A PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTI-CENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PF-04965842 MONOTHERAPY IN SUBJECTS AGED 12 YEARS AND OLDER, WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Investigational Product Number:	PF-04965842
Investigational Product Name:	Not applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2018-001136-21
Protocol Number:	B7451013
Phase:	3

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 3	06 December 2018	For Japan and Republic of Korea only: Similar to China, other countries in Asia, such as Japan and Republic of Korea, have a high prevalence of hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (HBcAb) positive, and hepatitis B surface antibody (HBsAb) positive serology. Therefore, Republic of Korea will adopt the same changes and Japan will adopt similar changes as those proposed for China in Amendment 2 to monitor the risk of hepatitis B reactivation. The following sections of the protocol are affected: Schedule of Activities, Sections 4.2, 6.1, 6.2.7, 7.6.2, 7.6.2.1 and Appendix 1. For Japan only: Based on local request, HBsAg, HBcAb and HBsAb testing will be performed concurrently at Screening for all subjects rather than performing HBsAb as a reflex test only. Based on local practices for tuberculosis testing in Japan, if QuantiFERON®- TB Gold In-Tube (QTF-G) testing is not possible, the T-SPOT®.*TB* test performed at a local laboratory is acceptable as the screening TB test. The following sections of the protocol are affected: Schedule of Activities, Sections 4.2, 6.1, 7.3.4 and 7.6.2.
Amendment 2	12 September 2018	The following changes were requested by an Ethics Committee in China. These changes are in effect for China 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 be randomized but will have repeat HBV DNA testing at Week 12 (or early termination). The following sections of the protocol are affected: • Schedule of Activities; • Section 4.2. Exclusion Criteria; • Section 6.1. Visit 1, Screening; • Section 6.2.7. Visit 8, Day 85/Week 12 (±3 days) or Early Termination Visit; • Table of Laboratory Tests in Section 7.6.2. Laboratory Testing; • Section 7.6.2.1. Hepatitis Testing. The protocol changes specified in Protocol Administrative Change Letter #1 (09 May 2018) have been incorporated in Section 4.1 Inclusion Criteria 3, 3rd bullet, and Section 7.8.1 Pruritus Numerical Rating Scale (NRS). The protocol changes specified in Protocol Administrative Change Letter #2 (23 Jul 2018) have been incorporated in Appendix 3. Prohibited Concomitant Medications.

Amendment 1	13 July 2018	Added European Clinical Trials Database (EudraCT) Number on the cover page. The following changes were requested from the Voluntary Harmonisation Procedure (VHP) for participating member states only (Czech Republic, Germany, Hungary, Latvia, Poland, United Kingdom): 1. In Section 1.2.4, additional text was added to present the model-estimated proportion of subjects achieving EASI-75 response in Phase 2B study B7451006. 2. In Section 4.2, exclusion criterion 19, the absolute lymphocyte count thresholds have been updated to age-specific ranges. The list of abbreviations has been updated to include VHP.
Final Protocol	27 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] 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 a child's 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.

There are a limited number of treatments available for AD. Current treatments include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. Crisaborole was approved as a topical 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).[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, and to reduce pruritus and the resulting sleep disturbance.[5,6]

Other systemic agents to treat AD are under clinical development or recently approved. 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, and offers a novel mechanism of action for the treatment of moderate to severe AD. However, the approved dosing for dupilumab as an initial dose of 2 x 300 mg subcutaneous injections followed by 300 mg every other week injections may limit the desirability of this route of treatment.

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 against other kinases: 28-fold selectivity over JAK2, >340-fold over JAK3 and 43-fold over tyrosine kinase 2 (TYK2), as well as a good selectivity profile over the broader range of human kinases. The selective inhibition of JAK1 will lead to modulation of

multiple cytokine pathways involved in the pathophysiology of AD, including IL-4, IL-5, IL-13, IL-31 and IFN-γ. Data from a Phase 2b proof of concept (POC) study (B7451006) that evaluated subjects with moderate to severe AD have shown positive efficacy, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

Objectives and Endpoints

Primary Objective:

- To assess the efficacy of PF-04965842 compared with placebo in subjects aged 12 years and older with moderate to severe AD.

Secondary Objective:

- To evaluate 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.

Safety Objective:

- To evaluate the safety and tolerability of PF-04965842 in subjects aged 12 years and older with moderate to severe atopic dermatitis following 12 weeks of treatment.

Pharmacokinetic Objective:

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

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Endpoints

Primary Efficacy Endpoints:

- Response based on the Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 12. The baseline will be defined as the IGA score on Day 1 pre-dose;

- Response based on the Eczema Area and Severity Index 75% improvement from baseline (EASI-75) response at Week 12. The baseline will be defined as the EASI score on Day 1 pre-dose.

Key Secondary Efficacy Endpoints:

- Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at Weeks 2, 4, and 12;
- Change from Baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at Week 12.

Secondary Efficacy Endpoints:

- Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at all scheduled time points other than Weeks 2, 4 and 12;
- Time to achieve at least 4 points improvement in the severity of pruritus NRS scale from baseline by Day 15;
- Response based on the EASI-75 at all scheduled time points except Week 12;
- Response based on the IGA of clear (0) or almost clear (1) and ≥2 point reduction from baseline at all scheduled time points except Week 12.

Other Efficacy Endpoints:

- Response based on a ≥50% and ≥90% improvement in the EASI total score (EASI-50 and EASI-90) at all scheduled time points;
- Change from baseline in the percentage Body Surface Area (BSA) affected at all scheduled time points;
- Response based on a ≥50% and ≥75% improvement in Scoring Atopic Dermatitis (SCORAD) (SCORAD-50, SCORAD-75) from baseline at all scheduled time points;
- Change from baseline at all scheduled time points in SCORAD-subjective assessments of itch and sleep loss.

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- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Safety Endpoints:

- Incidence of treatment emergent adverse events;
- Incidence of Serious Adverse Event (SAE)s and Adverse Event (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 Endpoint:

- Population PK characterization in subjects aged 12 years and older with moderate to severe atopic dermatitis.

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- [redacted]

Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects aged 12 years and older with moderate to severe AD and a body weight ≥40 kg. The treatment duration is 12 weeks. Subjects will be screened within 28 days prior to the first dose of investigational product to confirm that they meet the subject selection criteria for the study. A total of approximately 375 subjects will be enrolled from approximately 85 sites located globally. Adolescent subjects below the age of 18 years old (or country-specific age of majority) will only be enrolled in this study if instructed by the sponsor and approved by the country or regulatory/health authority. If these approvals have not been granted, only subjects aged 18 years (or country-specific age of majority) and older will be enrolled.

Qualified subjects completing the 12 week treatment period of the study will have the option to enter a long-term extension (LTE) study B7451015. Subjects discontinuing early from treatment, or who are otherwise ineligible for the LTE study will undergo a 4 week follow-up period in B7451013.

Subjects who have chronic moderate to severe AD as defined per the inclusion criteria will be randomized to receive 200 mg or 100 mg PF-04965842 once daily (QD), or matching placebo. Investigators, subjects, and the sponsor study team will be blinded as to treatment group.

After providing informed consent, subjects will be assessed for study eligibility at the screening visit. For subjects younger than 18 years old (or country-specific age of majority), their parent(s)/legal guardian will provide supplementary or sole written consent and minor children will provide assent, according to local regulations and rules regarding ability to give assent and consent. Subjects will undergo screening within 28 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Subjects may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions, unless the reason for the screen failure is the disease severity inclusion criteria.

Subjects who continue to meet eligibility criteria at baseline will undergo Day 1/baseline assessments and be randomized in a 2:2:1 ratio to receive 200 mg PF-04965842 (N=150) or 100 mg PF-04965842 QD (N=150) or matching placebo (N=75) from Day 1.

Randomization will be stratified by baseline disease severity (moderate [IGA = 3] vs. severe [IGA = 4] AD), and, age <18 and ≥18. Eligible subjects must have a documented history of inadequate response or intolerance to treatment with topical AD medications or have required systemic therapies for control of their disease.

Study Treatments

- Doses of PF-04965842 will be 200 mg or 100 mg taken QD orally, or matching placebo.

- Treatment duration will be 12 weeks (randomized period).

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

Statistical Methods

A total sample of 375 subjects, with 150 on PF-04965842 200 mg QD, 150 on PF-04965842 100 mg QD and 75 on placebo (2:2:1 randomization) would provide at least 95% power to detect a difference of at least 20% in IGA response rate between PF-04965842 200 mg QD (or PF-04965842 100 mg QD) and placebo, assuming the placebo response rate is 6% at Week 12.

Furthermore, this will also provide at least 99% power to detect a difference of at least 30% in EASI-75 response rate between PF-04965842 200 mg QD (or PF-04965842 100 mg QD) and placebo, assuming the placebo response rate is 15% at Week 12.

These two endpoints are co-primary and both must achieve statistical significance to meet the primary objective.

