the subject takes the investigational product at the site visit.

v. Subjects should take the medication from study Days 1 to 365. Subjects will be encouraged to take the medication in the morning whenever possible; however, at study visit days, subjects are to be instructed to refrain from dosing at home and are to take the dose in the clinic. Instruct subjects regarding proper storage conditions for investigational product on Day 1.

w. Subjects who are non responders but complete the 12 week run-in treatment and subjects who are reponders at EOT will be assessed for eligibility for participation in long-term extension study B7451015 as noted in Section 6.3.5.

x. Pruritus Numerical Rating Scale (NRS) will be assessed using an eDiary daily during the screening period and from Study Day 1 to 15. After Day 15, the Pruritus NRS will be completed only on study visit days in the eDiary. At the Screening visit, site staff will dispense the electronic tablet (ePRO device) and review instructions for completion of the subject eDiary for the NRS. 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.

y. DLQI will be completed by adult subjects only. Adolescents 12-17 years of age will complete the CDLQI instead.

z. Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) will be conducted (only in selected countries) to assess the severity and frequency of pruritus, symptoms and sleep collected daily in a subject e-diary during the screening period and from Day 1 through the End of Study visit (See Section 7.8.7). At the Screening visit, site staff will dispense the ePRO device 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.

aa. The EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) will be completed by adult subjects only. Adolescents 12-17 years of age will complete the EuroQol Quality of Life 5-Dimension, Youth Scale (EQ-5D-Y) in select countries.

bb. SF-36v2 will be completed by adult subjects only. Adolescents 12-17 years of age will not complete this assessment.

cc. FACIT-F will be completed by adult subjects only. Adolescents 12-17 years of age will complete the Peds-FACIT-F instead.

dd. Height is not required at the baseline visit. Only adolescents (12 to <18 years old) require repeated height measurement at screening, Week 12, and EOT/ET visits. Adults require one height measurement at the screening visit.

ee. Assess for the emergence of flare defined as a loss of at least 50% of the EASI response at Week 12 and an IGA of 2 or higher.

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

gg. A serum sample will be collected at baseline but analyzed only if the subject has suspected varicella or herpes zoster. In that event, the sample would be analyzed for HSV-1, HSV-2 and VZV.

hh. Chest X-ray or other appropriate diagnostic image (ie, CT or MRI) may be performed up to 12 weeks prior to Study Day 1. Chest X-rays (posterior-anterior and lateral views) are required for adults and recommended for adolescents as per local guidelines and standard of care. Official reading must be located and available in the source documentation.

ii. Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low-risk for Tuberculosis (ie, >10/100,000 prevalence) will undergo tuberculosis (TB) testing. A chest X-ray will be performed to aid in TB status determination for all adults and recommended for adolescents according to local guidelines and standard of care in countries with a high incidence rate of TB.

jj. In China 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) will be excluded. Subjects who are HBV DNA negative or below LLQ may enroll but will have HBV DNA testing repeated at Weeks 12, 28, 40, 52, and early termination from study during any treatment period. A single positive HBV DNA test result above the LLQ for a subject requires immediate and permanent discontinuation from treatment. Refer to Section 7.6.2.1.

kk. A single 12-Lead ECG will be performed at screening and at all other planned on-site visits and interpreted by a central reader. Clinically significant or exclusionary ECG findings at the screening or baseline visits will require screen failure.

SCHEDULE OF ACTIVITIES FOR RESCUE TREATMENT – FLARE AT SCHEDULED OR UNSCHEDULED VISIT

Visit Identifier	Day 1 Week 0	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 EOT/ET Week 12	EOS, Follow-up Week 16/ 4 Weeks post ET
	Rescue Visit 1	Rescue Visit 2	Rescue Visit 3	Rescue Visit 4	Rescue Visit 5	Rescue Visit 6	Rescue Visit 7	Rescue Visit 8
Visit Window	±3 Days	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days
Enrollment Procedure								
Review Prior/Concomitant Medications & Treatments	X	X	X	X	X	X	X	X
Medical Procedures								
Targeted Physical Exam[a]	X		X	X		X		X
Complete Physical Exam[a]							X	
Vital Signs[b]	X		X	X		X	X	X
Weight/Height[q]	X						X	
ECG (12-lead)	X		X	X		X	X	X
Tuberculosis Test[r]							X	
Laboratory Assessments								
Hematology[c]	X		X	X		X	X	X
Coagulation Panel[d]	X		X	X		X	X	X
Serum chemistry[e]	X		X	X		X	X	X
Urinalysis[f]	X		X	X		X	X	X
CCI								
Lipid Panel[h]	X			X			X	X
Urine Pregnancy Test (conducted at study site)[i]	X		X	X		X	X	X
HBV DNA testing for China and Taiwan[s]							X	
Trial Treatment								
Drug Dispensing	X			X		X		
Investigational Product Accountability	X		X	X		X	X	
Investigational Treatment Administration[j]	X----------						----------X	

Visit Identifier	Day 1 Week 0	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 EOT/ET Week 12	EOS, Follow-up Week 16/ 4 Weeks post ET
	Rescue Visit 1	Rescue Visit 2	Rescue Visit 3	Rescue Visit 4	Rescue Visit 5	Rescue Visit 6	Rescue Visit 7	Rescue Visit 8
Visit Window	±3 Days	±1 Day	±1 Day	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days
Review eDiary to assess completion	X	X	X	X	X	X	X	X
Assess eligibility for B7451015[k]							X	
Clinical Assessments								
Investigator's Global Assessment (IGA)	X		X	X		X	X	X
SCORing Atopic Dermatitis (SCORAD)	X		X	X		X	X	X
Eczema Area and Severity Index (EASI)	X		X	X		X	X	X
Total Body Surface Area (BSA from EASI)	X		X	X		X	X	X
Patient-reported Outcome								
Pruritus Numerical Rating Scale -eDiary (NRS)[l]	X----------X			X		X	X	X
Patient Global Assessment (PtGA)	X		X	X		X	X	X
Dermatology Life Quality Index (DLQI or CDLQI)[m]	X		X	X		X	X	X
Patient-Oriented Eczema Measure (POEM)	X		X	X		X	X	X
Hospital Anxiety and Depression Scale (HADS)	X		X	X		X	X	X
Pruritus and Symptoms Assessment for Atopic Dermatitis - eDiary (PSAAD)[l]	X----------X							
EQ-5D-5L (adults) or EQ-5D-Y (ages 12-17 years)[n]	X		X	X		X	X	X
SF-36v2, Acute[o] (adults)	X						X	X
FACIT-F (adults) or Peds-FACIT-F[p] (ages 12-17 years only)	X						X	X

Visit Identifier	Day 1 Week 0	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 EOT/ET Week 12	EOS, Follow-up Week 16/ 4 Weeks post ET
	Rescue Visit 1	Rescue Visit 2	Rescue Visit 3	Rescue Visit 4	Rescue Visit 5	Rescue Visit 6	Rescue Visit 7	Rescue Visit 8
Visit Window	**±3 Days**	**±1 Day**	**±1 Day**	**±2 Days**	**±3 Days**	**±3 Days**	**±3 Days**	**±3 Days**
Asthma Control Questionnaire (ACQ) for all subjects with a prior diagnosis of asthma	X						X	X
Safety								
C-SSRS[t]	X					X	X	X
Serious and non-serious adverse event monitoring	X→	→	→	→	→	→	→	→X
Contraception Check	X	X	X	X	X	X	X	X

a. 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.

b. Vital Signs include sitting blood pressure, pulse, respiratory rate, and temperature measured after at least 5 minutes of rest.

c. Hematology includes: Hemoglobin, hematocrit, red blood cells, white blood cells, neutrophils (%, absolute), lymphocytes (%, absolute), monocytes (%, absolute), eosinophils (%, absolute), basophils (%, absolute), platelets, reticulocyte count, RBC Indices (MCH, MCHC, MCV, RBC Morphology), lymphocyte subsets and markers (Total T cells [CD3+], CD4+ T cells [CD3+CD4+], CD8+ T cells [CD3+CD8+], NK cells [CD3-CD16+CD56+], B cells [CD3-CD19 +).

d. Coagulation panel includes: Activated Partial Thromboplastin Time (APTT), Prothrombin Time/International Normalized Ratio (PT/INR).

e. Serum chemistry includes: blood urea nitrogen (BUN), serum creatinine, creatine phosphokinase, glucose, Ca++, Na+, K+, Cl-, 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.

f. Urinalysis includes: pH, Glucose (qualitative), Protein (qualitative), Blood (qualitative), Ketones, Nitrites, Leukocyte esterase, Microscopy and/or culture (performed as appropriate).

[cc] [redacted].

h. Lipid Panel includes: 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 the following Rescue Visits: Day 1, Week 4, Week 12 and EOS visits.

i. Urine pregnancy test must be performed at every site visit prior to dosing with the investigational product for female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche.

j. Subjects should take the medication from study Days 1 to 85 of the rescue treatment. Subjects will be encouraged to take the medication in the morning whenever possible; however, at study visit days, subjects are to be instructed to refrain from dosing at home and are to take the dose in the clinic.

k. Subjects who complete EOT will be assessed for eligibility for participation in long-term extension study B7451015 as noted in Section 6.5.7.

l. Pruritus Numerical Rating Scale (NRS) will be assessed using an eDiary, and will be collected daily in the eDiary from Study Days 1-15 during the rescue treatment and then only on study visit days at the investigative site thereafter. PSAAD will be completed daily (in selected countries) in the eDiary from Day 1 through the End of Study (EOS) visit during rescue treatment. 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.

m. DLQI will be completed by adult subjects only. Adolescents 12-17 years of age will complete the CDLQI instead.

n. The EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) will be completed by adult subjects only. Adolescents 12-17 years of age will complete the EuroQol Quality of Life 5-Dimension, Youth Scale (EQ-5D-Y) in select countries.

o. SF-36v2 will be completed by adult subjects only. Adolescents 12-17 years of age will not complete this assessment.

p. FACIT-F will be completed by adult subjects only. Adolescents 12-17 years of age will complete the Peds-FACIT-F instead.

q. Collect weight for all subjects and height for adolescents only (12 to <18 years old).

r. Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low-risk for Tuberculosis (ie, >10/100,000 prevalence) will undergo tuberculosis (TB) testing. A chest X-ray will be performed to aid in TB status determination for all adults, and recommended for adolescents according to local guidelines and standard of care in countries with a high incidence rate of TB.

s. In China and Taiwan only: For subjects who had HBV DNA testing at Screening, HBV DNA testing is repeated at Rescue Week 12 or at an early termination visit. A single positive HBV DNA test result above the LLQ for a subject requires immediate and permanent discontinuation from treatment. Refer to Section 7.6.2.1.

t. Post-screening, if there are "yes" answers on items 4, 5 or on any behavioral question of the Since Last Visit C-SSRS a risk assessment by a qualified mental health professional (MHP) should be done to determine whether it is safe for the subject to continue to participate in the trial.

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, 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.[7]

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. Study B7451014 will investigate the time to loss of response to PF-04965842 in subjects with moderate to severe AD following a clinical response to open-label induction treatment with PF-04965842. Subjects who experience a loss of response denoted as flare (per protocol definition) will receive rescue treatment with PF-04965842 in combination with topical therapy per standard of care.

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).

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 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 beyond childhood reported to be 34%.[8] 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.[3] At every age, more than 80% of PEER study subjects had symptoms of AD and/or were using medication to treat their AD. 59% of 833 AD patients who were aged 20 years or older when they visited the clinic and were 45 years or older when they completed a follow up questionnaire, reported that they had persistent AD at some time during the last 12 months.[9]

The majority of studies conducted across multiple age groups suggest a continued decrease in prevalence with older age.[10] Adult-onset AD does also occur, though it is less common. The prevalence of AD in adults is estimated to be 10%.[11] 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.[12]

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.[13]

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.[13,14,7] Recent research showed that a small increase of Type 1 helper T cell (TH1)-associated genes has been also detected in acute phase.[15]

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.[13] 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.[14,7]

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 treatment 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 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. 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 then 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. The longer half-life of dupilumab also means that it may take a relatively long period of time for some undesirable pharmacodynamic effects (eg, treatment-related adverse event [AE]) to subside after its discontinuation. In this respect, the benefit of a shorter half-life with agents such as PF-04965842 is that an AE may potentially resolve more rapidly than is the case with dupilumab. 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-13, IL-22, 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 as an innovative oral therapeutic agent.