There are five key hypotheses to be tested for each of the two PF-04965842 doses (200 mg QD and 100 mg QD) versus placebo, for the co-primary endpoints and two key secondary endpoints. For these hypotheses, the familywise Type-I error rate will be strongly controlled at 5% using a sequential, Bonferroni-based iterative multiple testing procedure. This is described in further detail in the statistical analysis section of the protocol and in the statistical analysis plan (SAP).

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

For continuous endpoints, a mixed-effect model with repeated measures (MMRM) will be used. This model will include the factors (fixed effects) for treatment group, randomization strata (age group, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will be tested at the pre-specified primary time point, Week 12, as well as at the other time points by time point-specific contrasts from the MMRM model.

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

SCHEDULE OF ACTIVITIES

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

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

Visit Identifier[a]	**Day -28 Screening**	**Day 1 Week 0 Baseline**	**Day 8 Week 1 Call**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 43 Week 6 Call**	**Day 57 Week 8**	**Day 85 Week 12 (EOT/ET)**	**EOS, Follow- up Week 16 (4 Weeks after EOT or ET)**
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
Visit Window	**None**	**None**	**±1 Day**	**±1 Days**	**±2 Days**	**±3 Days**	**±3 Days**	**±3 Days**	**±3 Days**
Enrollment Procedure									
Informed consent	X								
Register subject using IRT system	X								
Inclusion/Exclusion Criteria	X	X							
Demographics, Medical History, Tobacco and Alcohol History, Atopic Dermatitis Disease History[b]	X								
Review Prior/Concomitant Medications & Treatments	X	X	X	X	X	X	X	X	X
Dispense e-Diary and instruct subjects on use	X								
Provide Patient Emergency Contact Card	X								
Medical Procedures									
Complete Physical Exam[c]	X	X						X	
Targeted Physical Exam[c]				X	X		X		X
Vital Signs[d]	X	X		X	X		X	X	X
Additional Blood Pressure and Pulse Rate (post dose)[d]		X						X	
Weight	X	X						X	
Height	X							X	
Chest X-ray[e]	X								

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 Week 12 (EOT/ET)	EOS, Follow- up Week 16 (4 Weeks after EOT or ET)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Visit Window	None	None	±1 Day	±1 Days	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days
ECG (12-lead)	X[f]	X		X	X		X	X	X
Laboratory Assessments									
Serum chemistry and hematology (including coagulation panel)[g]	X	X		X	X		X	X	X
Lipid Panel[g]		X			X			X	X
Urinalysis	X	X		X	X		X	X	X
Serum FSH (WONCBP only) or Pregnancy Test[h]	X								
Urine Pregnancy Test (conducted at study site)[i]		X		X	X		X	X	X
[redacted]									
HIV Testing[k]	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)[l]	X								
HBV DNA (for China, Japan and Republic of Korea only)[bb]	X							X	
Varicella Zoster Virus (VZV IgG Ab) (adolescents only, if applicable)[m]	X								
Tuberculosis Test[n]	X								
Pharmacokinetic									
Pharmacokinetic Blood Sampling (Pre-dose)[o]							X		
Pharmacokinetic Blood Sampling (Post-dose)[p]								X	
Trial Treatment									
Randomization		X							
Drug Dispensing		X			X		X		
Investigational Product Accountability				X	X		X	X	

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 Week 12 (EOT/ET)	EOS, Follow- up Week 16 (4 Weeks after EOT or ET)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Visit Window	None	None	±1 Day	±1 Days	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days
Investigational Treatment Administration[q]		X----------							----------X
Review eDiary to assess completion			X	X	X	X	X	X	
Assess eligibility for B7451015[r]								X	
Clinical Assessments									
Fitzpatrick Skin Type Assessment		X							
Investigator's Global Assessment (IGA)	X	X		X	X		X	X	X
SCORing Atopic Dermatitis (SCORAD)	X	X		X	X		X	X	X
Eczema Area and Severity Index (EASI)	X	X		X	X		X	X	X
Body Surface Area (BSA from EASI)	X	X		X	X		X	X	X
C-SSRS[s]	X								
SBQ-R[s]	X								
PHQ-8[s]	X								
Photography of representative AD lesions[t]		X		X	X		X	X	X
Patient-reported Outcome									
Pruritus Numerical Rating Scale (NRS)[u]	X----------	X----------			X		X	X	X
Night Time Itch Scale[u]	X----------	X----------			X		X	X	X
Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)[v]	X ----------	X----------							----------X
Patient Global Assessment (PtGA)		X		X	X		X	X	X
Dermatology Life Quality Index (DLQI or CDLQI)[w]		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
EQ-5D-5L (adults) or EQ-5D-Y (ages 12-17 years)		X		X	X		X	X	X
SF-36v2, Acute[x]		X						X	X
Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis (WPAI:AD)[x]		X						X	X
FACIT-F or Peds-FACIT-F[y]		X						X	X

Visit Identifier[a]	Day -28 Screening	Day 1 Week 0 Baseline	Day 8 Week 1 Call	Day 15 Week 2	Day 29 Week 4	Day 43 Week 6 Call	Day 57 Week 8	Day 85 Week 12 (EOT/ET)	EOS, Follow- up Week 16 (4 Weeks after EOT or ET)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Visit Window	None	None	±1 Day	±1 Days	±2 Days	±3 Days	±3 Days	±3 Days	±3 Days
Safety									
Serious and non-serious adverse event monitoring	X	X	X	X	X	X	X	X	X
Contraception Check[z]	X	X	X	X	X	X	X	X	X
Serum Sample for Baseline Viral Screen[aa]		X							

Abbreviations: AD = atopic dermatitis; 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; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1; HSV2 = herpes simplex virus type 2; IGA = Investigator's Global Assessment; IRT = Interactive Response System; LLQ = lower limit quantification; 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; 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; WPAI:AD = Work Productivity and Activity Impairment Questionnaire: Atopic Dermatitis; WONCBP = women of non-childbearing potential.

a. Day relative to start of study treatment (Day 1).
b. Atopic Dermatitis Disease History includes collection of details of AD: AD diagnosis and duration, the use of topical treatments, systemic treatments and other treatments for AD.
c. 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.
d. Vital Signs include sitting blood pressure, pulse rate, respiratory rate, and temperature measured after at least 5 minutes of rest. All vital signs at baseline and Week 12 must be performed prior to administration of investigational product and additional blood pressure and pulse rate assessments must be performed at least 1 hour following administration of investigational product. All vital signs at all other on-site visits must be performed at least 1 hour following administration of investigational product.

e. Chest X-ray or other appropriate diagnostic image (ie, CT or MRI) may be performed up to 12 weeks prior to Day 1. Chest X-rays (posterior-anterior and lateral views) are required 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.
f. A single 12-lead ECG will be performed at screening and all other 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.
g. 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. The lipid profile panel will include total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. A minimum of 8-hour fasting is required for lipid profile evaluation at Day 1, Week 4, Week 12 and EOS visits. Hematology includes: Hemoglobin, hematocrit, red blood cell count and indices (MCH, MCHC, MCV, RBC Morphology), WBC count with differential, total neutrophils (%, absolute), lymphocytes (%, absolute), monocytes (%, absolute), eosinophils (%, absolute), basophils (%, absolute), platelets, reticulocyte count and coagulation panel. Coagulation panel includes: Activated Partial Thromboplastin Time (APTT), Prothrombin Time/International Normalized Ratio (PT/INR). Laboratory tests with abnormal results (per Section 6.1 and Section 7.6.2) may be repeated once during the screening period; the last value will be used to determine eligibility.
h. 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.
i. Urine pregnancy test must be performed 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. [redacted]
k. HIV testing will be performed for all subjects. Subjects who are positive for HIV will be screen-failed.
l. 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.
m. VZV IgG antibody testing is required to confirm eligibility in adolescent subjects who have not received at least one dose of a varicella vaccine.
n. 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 7.3.3. For Japan only: While QuantiFERON® is the preferred testing method, the T-SPOT®.*TB* test is acceptable as the screening TB test. T-SPOT®.*TB* testing will be performed at the site's local laboratory. Borderline results from the T-SPOT®.*TB* test should be considered exclusionary. If the test results are indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, subjects may be screened using the Mantoux/PPD skin test with Pfizer Medical Monitor approval. See Section 7.3.4.
o. A pharmacokinetic (PK) blood sample will be collected 2.0 hours (±30 min) prior to dosing at the study site on Week 8.
p. PK blood samples will be collected at 1.0 hour (±15 min) and 2.0 hours (±30 min) post-dose at the Week 12 visit (EOT/ET). If the ET visit occurs after Week 8, collect PK samples only if the subject takes the investigational product at the site visit.
q. Subjects should take the medication from study Days 1 to 85. 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.

r. Subjects who complete EOT will be assessed for eligibility for participation in long-term extension study B7451015 as noted in Section 6.2.7.
s. 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. For subjects meeting exclusionary results on the C-SSRS, SBQ-R and PHQ-8, it is recommended the subject's primary care physician (PCP) should be informed, and the subject referred to a mental health professional, either by the PCP or the investigator according to their usual practice.
t. For subjects at selected study sites, photographs of treated AD will be obtained. Photographs will be utilized for illustrative purposes and not evaluated as an endpoint (see Section 7.7.5).
u. Pruritus Numerical Rating Scale (NRS) and Night Time Itch Scale will be assessed using an eDiary, daily during the screening period and from Day 1 to 15. After Day 15, the pruritus NRS and Night Time Itch Scale will be completed only on study visit days in the eDiary. At the Screening visit, site staff will dispense the ePRO device and review instructions for completion of the subject eDiary for the NRS and Night Time Itch Scale. 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.
v. Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) will be conducted 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 in selected countries (See Section 7.8.8). 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.
w. DLQI will be completed by adult subjects only. Adolescents 12-17 years of age will complete the CDLQI instead.
x. SF-36v2 and WPAI:AD will be completed by adult subjects only. Adolescents 12-17 years of age will not complete these assessments.
y. FACIT-F will be completed by adult subjects only. Adolescents 12-17 years of age will complete the Peds-FACIT-F instead.
z. 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.
aa. 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.
bb. For China and Republic of Korea only: Subjects who are HBsAg negative, HBcAb positive, HBsAb positive at screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ will have repeat HBV DNA repeated at Week 12 or early termination.
For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all subjects rather than as a reflex test. Subjects with negative results for HBsAg, HBcAb and HBsAb may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 or early termination.

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), IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF) and prolactin.

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.

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]

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 against other kinases: 28-fold selectivity over JAK2, >340-fold over JAK3 and 43-fold over TYK2, as well as a good selectivity profile over the broader range of human kinases. The selective inhibition of JAK1 will lead to modulation of multiple cytokine pathways involved in the pathophysiology of AD, including IL-4, IL-5, IL-13, IL-31 and IFN-γ. Data from a Phase 2b proof of concept (POC) study (B7451006) that evaluated subjects with moderate to severe AD have shown positive efficacy, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

1.2. Background and Rationale

1.2.1. Drug Development and Rationale

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

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

1.2.2. Atopic Dermatitis

Atopic dermatitis, also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in the quality of life. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the US.[1,2] AD is one of the most common, chronic, relapsing childhood dermatoses, impacting 15-30% of all children in the US and many have disease that persists into adulthood with a lifetime prevalence of those affected in childhood reported to be 34%.[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 a child's 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. In 833 AD patients who were aged 20 years or older when they visited the clinic and 45 years or older when they responded to a follow-up questionnaire, 59% responded that they had defined persistent AD at some time during the last 12 months.[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.[7,13,14] 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.[7,14]

There are a limited number of treatments available for AD. Current treatments for AD include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. Crisaborole was approved as a 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]

Currently available therapies for the treatment of AD have multiple limitations. The 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 topical therapies and phototherapy, 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.

Other systemic agents to treat AD are under clinical development or recently approved. 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, and offers a novel mechanism of action for the treatment of moderate to severe AD. However, the approved dosing for dupilumab as an initial dose of 2 x 300 mg subcutaneous injections followed by 300 mg every other week injections may limit the desirability of this route of treatment.

Therefore, the predominant unmet medical need is an oral therapy with an acceptable safety profile for long term use which is effective for refractory AD.

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.

1.2.3. Non-Clinical and Phase 1 Data

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

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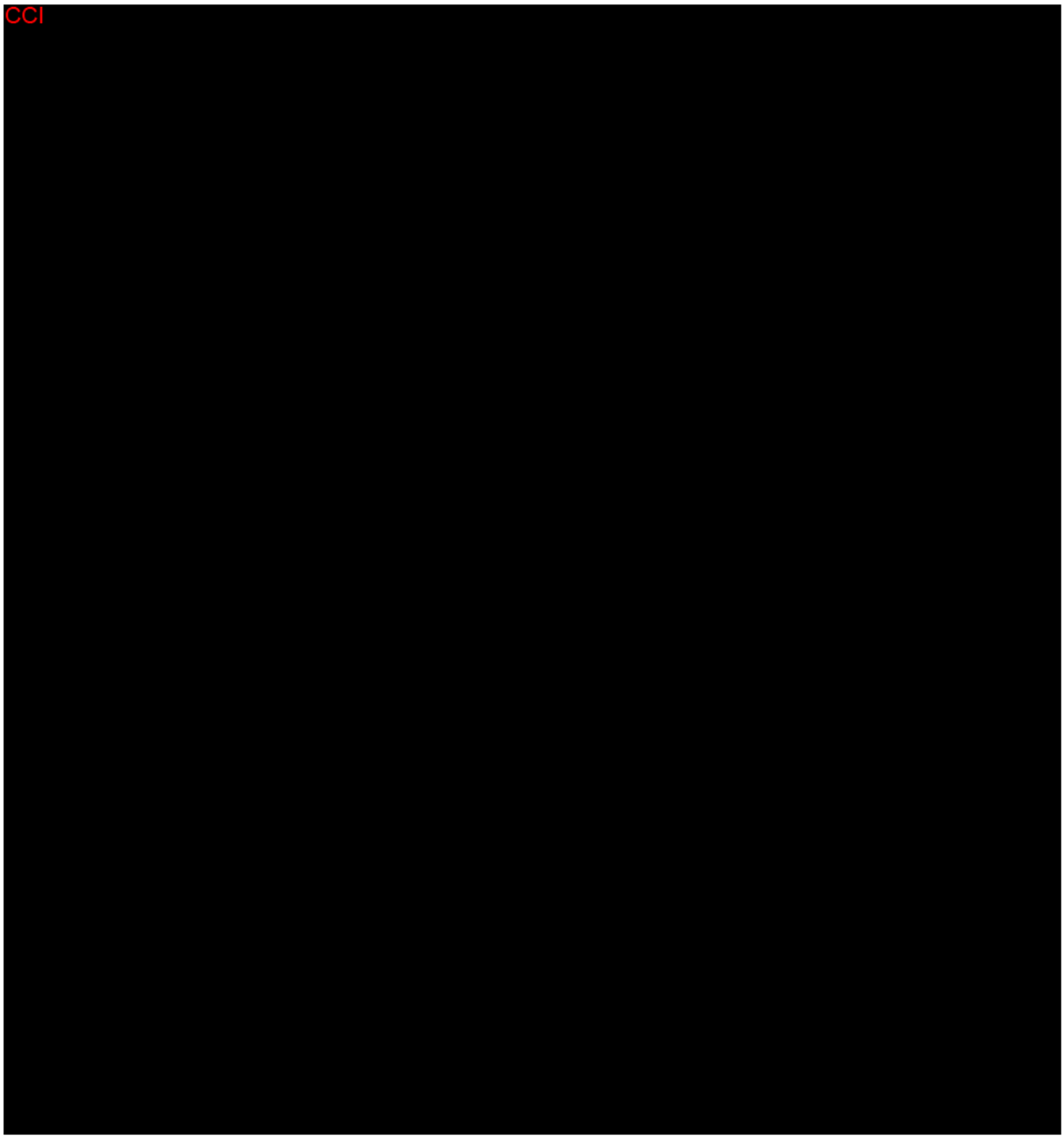

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2. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and corresponding endpoints are provided in Table 1.

Table 1. Objectives and Endpoints:

Primary Objective	Primary Endpoints
To assess the efficacy of PF-04965842 compared with placebo in subjects aged 12 years and older with moderate to severe AD.	The following co-primary endpoints will be tested: • Response based on the Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5 point scale) and a reduction from baseline of ≥2 points at Week 12. The baseline will be defined as the IGA score on Day 1 pre-dose; • Response based on the Eczema Area and Severity Index 75% improvement from baseline (EASI-75) response at Week 12. The baseline will be defined as the EASI score on Day 1 pre-dose.
Secondary Objective	**Secondary Endpoints**
To evaluate 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.	**Key Secondary Endpoints:** • Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at Weeks 2, 4, and 12; • Change from Baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at Week 12. **Secondary Efficacy Endpoints:** • Response based on at least 4 points improvement in the severity of pruritus numerical rating scale (NRS) from baseline at all scheduled time points other than Weeks 2, 4 and 12; • Time to achieve at least 4 points improvement in the severity of pruritus NRS scale from baseline by Day 15; • Response based on the EASI-75 at all scheduled time points except Week 12; • Response based on the IGA of clear (0) or almost clear (1) and ≥2 point reduction from baseline at all scheduled time points except Week 12. **Other Efficacy Endpoints:** • Response based on a ≥50% and ≥90% improvement in the EASI total score (EASI-50 and EASI-90) at all scheduled time points; • Change from baseline in the percentage Body Surface Area (BSA) affected at all scheduled time points; • Response based on a ≥50% and ≥75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points; • Change from baseline at all scheduled time points in SCORAD subjective assessments of itch and sleep loss. CCI [redacted]

	CCI [redacted]
Safety Objective	**Safety Endpoints**
To evaluate the safety and tolerability of PF-04965842 in subjects aged 12 years and older with moderate to severe atopic dermatitis following 12 weeks of treatment.	• Incidence of treatment emergent adverse events; • Incidence of SAEs and AEs leading to discontinuation; • The incidence of clinical abnormalities and change from baseline in clinical laboratory values, ECG measurements, and vital signs.
PK Objective	**PK Endpoint**
To evaluate the PK of PF-04965842 in subjects aged 12 years and older with moderate to severe atopic dermatitis following 12 weeks of treatment.	• Population PK characterization in subjects aged 12 years and older with moderate to severe atopic dermatitis.