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 Investigator's Brochure (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 (QD) 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 (% 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, -82.57% in the 200 mg group and -59.04% 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 Numerical Rating Scale (NRS) from baseline (Pruritus NRS 4) of PF-04965842 100 mg and 200 mg dose groups was greater than placebo. The estimated proportion of Pruritus NRS 4 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 this JAK1 inhibitor was 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 (AEs) and serious adverse events (SAEs) 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, 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 once daily (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.

Plasma profiling from the [^{14}C]PF-04965842 human mass balance study (B7451008) indicated parent as the most prevalent circulating species (26%), with 3 major and more polar mono-hydroxylated metabolites identified: PF-06471658 (3-hydroxypropyl, 11%), PF-07055087 (2-hydroxypropyl, 12%), and PF-07054874 (pyrrolidinone pyrimidine, 14%).

1.4. Population Pharmacokinetics

Population pharmacokinetic (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. Baseline body weight, race, age and sex were tested as covariates on clearance and did not appear to impact the PK of PF-04965842.

1.5. 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 Investigator's Brochure (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.

1.6. 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 also selected for Phase 3 evaluation. The 100 mg dose is expected to differentiate from the higher dose in terms of expected efficacy, safety and systemic exposure. 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.

Since body weight did not appear to be a significant determinant of PK across the weight range evaluated in the Phase 2b study, adolescents aged 12 years and older weighing 40 kg or more will be administered the same dose as the adults (ie, 100 mg QD and 200 mg QD.) (See Section 1.3 Population Pharmacokinetics). The PK efficacy and safety data collected in adolescents will be monitored periodically by an external data monitoring committee (E-DMC) to ensure acceptable benefit risk for this patient population.

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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 Endpoint:
• To evaluate and compare the maintenance of effect of two doses of PF-04965842 (200 mg and 100 mg once daily (QD)) and placebo in subjects aged 12 and above with moderate to severe atopic dermatitis who respond to initial open-label run-in treatment of 200 mg PF-04965842 QD.	1. Loss of response requiring rescue treatment will be evaluated and compared among groups during the blinded treatment period. Loss of response is denoted as flare and is defined as a loss of at least 50% of the Eczema Area and Severity Index (EASI) response at Week 12 and an Investigator's Global Assessment (IGA) score of 2 or higher.

Secondary Objectives:	Secondary Endpoints:
• To evaluate and compare the effect of PF-04965842 on additional efficacy endpoints and patient-reported outcomes over time in subjects aged 12 years and older with moderate to severe atopic dermatitis; • To assess the efficacy of open label rescue treatment consisting of 200 mg PF-04965842 in combination with topical therapy per standard of care in cases of flare (per protocol definition).	**Key Secondary Endpoint** 1. Loss of response based on an IGA score of 2 or higher. **Clinical Efficacy Assessments:** 1. Response based on the IGA (score of 0 or 1 and a reduction of ≥2 points) at all scheduled time points. 2. Response based on EASI total score (EASI-50, EASI-75, EASI-90, and EASI-100) at all scheduled time points. 3. Response based on achieving ≥4 point improvement in the severity of pruritus Numerical Rating Scale (NRS) from baseline at all scheduled time points. 4. Percent change from baseline in percent Body Surface Area (BSA) at all scheduled time points. 5. Percent change from baseline in SCORing Atopic Dermatitis (SCORAD) subjective assessments of itch and sleep loss at all scheduled time points. 6. Response based on achieving a ≥50% and ≥75% improvement in SCORAD (SCORAD-50, SCORAD-75) from baseline at all scheduled time points. **Clinical Efficacy Assessments in Subjects Requiring Rescue Treatment:** 1. Response based on the IGA at the end of rescue therapy. 2. Response based on the EASI total score at the end of rescue therapy. 3. Response based on achieving ≥4 point improvement in the severity of pruritus Numerical Rating Scale (NRS) at the end of rescue therapy relative to the start of rescue therapy baseline value. 4. Percent change in percent Body Surface Area (BSA) at the end of rescue therapy relative to the start of rescue therapy baseline value. 5. Percent change in SCORAD subjective assessments of itch and sleep loss at the end of rescue therapy relative to the start of rescue therapy baseline value. 6. Response based on achieving a ≥50% and ≥75% improvement in SCORAD (SCORAD-50, SCORAD-75) at the end of rescue therapy relative to the start of rescue therapy baseline value. **Patient-Reported Outcomes in All Subjects**: 1. Response based on achieving PtGA score of clear (0) or almost clear

	(1); and a reduction from baseline of ≥2 points at all scheduled time points (among subjects with a score ≥2 at baseline). 2. Change from baseline in Dermatology Life Quality Index (DLQI) or Children's DLQI (CDLQI) at all scheduled time points. 3. Change from baseline in Hospital Anxiety Depression Scale (HADS) at all scheduled time points. 4. Change from baseline in Patient Oriented Eczema Measure (POEM) at all scheduled time points. 5. Change from baseline in the Pruritus and Symptoms Assessment in Atopic Dermatitis (PSAAD) at all scheduled time points.
Safety Objective:	**Safety Endpoints:**
• To assess the safety and tolerability of PF-04965842 during open label and double blind treatment in subjects aged 12 and over with moderate to severe AD.	• Incidence of treatment emergent adverse events. • Incidence of Serious Adverse Events (SAE)s and Adverse Events (AE)s leading to discontinuation. • The incidence of clinical abnormalities and change from baseline in clinical laboratory values, electrocardiogram (ECG) measurements, and vital signs.
Pharmacokinetic Objective:	**Pharmacokinetic Endpoint**:
• To evaluate the PK of PF-04965842 and its metabolites in subjects aged 12 years and older with moderate to severe atopic dermatitis following 12 weeks of **maintenance** treatment.	1. Population PK characterization in subjects aged 12 years old and above with moderate to severe atopic dermatitis.
CCI [redacted]	[redacted]
[redacted]	CCI [redacted]

AD = Atopic dermatitis; AE = Adverse Event; BSA = Body Surface Area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = Electrocardiogram; HADS = Hospital Anxiety and Depression Scale; IGA = Investigator's Global Assessment; NRS = pruritus numerical rating scale; PK = pharmacokinetics; SCORAD = Scoring Atopic Dermatitis; POEM = Patient-Oriented Eczema Measure; PtGA = Patient Global Assessment; PSAAD = Pruritus and Symptoms Assessment for Atopic Dermatitis; QD = Once Daily; SAE = Serious Adverse Event.

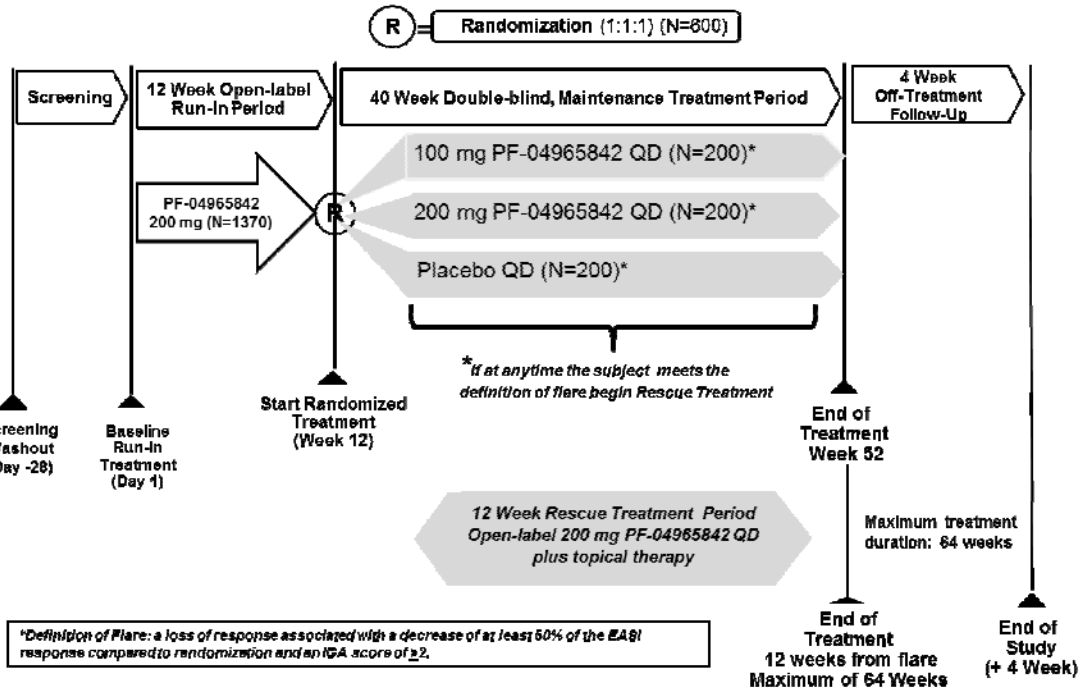
3. STUDY DESIGN

This is a randomized, responder-enriched, double-blind, placebo-controlled, Phase 3 withdrawal trial to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects aged 12 years and older with chronic moderate to severe AD as defined per the inclusion criteria and a body weight ≥40 kg. Adolescent subjects below the legal age of majority (legal adulthood) in the subject's country can be enroll in this study if instructed by the sponsor and approved by the country's regulatory/health authority. If these approvals have not been granted, only subjects ≥ the legal age of majority (legal adulthood) in the subject's country are allowed to enroll. For subjects younger than this, their legally acceptable representative/parent(s) or legal guardian provide written consent and minor children provide assent, according to local regulations and rules regarding ability to give assent and consent. After providing informed consent, subjects are assessed for study eligibility at the screening visit. During the screening period, treatments for AD are washed-out, as applicable, according to eligibility requirements. A baseline (Day 1) visit is to occur within 28 days after the screening visit.

Subjects may be re-screened once if they fail the screening evaluations 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 Monitory (or designee) to determine if re-screening is appropriate.

The trial consists of an open-label run-in period to determine responder status to an initial induction treatment with 200 mg PF-04965842 QD, a randomized, placebo-controlled, double-blinded PF-04965842 maintenance treatment period, and a 4 week untreated follow-up safety period. Subjects who meet the protocol definition of flare during blinded treatment enter an open-label rescue treatment period. A study design schematic is presented in Figure 1.

Figure 1. Study Design Schematic



Enrolled subjects initiate the 12-week, open-label run-in period to identify responders who have a positive clinical response to induction treatment with 200 mg PF-04965842 QD. **Responder criteria** are defined as a) achieving an IGA of clear (0) or almost clear (1) (on a 5-point scale), b) a reduction from IGA baseline of ≥2 points, and c) reaching an EASI-75 response compared to baseline. Baseline is defined as the IGA score and EASI score obtained prior to dosing on Day 1. Subjects meeting all responder criteria may be eligible for randomization. Subjects who do not reach the response threshold required for randomization are declared non-responders after completion of the open label run-in period.

Non-responders are not eligible for randomization in this study but may choose to enroll into the PF-04965842 Long Term Extension (LTE) study B7451015 providing they remain eligible; otherwise, they are permanently discontinued from treatment and enter the 4-week untreated follow-up period in this study.

Responders at the end of the 12-week open-label run-in period enter the 40 week, double-blind, maintenance treatment period in which they are randomized into 1 of 3 treatment arms in a 1:1:1 ratio:

1. 100 mg PF-04965842 QD;
2. 200 mg PF-04965842 QD;
3. Placebo.

All subjects who have started wash-out of AD treatment in the screening period will be allowed to enter the run-in and treatment periods providing all inclusion criteria and none of the exclusion criteria are met. Randomization is stratified by age category, ie, <18 years and ≥18 years. Eligible subjects must have a documented history of inadequate response with topical AD medications or have required systemic therapies for control of their disease.

Medicated topical and/or systemic standard of care therapies are not allowed during the open-label run-in and blinded treatment periods. 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 prescription only product).

Following completion of the 40-weeks of blinded treatment, all subjects are assessed for eligibility to enter the PF-04965842 LTE study B7451015. If a subject discontinues prematurely or is not eligible/willing to participate in B7451015, then the subject enters the 4-week untreated follow-up period.

During the blinded treatment period, subjects meeting the **protocol definition of flare** enter an open-label rescue period during which they receive another 12-week course of 200 mg PF-04965842 QD with topical therapy per local standard of care (SOC). In this study, flare requiring rescue treatment is defined as a loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher. For example, if a subject has a total EASI score of 40 at baseline and a score of 10 at Week 12 (achieving EASI-75 to be a responder at randomization), the EASI response is -30. To meet the definition of flare, the total EASI score for this subject would have to go up by at least 15 (50% of -30) from Week 12, which computes to a total EASI score of at least 25, this in addition to an IGA score of ≥2.

After completing the 12-week rescue period, subjects may enter the LTE study B7451015, if eligible. Subjects discontinuing early from treatment, or who are otherwise ineligible for the LTE study enter a 4 week follow-up period in B7451014.

An investigator can temporarily interrupt dosing for up to a maximum of 28 consecutive days for a subject, for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary. The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the subject during this time-frame. 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.

Laboratory tests are performed throughout this study as detailed in the Schedule of Activities and investigators will follow the instructions for more frequent monitoring in Appendix 4 if the specified laboratory values reach the listed thresholds.

The total study duration if a subject does not flare is 52 weeks (12 weeks open-label treatment +40 weeks blinded treatment). The maximum study duration is up to 64 weeks. This would only be achieved if a subject flared on the last day of the maintenance treatment period (52 weeks +12 weeks rescue). If subjects do not intend to enroll in the LTE study, the above durations are extended by +4 weeks of an untreated follow-up period. A total of approximately 1370 subjects will be enrolled from approximately 218 sites located globally.

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 (that is licensed to practice medicine in the state/province or country where the study is being conducted or by another healthcare practitioner as permitted by local law) before subjects are included in the study. Initial subject eligibility must be confirmed and documented prior to subjects receiving a dose of investigational product (IP).

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, or his/her legally acceptable representative/parent(s) or legal guardian if a minor, have been informed of all pertinent aspects of the study.

2. Male or female subjects of 12 years of age or older, at the time of informed consent and body weight ≥40 kg. Adolescent subjects below the legal age of majority (legal adulthood) in the subject's country will only be enrolled in this study if instructed by the sponsor and approved by the country's regulatory/health authority. If these approvals have not been granted, only subjects ≥ the legal age of majority (legal adulthood) in the subject's country will be enrolled.

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 of AD[43] (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 prescription only product).

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

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

5. Female subjects who are of child-bearing potential (which includes adolescents aged 12 years and older regardless of whether they have experienced menarche) 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 treatment with investigational product;

   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.

6. 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.

7. 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.

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;

   - Suicidal behaviors questionnaire – revised (SBQ-R) total score ≥8 (Appendix 17);

   - Clinically significant depression: patient health questionnaire – 8 items (PHQ-8) total score ≥15 (Appendix 18);

   - 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. Adolescent subjects 12 to <18 years old without documented evidence of having received at least one dose of the varicella vaccine in countries where the vaccine is approved and standard of care or those who do not have evidence of prior exposure to varicella zoster virus (VZV) based on serological testing (ie, varicella zoster virus immunoglobulin G antibody [VZV IgG Ab]) at screening.

8. Subjects who have received prior treatment with any JAK inhibitors.

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 6 weeks of first dose of investigational product:</u>

    - Use of dupilumab.

Within 4 weeks of first dose of investigational product:

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

Within 1 week of first dose of investigational product:

- 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.

Within 72 hours of first dose of investigational product:

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

Note: Corticosteroid inhalers and intranasal sprays are allowed for stable asthma and/or allergic rhinitis patients.

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

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

For China 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) will be excluded. Subjects who are HBV DNA negative or below LLQ may enroll but will have HBV DNA testing repeated at Weeks 12, 28, 40, 52, Rescue Week 12, and early termination from study during any treatment period.

d. 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.

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 (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 time frame prior to the first dose of study medication.

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.

- 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.

- A negative QFT-G or Mantoux/PPD tuberculin skin test 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) or active (acceptable multi-drug regimen) TB infection. If the current incidence rates of multi-drug resistant TB infection in the locale are unavailable, an adequate treatment regimen should be defined as the regimen recommended by the health ministry or expert panel in the locale;

- Chest 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 for adults and recommended for adolescents per local standard/guidelines, 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 ($<500/mm^3$);

    - 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.

23. Have known hypersensitivity to PF-04965842 or to any of the excipients of the study drug.

4.3. Randomization Criteria

Subjects will be enrolled into the open-label, run-in period of the study provided they or their legally acceptable representative/parent(s) or legal guardian if a minor, have signed an informed consent document at screening to participate in the study, have undergone all screening procedures, and have met all inclusion and none of the exclusion criteria for participation in the study at Day 1. Subjects who complete the run-in period and respond to open-label treatment will be randomized to one of three treatment arms and enter the double-blind period of the trial (see Section 3). Randomization is stratified by age category, ie, <18 years and ≥18 years. A computer-generated randomization schedule will be used to assign subjects to the treatment groups using an Interactive Response Technology (IRT).

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.

- On study visit days: Day 1, Weeks 4, 12, 52 and End of Study (EOS) and corresponding visits if a subject enters the rescue treatment period, 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 take the dose of 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, but subjects must not moisturize or apply emollient. Non-medicated emollient is allowed after the visit. Discontinue and avoid using certain medications and treatments (Section 4.2, Section 5.9.2, and Appendix 3).

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

4.4.1. Contraception

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

All female subjects who are of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche, 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 child bearing 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.

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. Adolescent subjects without documented evidence of having received at least one dose of the varicella vaccine or those who are without evidence of previous varicella zoster exposure as confirmed by VZV IgG Ab serological testing are excluded.

4.4.2.2. Guidance Regarding Household Contact Vaccine-Related Exposure

Current routine household contact with children and others who have been vaccinated with a live attenuated vaccine 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 intranasal flu vaccine. Following vaccination with live attenuated 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 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, their legally acceptable representative/parent(s) or legal guardian calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For this study, the investigational products are PF-04965842 and placebo. Enrolled subjects receive 12 weeks induction treatment of 200 mg PF-04965842 QD during an open-label run-in period. At the end of the 12 weeks, subjects responding to treatment as described in Section 3 are randomized into the double-blinded, maintenance treatment period during which they receive 200 mg PF-04965842 QD, 100 mg PF-04965842 QD, or placebo (1:1:1 randomization ratio) for 40-weeks. The last dose of open label run-in treatment (200 mg) is administered at the Week 12 visit; subjects initiate administration of randomized blinded treatment the day after the Week 12 visit. In the event of loss of response during blinded treatment denoted as flare, defined as a loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher, subjects will enter a 12-week open-label rescue period and receive 200 mg PF-04965842 QD with concomitant topical therapy per SOC.

An investigator can temporarily interrupt dosing for up to a maximum of 28 consecutive days for a subject for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary (Appendix 4). The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the subject during this time-frame. 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.

For the purposes of this study, and per International Conference on 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. Rescue Treatment

Subjects will be instructed to contact the site if they experience a significant worsening of their atopic dermatitis, such as a recurrence of pruritus, during the double-blind treatment period. Site staff will determine if the subject should return to the site for an unscheduled (see Section 6.5.1) or regularly scheduled visit (see Section 6.3). Subject will be reminded not to take study drug on the day of the site visit. At the visit (regular or unplanned) the subject will be assessed for flare, defined as a loss of at least 50% of the EASI response at Week 12 and an IGA of 2 or higher. Subjects who meet the definition of flare are to receive rescue treatment that day and enter an open-label rescue period during which they receive 12-weeks of 200 mg PF-04965842 QD with concomitant topical therapy per SOC. See Section 5.2.1 for guidance on topical therapies.

After completing the rescue period, subjects are allowed to enter the LTE study B7451015, if eligible. If a subject discontinues prematurely or is not eligible or willing to participate in B7451015, then the subject enters the 4-week, untreated follow-up safety period. Refer to Schedule of Activities for Rescue Treatment.

Subjects not meeting the definition of flare will continue on their blinded treatment. Physicians may continue to clinically evaluate for flare using the EASI and IGA assessments at their discretion.

5.2.1. Guidelines for Topical Rescue Treatment

Starting on Day 1 of rescue treatment, all subjects will initiate topical treatment and continue a topical regimen as long as needed during the rescue period. Three classes of treatment regimens, specifically, topical corticosteroids, topical calcineurin inhibitors, and a phosphodiesterase inhibitor 4 (PDE-4) inhibitor, are allowed alone or in combination during the rescue period. Investigators are to use these three treatment classes according to their usual practice.

Recommended topical treatments could include:

Topical Corticosteroids:

Topical corticosteroids (TCS) can be used according to the investigator's usual practice. The following use of TCS is suggested for this study:

- Apply medium potency TCS (eg, Triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment) once daily to areas with active lesions.
    - After lesions are under control (clear or almost clear), treat once daily for 7 days, then stop;
    - If lesions return during the rescue period, resume treatment with medium potency TCS, but use the approach described above upon lesion resolution.
- Low potency TCS (ie, hydrocortisone 1% cream) can be used once daily on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.).
- High or super-high potency TCS may be used for lesions persisting or worsening under once daily treatment with medium potency TCS, unless higher potency TCS are considered unsafe.

Subject should be monitored for signs of local or systemic TCS toxicity and stop TCS treatment as necessary. TCS treatment is not expected to last longer than 4 weeks.

Other Topical Treatments:

The use of topical calcineurin inhibitors (eg, tacrolimus, pimecrolimus) or a phosphodiesterase 4 (PDE-4) inhibitor (crisaborole) can be used according to locally approved label at the investigator's discretion based on prior response or intolerance to these medications.

In cases where the desired topical treatment regimen differs significantly from the above guidelines, the Pfizer medical monitor should be contacted for guidance.

5.3. Breaking the Blind

Investigators, subjects and the sponsor study team will be blinded as to treatment group. 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 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.

5.4. Subject Compliance

For self-administration of the investigational product at home, time of dose will be captured and completed by the subject. Subjects will be issued an electronic dosing diary (eDiary) and will be educated to record the time of daily dosing once they have taken the investigational product. When investigational product is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance with the dosing of investigational product will be monitored and verified by delegated site personnel through a combination of 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.

Subjects should take the investigational product from study Day 1 until instructed otherwise by the site staff (eg, temporary interruption to dosing). Investigational product should be taken in the morning whenever it is possible; however at study visit days, subjects are to be instructed to refrain from dosing at home, and are to take the dose in the clinic. Subjects should be instructed that if a dose is inadvertently missed then it should be taken as soon as remembered, but not within 12 hours of the next scheduled dose. The subject should enter a daily record in their eDiary every time they take a dose of investigational product.

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

- Subjects interrupting 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;
- Subjects who have an overall compliance of <80% or >120% between visits

Any deviation from protocol specified dosing should be recorded as a protocol deviation and the investigator or designee is to counsel the subject, legally acceptable representative/parent(s) or legal guardian (if applicable) and ensure steps are taken to improve compliance. In addition, if the compliance deviation reaches the thresholds defined above it should also be recorded as a medication error (see Section 8.4.4).

Note: temporary interruption to dosing per investigator judgement, as described in Appendix 4, will not be considered a protocol deviation or medication error.

5.5. Investigational Product Supplies

5.5.1. Dosage Form(s) and Packaging

PF-04965842 will be provided as 100 mg tablets for oral administration during the open-label run in administration of 200 mg PF-04965842 QD.

Blinded PF-04965842 and placebo will be provided as 100 mg tablets for oral administration. The 100 mg tablets and their placebos will be supplied in separate bottles and labeled according to local regulatory requirements.

When received by the pharmacy, PF-04965842 and placebo will be in containers that will sufficiently blind all site staff to content within the bottles (ie, active versus placebo).

5.5.2. 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 bottles provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the bottles provided throughout the course of dosing and return the bottles to the site at the next study visit.

5.6. Administration

During the open-label induction treatment and rescue treatment periods, subjects will receive 200 mg PF-04965842 daily. Two (2) bottles of investigational product will be dispensed to the subject at each dispensing visit and the subject given clear dosing instructions to take one tablet from each bottle, once daily, preferably in the morning at approximately the same time

of day. Subjects should take the investigational product orally once a day for up to 12 weeks, however, for study visit days, subjects are to be instructed to refrain from dosing at home, and are to take the dose in the clinic on site visit days.