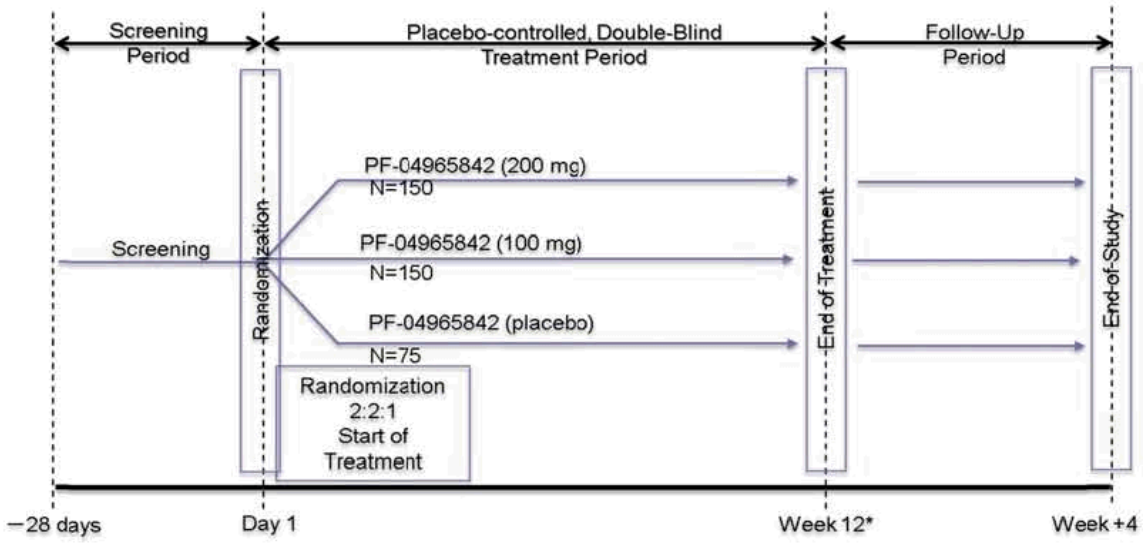
Exploratory Objectives	• Exploratory Endpoints
CCI [redacted]	[redacted]

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; EQ-5D-5L = EuroQol; Quality of Life measure; 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; Peds-FACIT-F = Pediatric FACIT-F; 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; SF-36v2 = Short Form-36 Version 2; SAE = Serious Adverse Event

3. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects aged 12 years and older with moderate to severe AD and a body weight ≥40 kg. The treatment duration is 12 weeks. Subjects will be screened within 28 days prior to the first dose of investigational product to confirm that they meet the subject selection criteria for the study. A total of approximately 375 subjects will be enrolled from approximately 85 sites located globally. Adolescent subjects below the age of 18 years old (or country-specific age of majority) will only be enrolled in this study if instructed by the sponsor and approved by the country or regulatory/health authority. If these approvals have not been granted, only subjects aged 18 years (or country-specific age of majority) and older will be enrolled. A study design schematic is presented in Figure 1.

Figure 1. Study Design Schematic



* At Week 12, eligible subjects may enter a long-term extension study; all other subjects enter the 4 week follow-up period.

Qualified subjects completing the 12-week treatment period of the study will have the option to enter a long-term extension (LTE) study B7451015. Subjects discontinuing early from treatment, or who are otherwise ineligible for the LTE study will undergo a 4 week follow-up period in B7451013.

Subjects who have chronic moderate to severe AD as defined per the inclusion criteria will be randomized to receive 200 mg or 100 mg PF-04965842 once daily (QD), or matching placebo. Investigators, subjects, and the sponsor study team will be blinded as to treatment group.

After providing informed consent, subjects will be assessed for study eligibility at the screening visit. For subjects younger than 18 years old (or country-specific age of majority), their parent(s)/legal guardian will provide supplementary or sole written consent and minor children will provide assent, according to local regulations and rules regarding ability to give assent and consent. Subjects will undergo screening within 28 days prior to randomization. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Subjects may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions, unless the reason for the screen failure the disease severity inclusion criteria.

Subjects who continue to meet eligibility criteria at baseline will undergo Day 1/baseline assessments and be randomized in a 2:2:1 ratio to receive 200 mg PF-04965842 (N=150) or 100 mg PF-04965842 QD (N=150) or matching placebo (N=75) from Day 1.

Randomization will be stratified by baseline disease severity (moderate [IGA = 3] vs. severe [IGA = 4] AD), and, age <18 and ≥18. Eligible subjects must have a documented history of inadequate response or intolerance to treatment with topical AD medications or have required systemic therapies for control of their disease.

4. SUBJECT ELIGIBILITY CRITERIA

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

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

4.1. Inclusion Criteria

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject or their parent(s)/legal guardian, if applicable, 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 age of 18 years old (or country-specific age of majority) will only be enrolled in this study if instructed by the sponsor and approved by the country or regulatory/health authority. If these approvals have not been granted, only subjects aged 18 years (or country-specific age of majority) and older 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 Hanafin and Rajka criteria for AD[16] (see Appendix 2).

    - Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks), or who have required systemic therapies for control of their disease.

    - Moderate to severe AD (affected BSA ≥10%, IGA ≥3, EASI ≥16, and Pruritus NRS severity score ≥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 all 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 randomization;

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

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

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.

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

4.2. Exclusion Criteria

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

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

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

   - Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS) (Appendix 17);

   - 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 18);

   - Clinically significant depression: patient health questionnaire – 8 items (PHQ-8) total score ≥15 (Appendix 19);

   - 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, cyclosporine A [CsA], azathioprine, methotrexate, systemic corticosteroids, mycophenolate-mofetil, IFN-γ) within 4 weeks of first dose of investigational product or within 5 half-lives (if known), whichever is longer;
- 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 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 Republic of Korea only: Subjects who are HBsAg negative, HBcAb positive, and 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 be randomized but will have repeat HBV DNA testing at Week 12 (or early termination).

For Japan only: Subjects with negative results for HBsAg, HBcAb and HBsAb may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have repeat HBV DNA testing at Week 12 (or early termination).

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 interval (QTcF) abnormalities including:

    - A marked prolongation of QTcF interval (>450 milliseconds [ms]) on the screening ECG;
    - A history of additional risk factors for Torsade de Pointes (TdP) (eg, heart failure, hypokalemia, family history of Long QT Syndrome);
    - Use of concomitant medications that prolong the QT/QTcF interval.

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

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

17. Require treatment with prohibited concomitant medication(s) (Section 5.8.2 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 defined by the following:

- A positive QuantiFERON®-TB Gold (QFT-G) In-Tube test or positive Mantoux/Purified Protein Derivative (PPD) tuberculin skin test (if appropriate per Section 7.3.4) performed at or within the 12 weeks prior to Day 1 is exclusionary; a negative test is required for eligibility. 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 QFT-G or Mantoux/PPD tuberculin skin test is not required if the subject has previously received a documented adequate course of therapy for either latent or active TB infection.

  For Japan only: While QuantiFERON® is the preferred testing method, the T-SPOT®. *TB* test is also acceptable as the screening TB test. Borderline results from the T-SPOT®.*TB* test should be considered exclusionary. If the test results are indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, subjects may be screened using the Mantoux/PPD skin test with Pfizer Medical Monitor approval. See Section 7.3.4.

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

- If a subject has previously received an 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, neither a QFT-G test, T-SPOT®.*TB* test (Japan only) nor a Mantoux/PPD tuberculin skin test is needed, but a chest radiograph(s) is required for adults, and recommended for adolescents per local standard/guidelines, if not performed within 12 weeks prior to Day 1. To be considered eligible for the study, the radiograph(s) must be negative for active tuberculosis infection as determined by a qualified radiologist. Documentation of adequate treatment for TB and negative chest radiograph(s) results must be obtained prior to Day 1. 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;

- 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 x 10^9 /L (<500/mm^3);
    - For the Voluntary Harmonisation Procedure (VHP) participating member states (Czech Republic, Germany, Hungary, Latvia, Poland, United Kingdom) only, the following absolute lymphocyte count thresholds apply:
        - <0.95 x 10^9 /L (<950/mm^3) for subjects 12-17 years of age;
        - <0.91 x 10^9 /L (<910/mm^3) for subjects 18-59 years of age;
        - <0.80 x 10^9 /L (<800/mm^3) for subjects ≥60 years of age.
- Estimated Creatinine Clearance <40 mL/min based on the age appropriate calculation, or serum creatinine >1.5 times the upper limit of normal (ULN);
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 times the ULN;
- Total bilirubin ≥1.5 times the ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN.