During blinded treatment, subjects will be dispensed two (2) bottles at each dispensing visit and given clear dosing instructions to take one tablet from each bottle, once daily, preferably in the morning, at approximately the same time of day. Subjects should take the investigational product orally once a day for up to 40 weeks, however, for study visit days, subjects are to be instructed to refrain from dosing at home, and are to take the dose in the clinic on site visit days.

Refer to Table 2 for treatment administration and dispensing of investigational product.

Table 2. Investigational Product Administration

Treatment Assignment	During Open-label Run-In and Rescue Treatment - QD Dosing	During Blinded Treatment QD Dosing*
100 mg QD	Not applicable	Bottle A 100 mg - 1 tablet Bottle B Placebo - 1 tablet
200 mg QD	Bottle A 100 mg - 1 tablet Bottle B 100 mg - 1 tablet	Bottle A 100 mg - 1 tablet Bottle B 100 mg - 1 tablet
Placebo	Not applicable	Bottle A Placebo - 1 tablet Bottle B Placebo - 1 tablet

* Bottle A and B designations are used for example purposes only.

Subjects will swallow the investigational product whole, and will not manipulate or chew the medication prior to swallowing. Investigational product may be taken with or without food, other than on study visit days where fasting is required.

An investigator can temporarily interrupt dosing for up to a maximum of 28 consecutive days for a subject, for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary (Appendix 4). The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the subject during this time-frame. 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.

A guidance document with detailed dosing instructions and investigative product (IP) storage instruction will also be provided to subjects to support at-home dosing.

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

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.

For all bottles returned to the investigator by the subject, the investigator will maintain the returned supply until destruction is authorized. Pfizer will provide instructions as to the disposition of any unused investigational product.

5.9. Concomitant Treatment(s)

Subjects must continue to avoid use of medications that have been washed-out prior to enrollment and 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 on Day 1) will be documented as prior medications. Medications taken after the first dose of investigational product on Day 1 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.

Medicated topical therapies ie, 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 prescription only product), are only permitted in this trial during the rescue period.

5.9.1. Permitted Concomitant Medications

The following concomitant AD therapies are permitted during the study:

- Oral antihistamines;
- Topical non-medicated emollient.

The following concomitant medications are permitted during the study:

- Corticosteroid inhalers and intranasal sprays are allowed for stable asthma and/or allergic rhinitis patients;
- Ophthalmic corticosteroids are allowed for patients receiving a stable dose to treat rhinoconjuntivitis;
- Low dose acetyl salicylic acid (≤100 mg QD) is permitted, for the purpose of cardiovascular prophylaxis, at the discretion of the investigator;
- Acetaminophen/paracetamol may be used intermittently (not to exceed 1 g/day);
- Vitamin and mineral supplements of standard potency are allowed in amounts not known to be associated with adverse effects (such as 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 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 Section 4.2, 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. 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 JAK inhibitors are to be excluded from the study.

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

Restrictions on certain vaccinations are described in Section 4.4.2.

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 the Day 1 Baseline visit (Visit 2). 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 12, Week 52, EOS and Rescue Day 1, Rescue Week 4, Rescue Week 12). During the fasting period, subjects should refrain from all food and liquids (water and permitted non-study medications are allowed).

Urine pregnancy test must be performed at every visit, beginning with Day 1 through EOS prior to dosing with the investigational product for female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche.

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

ECGs will be interpreted by a central reader.

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 should be obtained for confirmation. Details for such collection will be provided in the laboratory manual.

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

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, legally acceptable representative/parent(s) or legal guardian (and assent from the subject, as appropriate), in accordance with the procedures described in the Subject Information and Consent in Section 12.3.

Subjects not meeting enrollment criteria (screen failures) for any reason should be contacted quickly to resume/initiate AD treatments.

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; for subjects under the legal age of majority (legal adulthood) in the subject's country, obtain written informed consent from legally acceptable representative/parent(s) or legal guardian and informed assent from the patient (if age appropriate according to local regulations);
- Register subject using the IRT system;
- Collect demography;
- Administer and score the C-SSRS, SBQ-R and PHQ-8. Subjects meeting any of the criteria specified in Exclusion Criterion 2 will be ineligible for 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;

- 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;

- 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;

- 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 topical treatments used for AD;

  - Any previous history of systemic treatment for AD;

  - Any previous history of intolerance/allergy to any drug, regardless of indication;

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

- Obtain weight and height of all subjects;

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

- Conduct complete physical examination;

- Dispense electronic patient reported outcome (ePRO) handheld device and instruct subject in how to use the device. Instruct the subject to begin daily completion of the PSAAD (in selected countries) and pruritus NRS questionnaire;

- Pruritus NRS 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;

- Chest X-ray or other appropriate diagnostic image (ie, computerized tomography [CT] or magnetic resonance imaging [MRI]) may be performed up to 12 weeks prior to Study Day 1. Chest X-rays (posterior-anterior and lateral views) are required for adults and recommended for adolescents as per local guidelines and standard of care. Official reading must be located and available in the source documentation;

- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel, red blood cell (RBC) and white blood cell (WBC) indices, and lymphocyte subsets and markers), urinalysis, serum FSH (post-menopausal women) or serum pregnancy test (women of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche), 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), VZV IgG antibody testing for adolescent subjects who have not received at least one dose of a varicella vaccine, and baseline viral screen sample. For China and Taiwan only: Subjects who are HBsAg negative, HBcAb positive, and HBsAb positive will have reflex testing for HBV DNA.

- QuantiFERON® – TB Gold test (unless performed within 12 weeks of Day 1). If Mantoux PPD tuberculin skin test is performed, 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);

- Conduct clinical evaluations including IGA, 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;

- 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;

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

6.2. Run-In Induction Treatment Period

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

Administer and score the Since Last Visit C-SSRS. Subjects meeting any of the criteria specified in Section 7.5.1 will be ineligible for participation; a risk assessment by a qualified mental health professional (MHP) should be done to determine whether it is safe for the subject to continue to participate in the trial.

- Administer patient-reported outcome (PRO)s including: PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y in select countries), SF-36v2, Acute and FACIT-F (or Peds-FACIT-F). SF-36v2 will be completed by adult subjects only;

- Adolescents 12-17 years of age will not complete the SF-36v2. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y in select countries instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;

- Review PSAAD daily completion (in selected countries) and pruritus NRS daily completion in the eDiary. Review eDiary procedures with subject as necessary;

- Review any changes in the subject's prior and concomitant medications and treatment information;

- Administer Asthma Control Questionnaire (ACQ) test for all subjects with a prior diagnosis of asthma;

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

- Obtain weight (height not required);

- Perform a single 12-lead ECG prior to dosing with investigational product. Clinically significant or exclusionary ECG findings require screen failure;

- Conduct complete physical examination;

- Conduct clinical evaluations including Fitzpatrick Skin Type Assessment, IGA, SCORAD, EASI and BSA (calculated in the EASI);

- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation, RBC/WBC Indices, and lymphocyte subsets and markers), lipid profile, and urinalysis;

- [redacted]

- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;

- Collect sample for viral surveillance: Herpes simplex virus (HSV) HSV-1, HSV-2 and VZV;

- 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 enroll subject into the study;
- Dispense investigational product to the subject;
- Administer first dose of investigational product to subject;
- Assess and record any Adverse Events since the last visit.

6.2.2. Visit 3, Day 8/Week 1 (±1 day)

- Call subject and confirm compliance with daily completion of pruritus NRS 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;
- 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.

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

- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ5D-Y in select countries);
- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y in select countries instead of the EQ-5D-5L;
- Review daily PSAAD completion (in selected countries) and daily pruritus NRS completion in the eDiary. Instruct subject that pruritus NRS will now be completed only at site visits, but the PSAAD will still be completed daily in the eDiary. Review eDiary procedures with subject as necessary;
- Review any changes in the subject's concomitant medications and treatment information;
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Perform a single 12-lead ECG;

- Conduct a targeted physical exam;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation, RBC/WBC indices, lymphocyte subsets and markers) and urinalysis;
- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). 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 investigational product to the subject;
- 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, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ-5D-Y in select countries);
- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y in select countries instead of the EQ-5D-5L;
- Review PSAAD daily completion (in selected countries) and pruritis NRS completion for this visit in the eDiary;
- Perform a single 12-lead ECG;
- Review any changes in the subject's concomitant medications and treatments information;
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Conduct targeted physical examination;

- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC indices, lymphycyte subsets and markers), lipid profile and urinalysis;
- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). 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 investigational product to the subject;
- Dispense investigational product to the subject;
- Assess and record any Adverse Events since the last visit.

6.2.5. Visit 6, Day 43/Week 6 (±3 days)

- Call subject and confirm compliance with daily completion of 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;
- 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.

6.2.6. Visit 7, Day 57/Week 8 (±3 days)

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;
- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ-5D-Y in select countries);
- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y in select countries instead of the EQ-5D-5L;
- Review PSAAD daily completion (in selected countries) and pruritis NRS completion for this visit in the eDiary;
- Review any changes in the subject's concomitant medications and treatments information;
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Perform a single 12-lead ECG;
- Conduct targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC Indices, lymphocyte subsets and markers) and urinalysis;
- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). 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 investigational product to the subject;

- Dispense investigational product to the subject;
- Assess and record any Adverse Events since the last visit.

6.3. Double-Blind Maintenance Treatment Period

6.3.1. Visit 8, Day 85/Week 12 (±3 days) Randomization into Maintenance Treatment

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;
- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y in select countries), SF-36v2, Acute and FACIT-F (or Peds-FACIT-F). SF-36v2 will be completed by adult subjects only;
- Adolescents 12-17 years of age will not complete the SF-36v2. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y in select countries instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;
- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary;
- Obtain weight for all subjects and height for adolescents only (12 to <18 years old);
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Perform a single 12-lead electrocardiogram (ECG);
- Conduct complete physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC Indices, lymphocyte subsets and markers), lipid profile, and urinalysis;
- [redacted]
- For China and Taiwan only: For subjects who had HBV DNA testing at Screening, collect blood sample for repeat HBV DNA testing;

- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;

- Determine if the subject meets all of the **responder criteria for randomization**:

    a. IGA of clear (0) or almost clear (1);

    b. A reduction in IGA from baseline (Day 1) of 2 points or more, and

    c. Reaching an EASI-75 response compared to baseline;

- Review of Inclusion/Exclusion Criteria;

- Randomize subject if all responder and inclusion criteria are met, and none of the exclusion criteria are met;

- Subjects not meeting the responder criteria required for randomization (ie, non-responders) are to be discontinued and enter the 4-week follow-up safety period; or enroll into the PF-04965842 Long Term Extension (LTE) study B7451015 providing they remain eligible;

- 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 any changes in the subject's concomitant medications and treatments information;

- Review eDiary to assess completion;

- Perform drug accountability procedures;

- Administer last dose of open-label run-in period study drug (200 mg);

- Obtain a blood sample for PK analysis at 2.0 hours (±30 min) postdose of open-label study drug (200 mg). For Early Termination (ET) visits, if the subject discontinues before Week 4, do not collect a PK sample. If the ET visit occurs at or after Week 4 and before Week 12, collect a PK sample only if the subject takes the investigational product at the site visit;

- Dispense blinded investigational product to the subject to initiate randomized treatment medication the day after the Week 12 visit;

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

- Administer ACQ test for all subjects with a prior diagnosis of asthma.

6.3.2. Visit 9, Day 113/Week 16 (±3 days)

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;

- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ-5D-Y in select countries);

- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y in select countries instead of the EQ-5D-5L;

- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary;

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

- Perform a single 12-lead ECG;

- Conduct targeted physical examination;

- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC Indices, lymphocyte subsets and markers) and urinalysis;

- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;

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

- Determine if the subject experienced a flare, defined as a loss of at least 50% of the EASI response at Week 12 and an IGA of 2 or higher. If flare, the subject will enter the rescue period (see Section 6.5);

- 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 any changes in the subject's concomitant medications and treatments information;

- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Administer investigational product to the subject;
- Dispense investigational product to the subject;
- Assess and record any Adverse Events since the last visit.