20. In the opinion of the investigator or sponsor, have any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the subject's participation in the study.
21. Have undergone significant trauma or major surgery within 1 month of the first dose of investigational product.
22. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they or their parent(s)/legal guardian, if applicable, have signed an informed consent document to participate in the study, have undergone all screening procedures, and have met all inclusion and none of the exclusion criteria for participation in the study at Day 1. 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 and End of Study [EOS]), 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 5.8.1).

- 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 5.8.2, 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

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.

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

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

The contraception check is an opportunity to confirm that contraception, if assigned, is used consistently and correctly. It also facilitates continual reassessment of 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.

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.

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 components 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 live vaccine components may pose a risk during treatment and for 6 weeks following completion of the study. Some of these vaccines include varicella ("chickenpox") vaccine, oral polio vaccine, and the inhaled flu vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted. General guidelines for immunosuppressed 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® (inhaled 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 or their parent(s)/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. PF-04965842 will be administered orally at doses of 100 mg or 200 mg given QD for 12 weeks based on treatment assignment. In addition, one treatment group will be assigned to receive PF-04965842-matching placebo.

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. Breaking the Blind

Investigators, subjects and the sponsor study team will be blinded as to treatment group. The study will be subject and investigator blinded. At all times, treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, or the sponsor's study team until following the conclusion of the study, with the exception described in this section.

At the initiation of the study, the study site will be instructed on procedures for breaking the blind. Blinding codes should only be broken in emergency situations for reasons of subject safety. The method will be an electronic process. When the blind for a subject has been broken, the reason must be fully documented and entered on the Case Report Form (CRF). Whenever possible, the investigator should contact Pfizer before breaking the blind. If the blind is broken, the investigator should promptly inform the Pfizer Clinician or Medical Monitor. The subject for whom the blind has been broken will be discontinued from the study and undergo the early termination (ET) procedures.

5.3. Subject Compliance

For self-administration of the investigational product at home, compliance 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 their 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.

Investigational product should be taken in the morning. 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 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 and parent(s)/legal guardian (if applicable) and ensure steps are taken to improve compliance. In addition, if the compliance deviation reaches the thresholds defined above it should also be recorded as a medication error (see Section 8.4.4).

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

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

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

5.4.2. Preparation and Dispensing

The investigational product should be dispensed using a drug management system at each dispensing visit. A qualified staff member will dispense the investigational product via unique container numbers in 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.

5.5. Administration

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 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.

Table 2. Investigational Product Administration

Treatment Assignment	QD Dosing*
100 mg QD	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
Placebo	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.

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

5.6. 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.

5.7. 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).

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

Subjects will abstain from all concomitant medications as described in Section 4.2 and Appendix 3 of the protocol. Medications that are taken in the Screening/Washout period (after informed consent is obtained and before the first dose of investigational product) will be documented as prior medications. Medications taken after the first dose of investigational product has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in study records with indication (if atopic dermatitis), reference to any associated adverse event, dose, and start and

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

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

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

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

Subjects are required to fast for at least 8 hours prior to all visits that include lipid profile panel testing (Day 1, Week 4, Week 12, and EOS). During the fasting period, subjects should refrain from all food and liquids (water and permitted non-study medications are allowed).

ECGs will be interpreted by a central reader for all visits.

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

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

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

6.1. Visit 1, Screening

Subjects will be screened (Visit 1) within 28 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject, or parent(s)/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.

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 aged less than the legal age of majority (legal adulthood) in the subject's country, obtain written informed consent from parent(s)/legal guardian, and informed assent from the patient (if age appropriate according to local regulations);
- Register subject using the IRT system;
- Collect demography;
- Administer C-SSRS, SBQ-R and PHQ-8. Subjects meeting any of the criteria specified in Exclusion Criterion 2 as described in Section 4.2 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;
- 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 drug treatments for AD including the use of topical treatments, systemic treatments and other treatments;

  - 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;

- Obtain height;

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

- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), 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;

- For China and Republic of Korea only: Subjects who are HBsAg negative, HBcAb positive, and HBsAb positive will have reflex testing for HBV DNA;

- For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all subjects rather than as a reflex test. Subjects with negative results for HBsAg, HBcAb and HBsAb may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 or early termination.

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

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

6.2. Treatment Period

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

- Administer patient-reported outcomes (PROs) including: PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y), SF-36v2, Acute, WPAI:AD and FACIT-F (or Peds-FACIT-F). SF-36v2 and WPAI:AD will be completed by adult subjects only;
- Adolescents 12-17 years of age will not complete the SF-36v2 or WPAI:AD. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;
- Review eDiary pruritus NRS, Night Time Itch Scale, and PSAAD completion (in selected countries) and review eDiary procedures with subject as necessary;
- Review any changes in the subject's prior and concomitant medications and treatment information;
- 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;
- Perform a single 12-lead electrocardiogram (ECG). Clinically significant or exclusionary ECG findings require screen failure;
- Conduct complete physical examination;
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel), 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;
- CCI [redacted]
- Collect sample for viral surveillance: Herpes simplex virus (HSV) HSV-1, HSV-2 and VZV;
- Conduct clinical evaluations including Fitzpatrick Skin Type Assessment, IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Photography of AD lesions (at selected sites; Section 7.7.5);

- 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 of Inclusion/Exclusion Criteria;
- If subject continues to meet all Inclusion/Exclusion criteria, officially randomize subject into the study;
- Dispense investigational product to the subject;
- Administer first dose of investigational product to subject;
- Obtain an additional pulse rate and blood pressure (after at least 5 minutes of rest). Pulse rate and blood pressure must be performed at least 1 hour following the first dose of investigational product;
- 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, Night Time Itch Scale, 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 EQ-5D-Y);
- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y instead of the EQ-5D-5L;
- Review pruritus NRS, Night Time Itch Scale, and PSAAD completion (in selected countries) and review eDiary procedures with subject as necessary. Instruct subject that pruritus NRS and Night Time Itch Scale will now be completed only at visits on site and in the eDiary and will no longer be completed on a daily basis at home;

- 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;
- Administer investigational product at clinic;
- Perform a single 12-lead electrocardiogram (ECG);
- Conduct targeted physical examination;
- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), and urinalysis;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Photography of AD lesions (at selected sites; Section 7.7.5);
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest). Vital signs must be performed at least 1 hour following administration of 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 any changes in the subject's concomitant medications and treatments information;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Assess and record any Adverse Events since the last visit.

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

- Administer PROs including PtGA, DLQI (or CDLQI), POEM, HADS and EQ-5D-5L (or EQ-5D-Y);
- Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI and the EQ-5D-Y instead of the EQ-5D-5L;
- Review PSAAD daily completion (in selected countries), Night Time Itch Scale, and pruritus NRS completion for this visit in the eDiary;

- Perform a single 12-lead electrocardiogram (ECG);
- Conduct targeted physical examination;
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel), 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;
- Administer investigational product at clinic;
- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest) and oral or tympanic temperature. Vital signs must be performed at least 1 hour following administration of investigational product;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Photography of AD lesions (at selected sites; Section 7.7.5);
- 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;
- 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 day)

- 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 day)

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

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

- Review PSAAD daily completion (in selected countries), Night Time Itch Scale, and pruritus NRS completion for this visit in the eDiary;

- 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;

- Obtain blood samples for PK analysis 2.0 hours (±30 min) pre-dose;

- Administer investigational product at clinic;

- Perform a single 12-lead electrocardiogram (ECG);

- Conduct targeted physical examination;

- Obtain samples for laboratory testing: serum chemistry, hematology (including coagulation panel), and urinalysis;

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

- Photography of AD lesions (at selected sites; Section 7.7.5);

- Obtain vital signs including pulse rate, blood pressure, respiratory rate and oral or tympanic temperature (after at least 5 minutes of rest). Vital signs must be performed at least 1 hour following administration of 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 any changes in the subject's concomitant medications and treatments information;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Dispense investigational product to the subject;
- Assess and record any Adverse Events since the last visit.