6.3.3. Visit 10, Day 197/Week 28 (±7 days)

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;
- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ-5D-Y in select countries);
- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y in select countries instead of the EQ-5D-5L;
- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary;
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Perform a single 12-lead ECG;
- Conduct targeted physical examination;
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC indices, lymphocyte subsets and markers) and urinalysis;
- For China and Taiwan only: For subjects who had HBV DNA testing at Screening, collect blood sample for repeat HBV DNA testing;
- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);

- Determine if the subject experienced a flare, defined as a loss of at least 50% of the EASI response at Week 12 and an IGA of 2 or higher. If flare, the subject will enter the rescue period (see Section 6.5);

- 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 any changes in the subject's concomitant medications and treatments information;

- Review eDiary to assess completion;

- Perform drug accountability procedures;

- Administer investigational product to the subject;

- Dispense investigational product to the subject;

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

6.3.4. Visit 11, Day 281/Week 40 (±7 days)

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;

- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ-5D-Y in select countries);

- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y in select countries instead of the EQ-5D-5L;

- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary;

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

- Perform a single 12-lead ECG;

- Conduct targeted physical examination;

- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC Indices, lymphocyte subsets and markers) and urinalysis;

- For China and Taiwan only: For subjects who had HBV DNA testing at Screening, collect blood sample for repeat HBV DNA testing;

- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;

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

- Determine if the subject experienced a flare, defined as a loss of at least 50% of the EASI response at Week 12 and an IGA of 2 or higher. If flare, the subject will enter the rescue period (see Section 6.5);

- 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 any changes in the subject's concomitant medications and treatments information;

- Review eDiary to assess completion;

- Perform drug accountability procedures;

- Administer investigational product to the subject;

- Dispense investigational product to the subject;

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

6.3.5. Visit 12, Day 365/Week 52 (±3 days) End of Treatment (EOT) or Early Termination (ET)

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;

- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y in select countries), SF-36v2, Acute and FACIT-F (or Peds-FACIT-F). SF-36v2 will be completed by adult subjects only;

- Adolescents 12-17 years of age will not complete the SF-36v2. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y in select countries instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;

- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary;
- Obtain weight for all subjects and height for adolescents only (12 to <18 years old);
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Perform a single 12-lead ECG;
- Conduct a complete physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Determine if the subject experienced a flare, defined as a loss of at least 50% of the EASI response at Week 12 and an IGA of 2 or higher. If flare, the subject will enter the rescue period (Section 6.5);
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC indices, lymphocyte subsets and markers), lipid profile, and urinalysis;
- [redacted]
- For China and Taiwan only: For subjects who had HBV DNA testing at Screening, collect blood sample for repeat HBV DNA testing;
- Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low risk for Tuberculosis (ie, >10/100,000 prevalence) will undergo tuberculosis (TB) testing. If so, ensure testing is performed as per Section 7.3.4. A negative test result for tuberculosis is required for ongoing eligibility for study participation;
- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;
- Subjects who completed the 40 weeks of blinded treatment without experiencing flare will be assessed for eligibility to enter LTE study B7451015. Subjects who are not eligible or are not interested are to continue in the 4-week, untreated safety follow-up period;
- 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 any changes in the subject's concomitant medications and treatments information;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Administer last dose of investigational product as part of the blinded maintenance period to the subject;
- Assess and record any Adverse Events since the last visit;
- Administer ACQ test for all subjects with a prior diagnosis of asthma.

6.4. Follow-up Visit

6.4.1. Visit 13, 4 Weeks Post End of Treatment/Early Termination - End of Study (±3 days)

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;
- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y in select countries), SF-36v2, Acute and FACIT-F (or Peds-FACIT-F). SF-36v2 will be completed by adult subjects only;
- Adolescents 12-17 years of age will not complete the SF-36v2. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y in select countries instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;
- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary;
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Perform a single 12-lead ECG;
- Conduct targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC Indices, lymphocyte subsets and markers), lipid profile, and urinalysis;

- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche);
- Assess adherence to contraception and applicable lifestyle requirements (Section 4.4);
- Review any changes in the subject's concomitant medications and treatments information;
- Assess and record any Adverse Events since the last visit;
- Administer ACQ test for all subjects with a prior diagnosis of asthma.

6.5. Rescue Treatment Period

Subjects will be instructed to contact the site if they experience a significant worsening of their atopic dermatitis, such as a recurrence of pruritus, during the double-blind treatment period. Site staff will determine if the subject should return to the site for an unscheduled (see Section 6.5.1) or regularly scheduled visit (see Section 6.3). At the visit (regular or unplanned) the subject will be assessed for flare, defined as a loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher. Subjects who meet the definition of flare are to receive rescue treatment and enter an open-label rescue period during which they receive 12-weeks of 200 mg PF-04965842 QD with concomitant topical therapy per SOC. See Section 5.2.1 for guidance on topical therapies.

After completing the rescue period, subjects are allowed to enter the LTE study B7451015, if eligible. If a subject discontinues prematurely or is not eligible or willing to participate in B7451015, then the subject enters the 4-week, untreated follow-up safety period. Refer to Schedule of Activities for Rescue Treatment.

Subjects not meeting the definition of flare will continue on their blinded treatment. Physicians may continue to clinically evaluate for flare using the EASI and IGA assessments at their discretion.

6.5.1. Rescue Treatment - Flare Occurring at an Unplanned Visit (Rescue Visit 1, Day 1/Week 0 (±3 days))

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;
- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y in select countries), SF-36v2, Acute and FACIT-F (or Peds-FACIT-F). SF-36v2 will be completed by adult subjects only;
- Adolescents 12-17 years of age will not complete the SF-36v2. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y in select countries instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;

- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary. Instruct the subject that the pruritis NRS completion will be collected daily in the eDiary from Days 1-15 during rescue treatment and then only on study visit days at the investigator site thereafter. PSAAD will be completed daily (in selected countries) in the eDiary from Day 1 through the EOS visit during rescue treatment. Review eDiary procedures with subject as necessary;

- Obtain weight for all subjects and height for adolescents only (12 to <18 years old);

- Conduct targeted physical examination;

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

- Perform a single 12-lead ECG;

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

- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation, RBC/WBC Indices, lymphocyte subsets and markers), lipid profile, and urinalysis;

- [redacted]

- Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low risk for Tuberculosis (ie, >10/100,000 prevalence) will undergo tuberculosis (TB) testing. If so, ensure testing is performed as per Section 7.3.4. A negative test result for tuberculosis is required for ongoing eligibility for study participation;

- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). A negative urine pregnancy test must be obtained prior to dosing with the investigational product;

- Review any changes in the subject's prior and concomitant medications and treatment information;

- 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 investigational product to the subject;
- Dispense investigational product to the subject;
- Assess and record any Adverse Events since the last visit;
- Administer ACQ test for all subjects with a prior diagnosis of asthma.

6.5.2. Rescue Treatment – Visit 2, Day 8/Week 1 (±1 day)

- Call subject and confirm compliance with daily completion of pruritus NRS 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;
- 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.

6.5.3. Rescue Treatment – Visit 3, Day 15/Week 2 (±1 day)

- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ-5D-Y in select countries);
- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y in select countries instead of the EQ-5D-5L;
- Review daily PSAAD completion (in selected countries) and daily pruritus NRS completion in the eDiary; Instruct subject that pruritus NRS will now be completed only at site visits, but the PSAAD will still be completed daily in the eDiary. Review eDiary procedures with subject as necessary;
- Review any changes in the subject's concomitant medications and treatment information;
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Perform a single 12-lead ECG;
- Conduct a targeted physical exam;

- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation, RBC/WBC indices, lymphocyte subsets and markers) and urinalysis;
- Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low risk for Tuberculosis (ie, >10/100,000 prevalence) will undergo tuberculosis (TB) testing. If so, ensure testing is performed as per Section 7.3.4. A negative test result for tuberculosis is required for ongoing eligibility for study participation;
- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). 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 investigational product to the subject;
- Assess and record any Adverse Events since the last visit.

6.5.4. Rescue Treatment – Visit 4, Day 29/Week 4 (±2 days)

- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ-5D-Y in select countries);
- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y in select countries instead of the EQ-5D-5L;
- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary. Review eDiary procedures with subject as necessary;
- Review any changes in the subject's prior and concomitant medications and treatment information;
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);

- Perform a single 12-lead electrocardiogram (ECG);
- Conduct targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation pane, RBC/WBC indices, lymphocyte subsets and markers), lipid profile and urinalysis;
- Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low risk for Tuberculosis (ie, >10/100,000 prevalence) will undergo tuberculosis (TB) testing. If so, ensure testing is performed as per Section 7.3.4. A negative test result for tuberculosis is required for ongoing eligibility for study participation;
- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). 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 investigational product to the subject;
- Dispense investigational product to the subject;
- Assess and record any Adverse Events since the last visit.

6.5.5. Rescue Treatment – Visit 5, Day 43/Week 6 (±3 days)

- Call subject and confirm compliance with daily completion of 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;

- 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.

6.5.6. Rescue Treatment – Visit 6, Day 57/Week 8 (±3 days)

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;

- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ-5D-Y in select countries);

- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y in select countries instead of the EQ-5D-5L;

- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary. Review eDiary procedures with subject as necessary;

- Review any changes in the subject's prior and concomitant medications and treatment information;

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

- Perform a single 12-lead ECG;

- Conduct targeted physical examination;

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

- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC indices, lymphocyte subsets and markers) and urinalysis;

- Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low risk for Tuberculosis (ie, >10/100,000 prevalence) will undergo tuberculosis (TB) testing. If so, ensure testing is performed as per Section 7.3.4. A negative test result for tuberculosis is required for ongoing eligibility for study participation;

- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche). 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 investigational product to the subject;

- Dispense investigational product to the subject;

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

6.5.7. Rescue Treatment - Visit 7, Day 85/Week 12 (±3 days) End of Treatment (EOT)/Early Termination (ET)

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;

- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y in select countries), SF-36v2, Acute and FACIT-F (or Peds-FACIT-F). SF-36v2 will be completed by adult subjects only;

- Adolescents 12-17 years of age will not complete the SF-36v2. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y in select countries instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;

- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary. Review eDiary procedures with subject as necessary;

- Review any changes in the subject's concomitant medications and treatments information;

- Obtain weight for all subjects and height for adolescents only (12 to <18 years old);

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

- Perform a single 12-lead ECG;
- Conduct a complete physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC indices, lymphocyte subsets and markers), lipid profile, and urinalysis;
- For China and Taiwan only: For subjects who had HBV DNA testing at Screening, collect blood sample for repeat HBV DNA testing;
- Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low risk for Tuberculosis (ie, >10/100,000 prevalence) will undergo tuberculosis (TB) testing. If so, ensure testing is performed as per Section 7.3.4. A negative test result for tuberculosis is required for ongoing eligibility for study participation;
- [redacted]
- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche);
- 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;
- If the subject completed the 12 weeks of rescue treatment they will be assessed for eligibility to enter LTE study B7451015. Subjects who are not eligible or unwilling to participate are to continue in the 4-week, untreated safety follow-up period;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Administer last dose of investigational product as part of the rescue treatment period to the subject;
- Assess and record any Adverse Events since the last visit;
- Administer ACQ test for all subjects with a prior diagnosis of asthma.

6.5.8. Rescue Treatment - Visit 8, Follow-up Visit and End of Study (±3 days)

- Administer and score the Since Last Visit C-SSRS. For subjects meeting any of the criteria specified in Section 7.5.1 a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial;
- Administer PROs including: PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y in select countries), SF-36v2, Acute and FACIT-F (or Peds-FACIT-F). SF-36v2 will be completed by adult subjects only;
- Adolescents 12-17 years of age will not complete the SF-36v2. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y in select countries instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;
- Review PSAAD daily completion (in selected countries) and pruritus NRS completion for this visit in the eDiary;
- Review any changes in the subject's concomitant medications and treatments information;
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest);
- Perform a single 12-lead ECG;
- Conduct a targeted physical examination;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel, RBC/WBC indices, lymphocyte subsets and markers), lipid profile, and urinalysis;
- Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low risk for Tuberculosis (ie, >10/100,000 prevalence) will undergo tuberculosis (TB) testing. If so, ensure testing is performed as per Section 7.3.4. A negative test result for tuberculosis is required for ongoing eligibility for study participation;
- Urine pregnancy test (female subjects of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche);
- Assess adherence to contraception and applicable lifestyle requirements (Section 4.4);
- Review eDiary to assess completion;

- Assess and record any Adverse Events since the last visit;
- Administer ACQ test for all subjects with a prior diagnosis of asthma.