6.2.7. Visit 8, Day 85/Week 12 (±3 days) or Early Termination Visit

- Administer PROs including PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y), SF-36v2, Acute, WPAI:AD and FACIT-F (or Peds-FACIT-F). SF-36v2 and WPAI:AD will be completed by adult subjects only;
- Adolescents 12-17 years of age will not complete the SF-36v2 or WPAI:AD. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;
- Review PSAAD daily completion (in selected countries), Night Time Itch Scale, and pruritus NRS completion for this visit in the eDiary;
- 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;
- 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;
- Obtain height;
- Perform a single 12-lead electrocardiogram (ECG);
- Conduct complete physical examination;
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel), lipid profile, and urinalysis;

- For China, Japan and Republic of Korea only: In subjects who had HBV DNA testing at Screening, collect blood sample for repeat HBV DNA testing, as appropriate;
- CCI [redacted];
- Administer investigational product at clinic;
- Obtain blood samples for PK analysis 1.0 hour (±15 min) and 2.0 hours (±30 min) post-dose. If the ET visit occurs after Week 8, collect PK samples only if the subject takes the investigational product at the site visit;
- Obtain an additional pulse rate and blood pressure (after at least 5 minutes of rest). Pulse rate and blood pressure must be performed at least 1 hour following administration of investigational product;
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Photography of AD lesions (at selected sites; Section 7.7.5);
- 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 medication and treatments information;
- Review eDiary to assess completion;
- Perform drug accountability procedures;
- Assess and record any Adverse Events since the last visit;
- Subjects who complete the trial to this visit will be assessed for eligibility for participation in long-term extension study B7451015. Subjects who are not eligible or are not interested are to continue to Visit 9 (see Section 6.3.1).

6.3. Follow-up Visits

6.3.1. Visit 9, Day 120/Week 16 (±3 day)

- Administer PROs including PtGA, DLQI (or CDLQI), POEM, HADS, EQ-5D-5L (or EQ-5D-Y), SF-36v2, Acute, WPAI:AD and FACIT-F (or Peds-FACIT-F). SF-36v2 and WPAI:AD will be completed by adult subjects only;
- Adolescents 12-17 years of age will not complete the SF-36v2 or WPAI:AD. Adolescents 12-17 years of age will complete the CDLQI instead of the DLQI, the EQ-5D-Y instead of the EQ-5D-5L and Peds-FACIT-F instead of the FACIT-F;

- Review PSAAD daily completion (in selected countries), Night Time Itch Scale, 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 electrocardiogram (ECG);
- Conduct targeted physical examination;
- Obtain fasting samples for laboratory testing: serum chemistry, hematology (including coagulation panel), 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);
- Conduct clinical evaluations including IGA, SCORAD, EASI and BSA (calculated in the EASI);
- Photography of AD lesions (at selected sites; Section 7.7.5);
- 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;
- Assess and record any Adverse Events since the last visit.

6.4. Subject Withdrawal

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

If a subject has a clinically significant, treatment-emergent, abnormality at the time of withdrawal from the study, the Pfizer Medical Monitor (or designee) should be notified and every effort should be made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormality. All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels or are deemed clinically stable. Follow-up for abnormal laboratory findings and adverse events by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. Refer to Appendix 4 for Guidelines for Monitoring and Discontinuation.

Withdrawal of consent:

Subjects (or parent(s)/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, 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 (or parent(s)/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 (or parent(s)/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 (or parent(s)/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. 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 visits to confirm the subject has not become pregnant during the study, and at the follow-up visit.

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (Ecs) or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

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

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

7.3. Safety Assessments

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

7.3.1. Vitals Signs

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

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

Blood pressure (BP) will be measured using a standard calibrated blood pressure measuring device. A BP device that uses multiple cuff sizes based on the arm circumference is the required type of device. The appropriate cuff size for the subject must be used to ensure accurate measurement. The arm circumference at the midpoint of the length of the upper arm should be measured to determine the appropriate cuff size in accordance with the specifications of the BP measuring device. The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time.

Subjects should be seated in a chair, back supported, and arms bared (free of restrictions such as rolled-up sleeves, etc.) and supported at heart level. Measurements should be taken on the same arm at each visit (preferably non-dominant). Subjects should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements. Measurements should begin after at least 5 minutes of rest.

Heart rate should be measured at approximately the same time as BP for a minimum of 30 seconds. When the timing of BP and pulse (heart) rate measurements coincides with a blood collection or other study procedure, BP and pulse (heart) rate should be obtained first.

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

Complete AD disease history includes collection of details of AD at Screening: AD diagnosis, the use of topical treatments, systemic treatments and other treatments for AD. Medical history in addition to AD history including disease duration will be collected at screening. Medical history also includes history of alcohol and tobacco use. Smoking status and average weekly alcohol consumption (units/week) will be collected, where a unit contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz/150 mL (a glass) of wine, 12 oz/360 mL of beer, or 1.5 oz/45 mL of 90 proof of spirits. Height and weight will be measured without the subject wearing shoes. Height (inches or centimeters) and weight (lbs. or kg) will be measured and recorded in the source document at the screening visit. Weight (lbs. or kg) will continue to be measured and recorded 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.

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

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

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

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

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

Purified Protein Derivative (PPD) Test

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

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

7.3.5. Electrocardiogram

A single 12-lead ECG will be collected at screening and all other on-site visits as specified in the Schedule of Activities. ECGs reading 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.

A subject's screening ECG must be within normal limits prior to randomization.

7.3.6. Special Safety Assessment

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

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

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

7.4. Skin Type Assessment

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

7.5. Assessment of Suicidal Ideation and Behavior

Subjects meeting exclusionary results as described in Section 4.2 on the C-SSRS, 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.

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 17).[17] At the screening visit, if there are "yes" answers on items 4 or 5 in the past year or on any question in the suicidal behavior section of the C-SSRS in the past 5 years, the subject will not be included in the study. Trained site staff is to administer the C-SSRS to all subjects at screening and assess the subject's eligibility based on the answers.

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

The Suicidal Behaviors Questionnaire-Revised (Appendix 18) 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.[18] Site staff is to 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 19) is a patient-reported questionnaire consisting of 8 items to assess the subject's depression level. At Screening Visit, if PHQ-8 total score ≥15, the subject will not be included in the study.[19] Site staff is to administer the PHQ-8 to all subjects at screening and score immediately.

7.6. Clinical Laboratory Tests

7.6.1. Blood Volume

Total blood sampling volume planned for this study is approximately 124 mL. Further details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the lab manual.

7.6.2. Laboratory Tests

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

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

Subjects must abstain from all food and drink (except water and non-study medications) for an 8-hour overnight fast prior to labs that include the lipid profile panel on Day 1, Week 4, Week 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 count and indices	Glucose	Protein (qual)	HBcAb[a]
(MCH, MCHC, MCV, RBC	Na+, K+, Cl- ,Ca++	Blood (qual)	HBsAb[b]
Morphology)	Total CO2 (Bicarbonate)	Ketones	HCVAb[a]
Reticulocyte count	AST, ALT	Nitrites	HCV RNA[b]
Platelet count	GGT	Leukocyte esterase	VZV IgG Ab[g]
WBC count with differential	Total, Indirect & Direct Bilirubin	Microscopy and/or culture[d]	Serum FSH (WONCBP only) or Pregnancy Test[a, c]
Total neutrophils (%, Abs)	Alkaline phosphatase		Urine pregnancy test[c]
Eosinophils (%, Abs)	Lactate dehydrogenase		QFT-G or PPD (if applicable) or T-SPOT®.*TB* test (Japan only)[e]
Monocytes (%, Abs)	Uric acid		HSV-1, HSV-2, VZV
Basophils (%, Abs)	Albumin		HBV DNA[h]
Lymphocytes (%, Abs)	Total protein		
Coagulation Panel	Lipid Profile Panel[f]		
Activated Partial Thromboplastin Time (APTT)	Total cholesterol		
	LDL		
	HDL		
Prothrombin Time/International Normalized Ratio (PT/INR)	Triglycerides		

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. For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all subjects rather than as a reflex test.

c. Pregnancy testing for females 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. For Japan only: QFT-G is preferred but T-SPOT®.*TB* test may be performed instead through the site's local laboratory.

f. Lipid Profile Panel requires at least an 8 hour fast. Lipid profile panel will be completed at Day 1, Week 4, Week 12, and EOS, and will include total cholesterol, LDL, HDL, and triglycerides.

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

h. For China and Republic of Korea 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 LLQ will be excluded. Subjects who are HBV DNA negative or below LLQ may be randomized but will have repeat HBV DNA testing at Week 12 (or early termination).

For Japan only: Subjects with negative results for HBsAg, HBcAb and HBsAb tests may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 or early termination.

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

7.6.2.1. Hepatitis Testing

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

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 Republic of Korea 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 LLQ will be excluded. Subjects who are HBV DNA negative or below LLQ may be randomized but will have repeat HBV DNA testing at Week 12 (or early termination).

For Japan only:

- In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all subjects rather than as a reflex test. Subjects with negative results for HBsAg, HBcAb and HBsAb may be eligible. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Subjects who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND subjects who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Subjects who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 or early termination.

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

- 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 AD clinical trials may be permitted to perform the clinical evaluations of atopic dermatitis when designated by the primary site Investigator. The evaluator must receive and document protocol specific and applicable efficacy assessment scales training prior to performing these evaluations. **To assure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual subject throughout the study whenever possible**; a back-up experienced and qualified, protocol-trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation.