6.6. 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 (legally acceptable representative/parent(s) or legal guardian, as applicable) 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 after their last dose, 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 (legally acceptable representative/parent(s) or legal guardian, as applicable) specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects (legally acceptable representative/parent(s) or legal guardian, as applicable) 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 (legally acceptable representative/parent(s) or legal guardian, as applicable) 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 with an End of Study visit 4 weeks after End of Treatment visit. 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 including adolescents aged 12 years and older regardless of whether they have experienced menarche, 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 visit 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 until completion of the 4 week untreated follow-up period.

CCI

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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 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 drug, 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 (lbs. or kg) will be measured and recorded in the source document at the screening visit and at various time points, see Schedule 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 Schedule of Activities.

7.3.3. Chest X-Ray

Chest radiograph (posterior-anterior and lateral views) are required for adults and recommended for adolescents (as per local guidelines and standard of care) 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. 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 QuantiFERON®-TB Gold In-Tube test cannot be performed, or if the results cannot be determined by the reference laboratory to be either positive or negative, 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 for all adults, and recommended for adolescents according to local guidelines and standard of care and/or in countries with a high incidence rate of TB. Following one year of total exposure to study drug since the last TB test, all subjects in regions which are above a low-risk for Tuberculosis (ie, >10/100,000 incidence) will undergo tuberculosis testing.

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.

Purified Protein Derivative (PPD) Test

If the QuantiFERON®-TB Gold In-Tube test 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

Single 12-lead ECGs should be collected at times specified in the Schedule of Activities using a machine provided by the central reader. ECG readings will be performed 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 and prior to any blood collection.

The screening ECG values will serve as each subject's baseline values. Subjects with clinically significant ECG abnormalities at screening are to be excluded from the study.

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 or 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 herpes simplex virus (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 on the C-SSRS, SBQ-R and 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. Such subjects may be rescreened, at a later date, if they were evaluated and treated as appropriate, and the repeat scores permit inclusion.

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 will administer the C-SSRS to all subjects at screening and score immediately to assess the subject's eligibility based on the answers.

At post-baseline visits, if there are "yes" answers on items 4, 5 or on any behavioral question of the Since Last Visit C-SSRS (Appendix 16), a risk assessment by a qualified MHP should be done to determine whether it is safe for the subject to continue to participate in the trial.

Subjects who have recurrent suicidal ideation and behavior (SIB) during a clinical trial should be discontinued from the study and treated appropriately. If a study subject endorses a 4 or 5 on the ideation subscale or any behavioral item of the C-SSRS on more than 2 occasions and is confirmed to have active SIB on both occasions by a risk assessment conducted by a qualified MHP, then the subject should be discontinued from the study and treated appropriately. These subjects should be discussed with the Pfizer Medical Monitor.

7.5.2. Suicidal Behaviors Questionnaire-Revised (SBQ-R)

The Suicidal Behaviors Questionnaire-Revised (Appendix 17) is a patient-reported questionnaire consisting of 4 items to assess suicidal ideation, suicide attempts, threat of suicidal behavior, and likelihood of suicidal behavior. At the Screening Visit, if SBQ-R total score ≥8, the subject will not be included in the study.[40] Site staff will administer the SBQ-R to all subjects at screening and score immediately.

7.5.3. Patient Health Questionnaire – 8 items (PHQ-8)

The Patient Health Questionnaire – 8 items (Appendix 18) 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.[41] Site staff will 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 estimated for this study depends upon subject response:

- Total blood volume for non-responders completing 12 weeks is approximately 113 mls;
- Total blood volume for responders completing 52 weeks is approximately 166 mls;
- Maximum total blood volume estimated for a responder that flares on the last day of the maintenance period and completing 64 weeks is approximately 198 mls.

An additional 5 mls is added to these volumes for adolescents requiring VZV testing.

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 12, Week 52, and EOS for subjects who complete double-blind treatment. For subjects that enter the rescue period, fasting labs are required at Rescue Day 1, Week 4, Week 12, and EOS. All other labs do not require fasting.

Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Other
Hemoglobin	BUN and Creatinine	pH	HIV[a]
Hematocrit	Creatine Phosphokinase	Glucose (qual)	HBsAg[a]
RBC indices	Glucose	Protein (qual)	HBcAb[a]
MCH	Na+, K+, Cl- ,Ca++	Blood (qual)	HBsAb[b]
MCHC	Total CO2 (Bicarbonate)	Ketones	HCVAb[a]
MCV	AST, ALT	Nitrites	HCV RNA[b]
RBC Morphology	GGT	Leukocyte esterase	VZV IgG Ab[g]
RBC count	Total, Indirect & Direct Bilirubin	Microscopy and/or culture[d]	Serum FSH (post-menopausal women) or Pregnancy Test [a, c]
Reticulocyte count	Alkaline phosphatase		
Platelet count	Lactate dehydrogenase		
WBC count with differential	Uric acid		Urine pregnancy test [c]
Total neutrophils (%, Abs)	Albumin		QFT-G or PPD (if applicable)[e]
Eosinophils (%, Abs)	Total protein		HSV-1, HSV-2, VZV
Monocytes (%, Abs)	Lipid Profile Panel [f]		Lymphocyte Subsets (Lymphocyte Markers)
Basophils (%, Abs)	Total cholesterol		Total T cells (CD3+)
Lymphocytes (%, Abs)	LDL		CD4+ T cells (CD3+CD4+)
Coagulation Panel	HDL		CD8+ T cells (CD3+CD8+)
Activated Partial Thromboplastin Time	Triglycerides		NK cells (CD3-CD16+CD56+)
Prothrombin Time/International Normalized Ratio (PT/INR)			B cells (CD3-CD19+)
			HBV DNA[h]

[a] At Screening only. HIV testing will be performed for all subjects.

[b] HBsAb reflex testing only if HBsAg negative but HBcAb positive. HCV RNA is reflex testing only if HCVAb is positive.

[c] Pregnancy testing for women of childbearing potential including adolescents aged 12 years and older regardless of whether they have experienced menarche; serum FSH for women 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.

[f] Lipid Profile Panel requires at least an 8 hour fast. Lipid profile panel will be completed at Day 1, Week 4, Week 12, Week 52, and EOS, and will include total cholesterol, LDL, HDL, and triglycerides. For subjects receiving rescue therapy, a lipid profile will be completed at rescue Day 1, Weeks 4, 12 and EOS.

[g] Only for adolescents who do not have documentation of at least one dose of varicella vaccine.

[h] For China and Taiwan only: Subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Subjects who have HBV DNA above the lower limit of quantification (LLQ) will be excluded. Subjects who are HBV DNA negative or below LLQ may enroll but will have HBV DNA testing repeated at Weeks 12, 28, 40, 52, Rescue Week 12, and early termination from study during any treatment period.

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. Subjects who are positive for HIV will be screen-failed. 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).

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 and Taiwan only: Subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Subjects who have HBV DNA above the LLQ will be excluded. Subjects who are HBV DNA negative or below LLQ may enroll but will have HBV DNA testing repeated at Weeks 12, 28, 40, 52, Rescue Week 12, and early termination from study during any treatment period.

  A single positive 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 8.1.4.1.

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. Varicella Zoster Virus (VZV) IgG Antibody (Ab) Testing

Adolescent subjects without documented evidence of having received at least a single dose of the varicella vaccine in countries where the varicella vaccine is approved and standard of care will be tested for varicella zoster virus IgG Ab as described in the lab manual. Subjects that lack evidence of prior exposure to varicella zoster virus based on serological VZV IgG Ab testing are excluded.

7.6.2.3. Baseline Viral Screen

A serum sample will be collected at baseline but analyzed only if the subject has suspected varicella or herpes zoster. In that event, the sample would be analyzed for HSV1, HSV2 and VZV. 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.

7.7. Efficacy Assessments

7.7.1. 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 dermatology clinical trials may be permitted to perform the clinical evaluations of atopic dermatitis when designated by the primary site Investigator. The evaluator must receive and document protocol specific and applicable efficacy assessment scales training prior to performing these evaluations. **To 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.

7.7.2. Investigator's Global Assessment (IGA)

The IGA of atopic dermatitis is scored on a 5-point scale (0-4), reflecting a global consideration of 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 3. The assessment will be a static evaluation without regard to the score at a previous visit.

Table 3. 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.

7.7.3. 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 4.

Table 4. 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 5). When measuring, the handprint unit refers to the size of each individual subject's hand with fingers in a closed position.

Table 5. 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 6).

Table 6. 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 7).

Table 7. 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.

7.7.3.1. 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 5). 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%.

7.7.4. Scoring Atopic Dermatitis (SCORAD)

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

Extent (A, maximum score of 100%)

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

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

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

Severity (B, maximum score of 18)

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

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

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

Subjective Symptoms (C, maximum score of 20)

Subjective symptoms, ie, itch and sleep loss, are each scored by the 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. Patient-Reported Outcomes (PROs)

Subjects will complete PROs and AD clinical assessments at the clinic in the order they are presented in the electronic tablet (ePRO device). All PROs and AD clinical assessments should be completed prior to other clinical activities and investigator product administration. Results of clinical assessment of AD should not be shared with the subject until they have completed their PROs. The PROs should be checked for completeness by the study site staff before proceeding with other steps of the clinical visit procedures. 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 and PSAAD on a daily basis. 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.

Some examples of the validated paper versions of Patient Reported Outcomes instruments are included in the Appendices of this protocol. In instances where an electron 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.

7.8.1. 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).[44] 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). This item will be administered to all subjects. Subjects will enter pruritus NRS assessment into an eDiary. Severity of pruritus score as it is assessed on the day of the baseline visit will be included in the evaluation of Inclusion Criteria 3.

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). This item will be administered to all subjects. Subjects will enter pruritus NRS assessment into an eDiary. Frequency of pruritus will not be included in the evaluation of Inclusion Criteria 3.

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

7.8.2. 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 7). 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. This single-item scale will be administered to all subjects.

7.8.3. EuroQol Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) and EuroQol Quality of Life 5-Dimension Youth Scale (EQ-5D-Y in select countries)

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 8).[19-22] 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.[19,21,23,24,25] A version of the instrument specifically developed and validated for use by youths age 12 through 17 years is called the EQ-5D-Y and is only available in select countries.[26,27,28]

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.[21,20,23,25] 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 visual analogue scale (VAS).[22,28] The EQ-5D-3L was used previously in AD studies, including the dupilumab trials, to measure utilities.[29-32]

7.8.4. Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI)

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 9).[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. A version of the instrument specifically developed and validated for use by adolescents from age 12 to 17 is called the CLDQI.[34] The DLQI should be completed as per Schedule of Activities.

7.8.5. Patient-Oriented Eczema Measure (POEM)

The POEM is a validated 7-item PRO measure used to assess the impact of AD recalled over the past week (Appendix 10). This instrument is appropriate for use by subjects aged 12 and older.[35,36] The POEM should be completed as per Schedule of Activities.

7.8.6. Hospital Anxiety and Depression Scale (HADS)

The HADS is a validated 14-item PRO measure used to assess states of anxiety and depression over the past week (Appendix 11). The instrument has been validated for use by adolescents aged 12 and older.[37] The HADS should be completed as per Schedule of Activities.

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

The PSAAD is a daily patient reported symptom diary. The preliminary version (Appendix 12) 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. Four additional items were added for exploratory and psychometric validation purposes (Sleep & Usual Activities Questions and Patient Global Impression of Severity [PGIS] and Patient Global Impression of Change Questions [PGIC]). The PSAAD is an electronic PRO that was developed through concept elicitation and cognitive debriefing in AD patients ages 12 to 67; the questionnaire utilized in B7451006 as an exploratory endpoint will be implemented in this study with any refinements and changes assessed as a result of the preliminary psychometric validation. 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 (only in selected countries) as per Schedule of Activities on an eDiary.