7.7.2. Investigator's Global Assessment (IGA)

The Investigator's Global Assessment of atopic dermatitis is scored on a 5-point scale (0-4), reflecting a global consideration of the erythema, induration and scaling. The clinical evaluator of atopic dermatitis will perform an assessment of the overall severity of atopic dermatitis and assign an IGA score and category as described in Table 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 (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 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).

7.7.5. Photography of Representative AD Lesions

For subjects at selected study sites, photographs of treated AD will be obtained (according to the separately provided Photography Instructions) at Baseline/Day 1, Week 2, Week 4, Week 8, EOT, and EOS. Areas photographed should be recorded in source documents so that the same AD body region(s) will be photographed at each time point. Photographs will be utilized for illustrative purposes and not formally evaluated as an endpoint for analysis.

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

CCI [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

7.8.2. Night Time Itch Scale

Severity of Night Time Itch

The severity of itch (pruritus) during the night due to atopic dermatitis will be assessed using the Night Time Itch Scale, a horizontal NRS (Appendix 7). Subjects will be asked to assess their worst itching due to atopic dermatitis during their most recent night's sleep 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 the Night Time Itch NRS assessment into an eDiary.

Frequency of Night Time Itch

The frequency of itch (pruritus) during the night due to atopic dermatitis will be assessed using a horizontal NRS (Appendix 7). Subjects will be asked to assess frequency of itching due to atopic dermatitis during their most recent night's sleep 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 the Night Time Itch NRS assessment into an eDiary.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

7.9. Pharmacokinetics

7.9.1. Plasma for Analysis of PF-04965842

During the study, blood samples (3 mL) to provide minimum 1 mL of plasma for PK analysis will be collected into appropriately labeled tubes containing potassium ethylenediaminetetraacetic acid (K_2EDTA) at times specified in the STUDY PROCEDURES section of the protocol.

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

- At 2.0 hours (±30 min) pre-dose at Week 8;
- At 1.0 hour (±15 min) and 2.0 hours (±30 min) post-dose at Week 12.

All efforts will be made to obtain the PK samples 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). Samples obtained outside the windows specified in the SOA will be considered a protocol deviation. For ET visits, if the subject discontinues before Week 8 do not collect PK samples. If the ET visit occurs after Week 8, collect PK samples 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 samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

- 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. The contract analytical laboratory will be provided with randomization codes so that only samples in the PF-04965842 treatment groups are assayed. Placebo samples may be assayed in the event of suspected error in subject randomization. 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.

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/parent(s)/legal guardian, if applicable. In addition, each study subject/parent(s)/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/parent(s)/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 5.3 for examples of medication errors related to compliance with investigational product.

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

In the event of a medication dosing error, the sponsor should be notified immediately.

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

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

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

Sample size for the study was based on the co-primary endpoints. A total sample of 375 subjects with 150 subjects randomized to PF-04965842 200 mg QD, 150 subjects randomized to PF-04965842 100 mg QD and 75 subjects randomized to placebo (2:2:1 randomization) would provide at least 95% power to detect a difference in IGA response rate of at least 20% between PF-04965842 200 mg QD (or PF-04965842 100 mg QD) and placebo, assuming the placebo response rate is 6% at Week 12. Furthermore, this will also provide at least 99% power to detect a difference in EASI-75 response rate of at least 30% between PF-04965842 200 mg QD (or PF-04965842 100 mg QD) and placebo, assuming the placebo response rate is 15% at Week 12.

The Type-I error for testing each individual co-primary endpoint was fixed at 5%. Since both endpoints are co-primary, the study will meet its primary endpoint only if both hypotheses (corresponding to each co-primary endpoint) are rejected. Therefore, the Type-I error rate remains controlled at 5% for testing the primary endpoint. The power to reject both hypotheses when a true difference exists (alternative hypothesis is true) could be at least 94% depending on the correlation between the endpoints.

9.2. Efficacy Analysis

9.2.1. Analysis Sets

The primary analysis population for efficacy data will be the Full Analysis Set (FAS) defined as all randomized subjects receiving at least one dose of study medication. The primary efficacy endpoint and the key secondary efficacy endpoints will also be analyzed for the Per-Protocol Analysis Set (PPAS) defined as a subset of FAS who had no major protocol violations. 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.

9.2.2. Testing Procedure for Multiple Comparisons

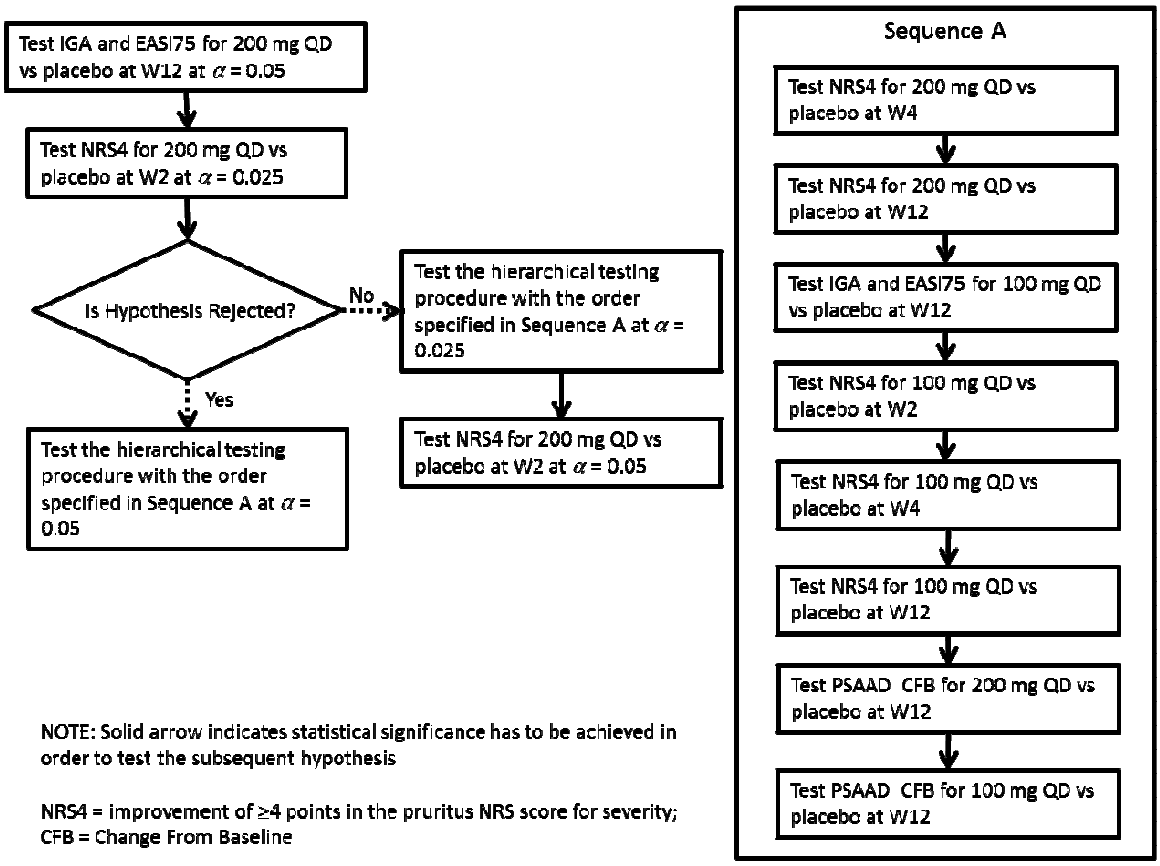
There are five key hypotheses to be tested for each of the two PF-04965842 doses (200 mg QD and 100 mg QD) versus placebo, for the co-primary endpoints and two key secondary endpoints. The familywise Type-I error rate will be strongly controlled at 5% using a sequential, Bonferroni-based iterative multiple testing procedure.

The procedure will first test the co-primary endpoints (IGA and EASI75 at Week 12 for 200 mg QD vs placebo) at the 5% level. If this hypothesis is not rejected, then no further testing will be conducted. If this hypothesis is rejected, then testing may continue on two paths:

- The hypothesis for severity of pruritus (200 mg QD vs placebo at Week 2) will be tested at the 2.5% level. If this hypothesis is rejected, then the unused alpha level of 2.5% will be passed on to the testing for the key secondary endpoints and the co-primary endpoints for 100 mg QD vs placebo, in the order specified in Sequence A at a 5% significance level (see figure below). Testing stops at any point where a hypothesis cannot be rejected.

- If the hypothesis for severity of pruritus (200 mg QD vs placebo at Week 2) is not rejected at the 2.5% level, then the hypotheses for the key secondary endpoints and the co-primary endpoints for 100 mg QD vs placebo, in the order specified in Sequence A will be tested at a 2.5% significance level (see figure below). If all hypotheses in this sequence are rejected, then the unused alpha level of 2.5% will be passed on to the testing of the hypothesis for severity of pruritus (200 mg QD vs placebo) at Week 2 at the 5% level.