7.8.8. Short Form-36 Health Survey, Version 2, Acute (SF-36v2, Acute)

The SF-36v2 is a validated generic health status measure (Appendix 13). It measures 8 general health domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. These domains can also be summarized as physical and mental component summary scores. The use of this scale is restricted to adult subjects and not for adolescents to complete.[38] SF-36v2 will be completed by adult subjects only. Adolescents 12-17 years of age will not complete this assessment.

7.8.9. FACIT Fatigue Scale (FACIT-F) and Pediatric FACIT-F (Peds-FACIT-F)

The Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT–F) is a validated subject completed questionnaire consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better overall health status (less fatigue) (Appendix 14).[39] The FACT-F should be completed as per Schedule of Activities. FACIT-F will be completed by adult subjects only. Adolescents 12-17 years of age will complete the Pediatric FACIT-F (Peds-FACIT-F) instead of the FACIT-F.[42]

7.8.10. Asthma Control

Asthma control for all subjects with asthma should be assessed at times specified in the Schedule of Activities using the Asthma Control Questionnaire (ACQ; Appendix 19). The ACQ measures the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. The ACQ has 5 questions (the top scoring 5 symptoms). Subjects are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment). The questions are equally weighted and the ACQ score is the mean of the 5 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).[16,17,45]

7.9. Pharmacokinetics

7.9.1. Plasma for Analysis of PF-04965842 and Metabolites

During the study, blood samples (8 mL) to provide minimum 3.2 mL of plasma for PK analysis will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) for measurement of plasma concentration of PF-04965842 and its metabolites PF-06471658, PF-07055087, and PF-07054874 at times specified in the Schedule of Activities. The actual date and time (24-hour clock time) of each sample will be recorded.

A blood sample for PK analysis will be collected at 2.0 hours (±30 min) postdose at Week 12.

All efforts will be made to obtain the PK sample at the exact nominal time relative to dosing. The exact time of the sample collection is to be noted on the source document and data collection tool (eg, CRF). A sample obtained outside the windows specified in the Schedule of Activities will be considered a protocol deviation. For ET visits, if the subject discontinues before Week 4 do not collect the PK sample. If the ET visit occurs after Week 4, collect the PK sample only if the subject takes the investigational product at the site visit.

- The plasma will be stored in appropriately labeled screw-capped polypropylene tube at approximately -20°C within 1 hour of collection.
- Further details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- The PK sample must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.
- As part of understanding the PKs of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.9.2. Shipment of Pharmacokinetic Samples

The central laboratory will provide collection materials and directions for packaging and shipment of samples and will forward samples to the contract analytical laboratory. Refer to the central lab vendor manual for further information.

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 time frame 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.

Any clinically significant worsening of AD is considered an AE regardless of meeting the definition of flare.

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, legally acceptable representative/parent(s) or legal guardian, if applicable. In addition, each study subject, legally acceptable representative/parent(s) or legal guardian, if applicable, 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, legally acceptable representative/parent(s) or legal guardian, if applicable, 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 5.4 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**.

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 of 600 subjects with 200 receiving PF-04965842 200 mg QD, 200 receiving PF-04965842 100 mg QD, and 200 receiving placebo (1:1:1 randomization) will provide 94% power to detect a ratio of median time to flare of at least 1.5 times between either dose of PF-04965842 (200 mg or 100 mg) and placebo. The Type I error rate is set at 5% (2-sided). Assuming based on prior data, that about 44% of subjects would meet the protocol-defined criteria to be a responder at Week 12, approximately 1370 subjects would need to enter the open label run-in period of the study to ensure that 600 subjects are available for randomization.

9.2. Efficacy Analysis

9.2.1. Analysis Sets

The statistical objective of the study is to characterize the loss of response with each randomized group after achieving response at Week 12 following open-label treatment with 200 mg PF-04965842 QD.

The primary analysis population for efficacy data will be the Full Analysis Set (FAS-RA) defined as all randomized subjects who are dispensed at least one dose of study medication. This is a responder-enriched population who are eligible to enter the randomized, double-blind period of the study. All analyses will be reported by treatment regimen/sequence. 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-RA who had no major protocol violations. Major protocol violations would consist of not meeting inclusion criteria or meeting an exclusion crtieria or not having taken the correct randomized treatment for at least 80% of the assigned amount or having taken a prohibited concomitant medication (as detailed in Section 5.9.2) 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.

An additional subgroup of subjects who have received at least one dose of rescue treatment (following a protocol-defined flare during the randomized, double-blind period) will also be defined as the FAS-RE subgroup. In addition to these subgroups, analyses will also be performed for all subjects participating in the open-label run-in period (defined as the FAS-OL subgroup).

9.2.2. Testing Procedure for Multiple Comparisons

There are six key hypotheses to be tested for each pairwise comparison between two PF-04965842 doses (200 mg QD and 100 mg QD) and placebo, for the primary and key secondary endpoints. For these hypotheses, the familywise Type-I error rate will be strongly controlled at 5% using a sequential, gatekeeping procedure.

The procedure will first test the hypothesis of no difference for the primary endpoint between 200 mg QD and placebo at 5% level of significance. If this hypothesis is rejected, statistical significance will be assessed for the hypothesis of no difference for the key secondary endpoint between 200 mg QD and placebo at 5% level of significance. If rejected, the procedure will continue with the hypothesis of no difference for the primary endpoint between 100 mg QD and placebo and if rejected, continuing with the hypothesis of no difference between 100 mg QD and placebo for the key secondary endpoint. Finally, if all the above hypotheses are rejected, the procedure will continue with the hypothesis of no difference between 200 mg QD and 100 mg QD for the primary endpoint and if rejected, continuing with the hypothesis of no difference between 200 mg QD and 100 mg QD for the key secondary endpoint. All tests will be conducted at 5% level of significance. Statistical significance for subsequent tests will not be formally claimed if the previous hypothesis has not been rejected.

Hypotheses for all other endpoints not described here are to be tested at the nominal 5% level, without making adjustments for multiple comparisons.

9.2.3. Analysis of the Primary and Key Secondary Endpoints

The primary analyses for both endpoints will be based on the FAS-RA subset. Secondary analyses will be based on the PPAS. For analysis of the primary and key secondary endpoints, a combination of graphical and analytical methods will be used. The time (in weeks) to protocol-defined flare will be used to evaluate the primary endpoint while the time (in weeks) to achieve an IGA score of ≥2 will be used to evaluate the key secondary endpoint. Subjects who do not report an event (ie protocol-defined flare or IGA ≥2) or discontinue the study during the double-blind randomized period will have their time to event censored at their last known visit in this period. Kaplan-Meier curves will be used to display the time to event and report the median time to event (and its 95% confidence interval) among the three randomized groups. The log-rank test will be used to compare these curves. Proportions of subjects with an event and confidence intervals will also be reported by randomized group.

9.2.4. Analysis of Secondary Endpoints

In general, binary endpoints (such as EASI-50, EASI-90 or the proportion of subjects achieving ≥4 point improvement in severity of pruritus NRS measure) will be analyzed using the (Cochran-Mantel-Haenszel) test adjusted by randomization strata (age groups) and baseline disease severity. The difference between treatment groups in the proportion of subjects achieving a response 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 a non-responder for endpoints

after withdrawal. In addition, a subject in the FAS-RA subset who receives rescue treatment due to protocol-defined flare will be considered a non-responder.

For continuous endpoints, such as percent change from baseline in the EASI total score and BSA or change from baseline in SCORAD, PSAAD, DLQI/CDLQI, POEM, HADS, and change from baseline in the pruritus severity using the NRS measure, a mixed-effect model with repeated measures (MMRM) will be used. This model will include the factors (fixed effects) for treatment group, randomization strata (age groups), and baseline disease severity, visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, differences between groups will be tested using estimates from the MMRM model.

For all binary endpoints, missing data will be handled by considering subjects who withdraw or randomized subjects receiving rescue treatment as non-responders. No imputations will be made for continuous data and missing data will be considered to be MAR.

In general all secondary endpoints will be analysed for the FAS-RA subset. For the subjects requiring rescue therapy (FAS-RE subset), the response achieved at the end of the rescue period will be assessed in relation to the start of the rescue period. In addition to these two analysis sets, secondary endpoints will also be summarized for all subjects participating in the open-label run-in period (FAS-OL subset).

Hypotheses for all relevant secondary endpoints will be tested at the nominal 5% level of significance, without adjustments for multiple comparisons.

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 or meets other criteria that require it to be classified as a serious advere event, will be summarized;
- 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.

Subject listings will also be produced for these safety endpoints.

All safety data will be summarized separately for each of the following key subgroups:

- Subjects who have received at least one dose of study drug during the open label run-in period. These subjects would have a cumulative exposure to 200 mg QD PF-04965842 of up to 12 weeks;
- Subjects who have been randomized and have received at least one dose of randomized study treatment. Summaries of safety data will be reported for these subjects by randomized treatment regimen;
- Subjects who meet loss of response criteria during the randomized, double-blind period and receive at least one dose of rescue treatment. Summaries of safety data will be reported for these subjects by randomized treatment regimen.

9.4. Analysis of Pharmacokinetic Endpoints

Population PK data for PF-04965842 will be summarized through appropriate data tabulations, descriptive statistics, and graphical presentation. A population PK model will be developed for the purpose of estimating PK parameters. Additional details of the methodology will be captured in a separate modeling plan and the results will also be reported separately.

9.5. 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 efficacy, safety and PKs 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.

9.6. 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.

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 (CRF)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF/DCT 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/DCT is required and should be completed for each included subject. The completed original CRFs/DCTs 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/DCTs 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/DCTs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs/DCTs are true. Any corrections to entries made in the CRFs/DCTs 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/DCTs must match the data in those charts.

In some cases, the CRF/DCT 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/DCT, and for which the CRF/DCT 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/DCTs and hospital records), all original signed informed consent/assent documents, copies of all CRFs/DCTs, 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/assent 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 laws.

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/assent 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/assent 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, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, 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, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, 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.

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

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s), or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent 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.

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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.

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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
ACQ	Asthma Control Questionnaire
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 0 to infinity
AUC_{last}	rea under the curve from 0 to last
CCI	[redacted]
BCG	Bacille Calmette Guérin
BID	twice a day
BP	blood pressure
BSA	body surface area
C_{max}	maximum concentration
CD	Cluster of differentiation
CDLQI	Children's Dermatology Life Quality Index
CFB	change from baseline
CI	confidence interval
CL/F	clearance/fraction of dose absorbed
CO2	carbon dioxide
CK	creatine kinase
CRF	case report form
CSA	clinical study agreement
CsA	cyclosporin A
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
CYP	Cytochrome P
DCT	Data Collection Tool
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index
EBV	Epstein Barr virus
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency

Abbreviation	Term
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
ePRO	electronic Patient Reported Outcome
EQ-5D-5L	EuroQol Quality of Life 5-Dimension 5-Level Scale
EQ-5D-Y	EuroQol Quality of Life 5-Dimension Youth Scale
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACIT-F	Functional Assessment of Chronic Illness Therapy Fatigue Scale
FACs	fluorescence-activated cell sorting
FAS	full analysis set
FAS-MAR	full analysis set – missing at randomization
FAS-OL	full analysis set – open label run-in
FAS-RA	full analysis set - randomized
FAS-RE	full analysis set - rescue
FDA	Food and Drug Administration
FEV	Forced expiratory volume
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
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
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
Hep B	hepatitis B
HIV	human immunodeficiency virus
HRQL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
HSV	herpes simplex virus
HTA	health technologies assessment
IB	Investigator's Brochure
ICH	International Conference on 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

Abbreviation	Term
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive web response
JAK	Janus kinase
JAK1	Janus kinase 1
JAK2	Janus kinase 2
JAK3	Janus kinase 3
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
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
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MHP	mental health professional
MMRM	mixed-effect model with repeated measures
MnB	meningitidis serogroup B
MRI	magnetic resonance imaging
MTX	methotrexate
N/A	not applicable
NB-UVB	narrowband ultraviolet B light
NK	Natural Killer
NRS	numerical rating scale
OTC	over the counter
PCD	primary completion date
PD	Pharmacodynamics
PDE-4	Phosphodiesterase 4
Peds-FACIT-F	Pediatric Functional Assessment of Chronic Illness Therapy Fatigue Scale
PEER	Pediatric Eczema Elective Registry
PFS	prefilled syringe
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGx	Pharmacogenomics
PHP	Primary Care Physician
PHQ8	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

Abbreviation	Term
QD	once daily
QFT-G	QuantiFERON®-TB Gold
QT	QT interval
R_{ac}	accumulation ratio
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBQ-R	Suicide Behaviors Questionnaire-Revised
SCORAD	SCORing Atopic Dermatitis
SF-36	Short Form-36
SIB	suicidal ideation and behavior
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	Half-life
T_{max}	time at which Cmax occurred
TARC	thymus and activation regulated chemokine
TB	tuberculosis
TBili	total bilirubin
TCI	Topical calcineurin inhibitors
TCS	topical corticosteroids
TdP	Torsades de Pointes
TH1	type 1 helper T cell
TH2	type 2 helper T cell
T_{max}	Time to maximum concentration
TPO	Thrombopoietin
TYK2	tyrosine kinase 2
ULN	upper limit of normal
US	United States
USA	United States of America
UVA	ultraviolet A light
UVB	ultraviolet B light
VAS	visual analog scale
V/F	volume of distribution/fraction absorbed
VZV	varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
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.[43]

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

Prohibited concomitant medication listed below should not be taken with study drug. Patients requiring treatment with a listed prohibited concomitant medication should be discussed with the Medical Monitor. Such subjects may still be eligible/continue in the study if they do not have to interrupt dosing with study drug for more than 28 consecutive days.

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)	

The washout period for all Cytochrome P (CYP) 2C9 and CYP2C19 inhibitors is 1 week or 5 half-lives, whichever is longer.

The washout period for all CYP2C9 and all CYP2C19 inducers is 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 in average 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.

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. 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. For example, fluoxetine and its metabolite norfluoxetine are both inhibotors 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 5 times the half-life of norfluoxetine, for a total of approximately 80 days prior to the first dose of investigational product.

Use of concomitant medications that prolong the QT/QTcF interval were exclusionary for enrollment in the study. After the completion of enrollment the restriction on these prohibited medications was removed.

Appendix 4. Guidelines for Monitoring and Discontinuation

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;
- Lymphocyte count <500/mm^3; confirmed promptly by repeat testing, within 48 hours;
- 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 28 consecutive days for a subject, for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary. The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the subject during this time-frame. 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 Fridericia-corrected QT (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).

- Other 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 temporary interruption to dosing of investigational product for >28 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 8.4.1 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 patient 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.

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

Appendix 7. 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 8. European Quality of Life 5-Dimension 5-Level Scale (EQ-5D-5L) and European Quality of Life 5-Dimension Youth Scale (EQ-5D-Y in select countries)

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

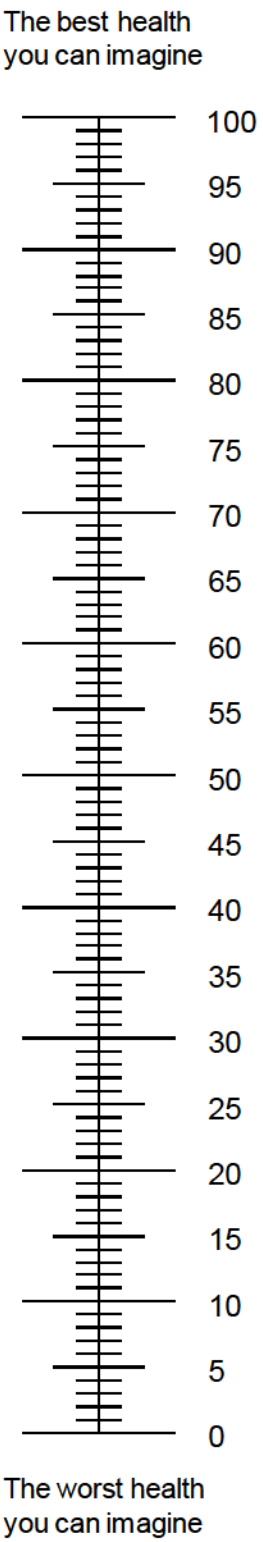
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

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 = ☐



EQ-5D-Y

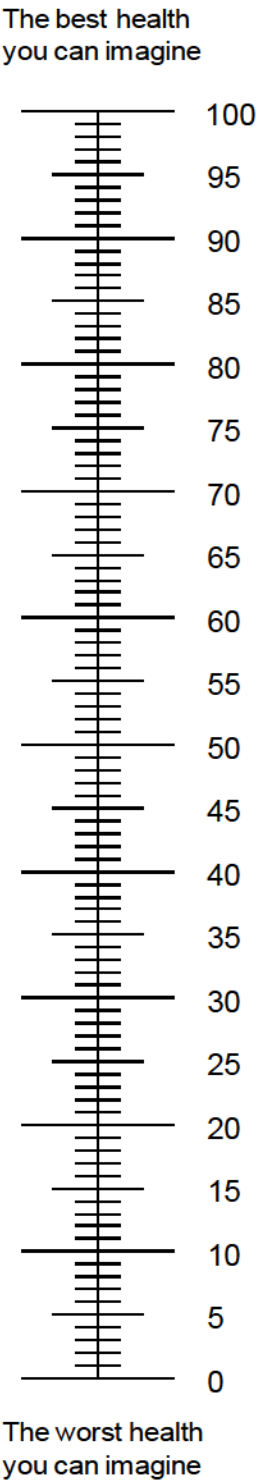
Describing your health TODAY

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

Mobility (walking around)	
I have no problems walking around	❑
I have some problems walking around	❑
I have a lot of problems walking around	❑
Taking care of myself	
I have no problems taking a bath or shower by myself or getting dressed by myself	❑
I have some problems taking a bath or shower by myself or getting dressed by myself	❑
I have a lot of problems taking a bath or shower by myself or getting dressed by myself	❑
Doing usual activities (for example, going to school, hobbies, sports, playing, doing things with family or friends)	
I have no problems doing my usual activities	❑
I have some problems doing my usual activities	❑
I have a lot of problems doing my usual activities	❑
Having pain or discomfort	
I have no pain or discomfort	❑
I have some pain or discomfort	❑
I have a lot of pain or discomfort	❑
Feeling worried, sad, or unhappy	
I am not worried, sad, or unhappy	❑
I am a little worried, sad, or unhappy	❑
I am very worried, sad, or unhappy	❑

How good is your health TODAY

- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.



Appendix 9. Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI)

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.

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

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

1.	Over the last week, how **itchy, "scratchy", sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time?** **OR** was it **holiday time?**	**If school time**: Over the last week, how much did your skin problem affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school Very much Quite a lot Only a little Not at all Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question. Thank you.

Appendix 10. 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): _____

Appendix 11. 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

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


CCI


CCI


CCI

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

Appendix 13. Short Form-36 Version 2 (SF-36v2)

SF36V2™ HEALTH SURVEY - Page 1 of 6

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	**Good**	**Fair**	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF36V2™ HEALTH SURVEY - Page 2 of 6

3. **The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?**

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a mile	☐ 1	☐ 2	☐ 3
h	Walking several hundred yards	☐ 1	☐ 2	☐ 3
i	Walking one hundred yards	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

SF36V2™ HEALTH SURVEY - Page 3 of 6

4. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF36V2™ HEALTH SURVEY - Page 4 of 6

6. **During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	**Slightly**	**Moderately**	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much bodily pain have you had during the past week?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	**Moderately**	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF36V2™ HEALTH SURVEY - Page 5 of 6

9. **These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. **During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF36V2™ HEALTH SURVEY - Page 6 of 6

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 14. Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-F)

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Pediatric (Paediatric) Functional Assessment of Chronic Illness Therapy – Fatigue

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		None of the time	A little bit of the time	Some of the time	Most of the time	All of the time
PF1	I feel tired	0	1	2	3	4
PF2	I have energy (or strength)	0	1	2	3	4
PF3	I could do my usual things at home	0	1	2	3	4
PF4	I had trouble starting things because I was too tired	0	1	2	3	4
PF5	I had trouble finishing things because I was too tired	0	1	2	3	4
PF6	I needed to sleep during the day	0	1	2	3	4
PF7	I got upset by being too tired to do things I wanted to do	0	1	2	3	4
PF8	Being tired made it hard for me to play or go out with my friends as much as I'd like	0	1	2	3	4
PF9	I needed help doing my usual things at home	0	1	2	3	4
PF10	I feel weak	0	1	2	3	4
PF11	I was too tired to eat	0	1	2	3	4
PF12	Being tired made me sad	0	1	2	3	4
PF13	Being tired made me mad (angry)	0	1	2	3	4

Appendix 15. Columbia Severity Suicide Rating Scale (C-SSRS) for Screening and Baseline Visits

Protocol ID: B7451014

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 12 Months**	
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:	Yes ☐	No ☐	Yes ☐	No ☐
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:	Yes ☐	No ☐	Yes ☐	No ☐
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:	Yes ☐	No ☐	Yes ☐	No ☐
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:	Yes ☐	No ☐	Yes ☐	No ☐
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:	Yes ☐	No ☐	Yes ☐	No ☐

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.	Most Severe	Most Severe
Lifetime - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*)		
Past 12 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	____	____

Template Version Date: 04 Dec 2017

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 5 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 ☐	Yes ☐	No ☐
	Total # of Attempts ____		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:	Yes ☐	No ☐	Yes ☐	No ☐
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	☐	☐	☐	☐

Template Version Date: 04 Dec 2017

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT dd - MMM - yyyy

Visit: _____

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* _____

Template Version Date: 04 Dec 2017

Appendix 16. Columbia Severity Suicide Rating Scale (C-SSRS) Since Last Visit

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.	**Since Last Visit**
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:	**Yes** ☐ **No** ☐
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 of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
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:	**Yes** ☐ **No** ☐
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:	**Yes** ☐ **No** ☐
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:	**Yes** ☐ **No** ☐
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). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
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)*	**Since Last Visit**
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_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve 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** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
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 _____
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 _____
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 attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal 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* _____
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* _____

Appendix 17. Suicide Behaviors Questionnaire – Revised (SBQ-R)

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

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

Visit: _____

SUICIDAL BEHAVIORS QUESTIONNAIRE-REVISED (SBQ-R)

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

Instructions: Please check the number beside the statement or phrase that best applies to you.

1. **Have you ever thought about or attempted to kill yourself?** (check one only)
   - ☐ 1. Never
   - ☐ 2 It was just a brief passing thought
   - ☐ 3a. I have had a plan at least once to kill myself but did not try to do it
   - ☐ 3b. I have had a plan at least once to kill myself and really wanted to die
   - ☐ 4a. I have attempted to kill myself, but did not want to die
   - ☐ 4b. I have attempted to kill myself, and really hoped to die

2. **How often have you thought about killing yourself in the past year?** (check one only)
   - ☐ 1. Never
   - ☐ 2. Rarely (1 time)
   - ☐ 3. Sometimes (2 times)
   - ☐ 4. Often (3-4 times)
   - ☐ 5. Very Often (5 or more times)

3. **Have you ever told someone that you were going to commit suicide or that you might do it?** (check one only)
   - ☐ 1. No
   - ☐ 2a. Yes, at one time, but did not really want to die
   - ☐ 2b. Yes, at one time, and really wanted to die
   - ☐ 3a. Yes, more than once, but did not want to do it
   - ☐ 3b. Yes, more than once, and really wanted to do it

4. **How likely is it that you will attempt suicide someday?** (check one only)
   - ☐ 0. Never
   - ☐ 1. No chance at all
   - ☐ 2. Rather unlikely
   - ☐ 3. Unlikely
   - ☐ 4. Likely
   - ☐ 5. Rather likely
   - ☐ 6. Very likely

Appendix 18. Patient Health Questionnaire – 8 items (PHQ-8)

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?	☐	☐	☐	☐

Appendix 19. Asthma Control Questionnaire (ACQ)

ASTHMA CONTROL QUESTIONNAIRE© Page 1 of 1

Please answer questions 1 - 5.

Circle the number of the response that best describes how you have been during the past week.

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal
5.	In general, during the past week, how much of the time did you **wheeze**?	0 Not at all 1 Hardly any of the time 2 A little of the time 3 A moderate amount of the time 4 A lot of the time 5 Most of the time 6 All the time

SYMPTOMS ONLY MODIFIED JUNE 2014 NORTH AMERICAN ENGLISH