Figure 2. Schematic for Multiple Testing Procedure



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

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

9.2.3. Analysis of the Primary Endpoints

The co-primary endpoints will be analyzed using the (Cochran-Mantel-Haenszel) test adjusted by randomization strata (baseline disease severity and age) and both must achieve statistical significance to meet the primary objective. The difference between each active group and the placebo group in the proportion of subjects achieving IGA response (similarly for EASI75) along with its 95% confidence interval (using the normal approximation for the difference in binomial proportions) will be reported. If a subject withdraws from the study, then this subject will be counted as non-responder for endpoints after withdrawal. Additional secondary analyses will utilize Missing at Random and Not at Random approaches (eg, Longitudinal Mixed models and jump to reference analyses).

9.2.4. Analysis of Secondary Endpoints

The key secondary endpoints which are expressed as proportions such as EASI50, EASI90 and the proportion of subjects achieving a 4-point improvement from baseline in the pruritus NRS measure will be analyzed using the same method as the for co-primary endpoints. This

would also apply to any other binary endpoint in the study. Endpoints which are continuous will be analyzed as described below.

For continuous endpoints, such as percent change from baseline in the EASI total score, 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 group, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will be tested at the pre-specified primary time point, Week 12, as well as at the other time points by time point-specific contrasts from the MMRM model.

Continuous endpoints such as the change from baseline i [redacted] For binary endpoints such as the SCORAD50 or SCORAD75 or the proportion of subjects with PtGA of AD of clear (0) or almost clear (1) and ≥2 point improvement from baseline over 12 weeks, the same method as used for the binary endpoints in Section 9.2.3 will be employed. All secondary endpoints except the key secondary endpoints will be evaluated at the 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;
- 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.

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/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

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

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

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source

documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

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 ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. 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 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 parent(s)/legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's parent(s)/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 he/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 parent(s)/legal guardian, 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 parent(s)/legal guardian and the subject's assent, when applicable, before any study-specific activity is performed. 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.

EudraCT

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

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

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

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

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

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

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

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

16. REFERENCES

1. Eichenfield LF, Ellis CN, Mancini AJ, et al. Atopic dermatitis: epidemiology and pathogenesis update. Semin Cutan Med Surg 2012;31(3 Suppl)(Sep):S3-5.

2. Leicht S, Hanggi M. Atopic dermatitis. How to incorporate advances in management. Postgrad Med 2001;109(6)(Jun):119-27.

3. Margolis JS, Abuabara K, Bilker W, et al. Persistence of mild to moderate atopic dermatitis. JAMA Dermatol 2014;150(6):593-600.

4. Slater NA, Morrell DS. Systemic therapy of childhood atopic dermatitis. Clin Dermatol 2015;33(3): 289-299.

5. Leung DY, Bieber T. Atopic dermatitis. Lancet 2003;361(9352):151-160.

6. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. J Eur Acad Dermatol Venereol 2012;26(8):1045-60.

7. Auriemma M, Vianale G, Amerio P, et al. Cytokines and T cells in atopic dermatitis Eur Cytokine Netw 2012; 24(1):37-44.

8. Mortz C, Andersen K, Dellgren C, et al. Atopic dermatitis from adolescents to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. Allergy 2015;70:836-45.

9. Sandstrom M., Faergemann J. Prognosis and prognostic factors in adult patients with atopic dermatitis: a long-term follow-up questionnaire study. British J. of Dermatology 2004;150:102-10.

10. Deckers I, McLean AS, Linssen S, Mommers M, et al. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies PLoS One 2012;7(7):e39803.

11. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol 2013;132(5): 1132-1138.

12. Lee CH, Chuang HY, Hong CH, Huang SK, et al. Lifetime exposure to cigarette smoking and the development of adult-onset atopic dermatitis.Br J Dermatol 2011;164(3): 483-9.

13. Homey B, Steinhoff M, Ruzicka T, et al. Cytokines and chemokines orchestrate atopic skin inflammation.J Allergy Clin Immunol 2006;118(1):178-89.

14. Cornelissen C, Luscher-Firzlaff J, Baron JM, et al. Signaling by IL-31 and functional consequences. Eur J Cell Biol 2012;91(6-7):552-66.

15. Gittler JK, Shemer A, Suarez-Farinas M, Fuentes-Duculan J, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol 2012;130(6):1344-54.

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

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

18. Osman A, Bagge CL, Gutierrez PM, et al. The Suicidal Behaviors Questionnaire-Revised (SBQ-R): validation with clinical and nonclinical samples. Assessment. 2001; 8(4):443-54.

19. Kroenke K., Strine, T., Spitzer C., et al, The PHQ-8 as a measure of current depression in the general population 2009. J Affect Disord 2009;114(1-3);163–73.

20. Yosipovitch G, Reaney M, Mastey V, et al. Validation of the peak pruritus numerical rating scale: Results from clinical studies of dupilumab in adult patients with moderate-to-severe atopic dermatitis: 5063. Journal of the American Academy of Dermatology. 2017 Jun 1;76(6):AB278.

21. Rabin R, Gudex C, Selai C, et al. From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value in Health 2014;17(1):70-6.

22. Van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012;15(5):708-15.

23. Ramos-Goñi JM, Pinto-Prades JL, Oppe M, et al. Valuation and modeling of EQ-5D-5L health states using a hybrid approach. Medical care 2017;55(7):e51-8.

24. Yang Y, Brazier J, Longworth L. EQ-5D in skin conditions: an assessment of validity and responsiveness. Eur J Health Econ. 2015;16(9):927-939.

25. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Quality of Life Research. 2013;22(7):1717-27.

26. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of life research 2011;20(10):1727-36.

27. Agborsangaya CB, Lahtinen M, Cooke T, Johnson JA. Comparing the EQ-5D 3L and 5L: measurement properties and association with chronic conditions and multimorbidity in the general population. Health and quality of life outcomes 2014;12(1):74.

28. Wille N, Badia X, Bonsel G, Burstrom K, Cavrini G, Devlin N, Egmar AC, Greiner W, Gusi N, Herdman M, Jelsma J Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res 2010 Aug;19(6):875-886.

29. Ravens-Sieberer U, Wille N, Badia X, et al. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. Qual Life Res 2010;19(6):887-97.

30. EuroQol Group. EuroQolea new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16:199-208.

31. Simpson EL, Gadkari A, Worm M, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): A phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). J Am Acad Dermatol. 2016;75(3):506-515.

32. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375:2335-2348.

33. Poole CD, Chambers C, Sidhu MK, et al. Health-related utility among adults with atopic dermatitis treated with 0.1% tacrolimus ointment as maintenance therapy over the long term: findings from the Protopic CONTROL study. Br J Dermatol 2009;161(6):1335-40.

34. Kim C, Park KY, Ahn S, et al. Economic impact of atopic dermatitis in Korean patients. Ann Dermatol. 2015;27(3):298-305.

35. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. Clinical and Experimental Dermatology 1994;19: 210-216.

36. Basra MK, Salek MS, Camilleri L, et al. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27-33.

37. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): Initial validation and practical use. British Journal of Dermatology 1995;132:942-49.

38. Ersser SJ, Cowdell F, Latter S, et al. Psychological and educational interventions for atopic eczema in children. The Cochrane Library. 2014;Jan 1.

39. Schmitt J, Langan S, Williams H, et al. What are the best outcome measurements for atopic eczema? A systematic review. J Allergy Clinical Immunol 2007;120(6):1389-98.

40. White D, Leach C, Sims R, et al. Validation of the Hospital Anxiety and Depression Scale for use with adolescents. Br J Psychiatry 1999;175(5):452-4.

41. Ware J, Kosinski M, Bjorner J, et al. Determining important differences in scores. User's Manual for the SF-36v2® Health Survey. Lincoln (RI): QualityMetric Incorporated; 2007:125-33.

42. Reilly MC, Tanner A, Meltzer EO. Work, classroom and activity impairment instruments. Validation studies in allergic rhinitis. Clin Drug Invest 1996;11(5):278-288.

43. Reilly MC, Zbrozek AS, Dukes EM. The Validity and Reproducibility of a Work Productivity and Activity Impairment Instrument. PharmacoEconomics 1993;4(5):353-365.

44. Reilly MC, Lavin PT, Kahler KH, et al. Validation of the Dermatology Life Quality Index (DLQI) and the Work Productivity and Activity Impairment: Chronic Hand Dermatitis Questionnaire (WPAI-ChHD) in Chronic Hand Dermatitis (ChHD). J Am Academy Dermatol. 2003;48:128-30.

45. Cella D, Lai JS, Chang CH, et al. Fatigue in cancer patients compared with fatigue in the general United States population. Cancer 2002;94(2):5 28-38.

46. Lai J, Cella D, Holm S, et al, Measuring Fatigue for Children with Cancer: Development and Validation of the Pediatric Functional Assessment of Chronic Illness Therapy Fatigue (PEDSFACIT-F). J Pediatr Hematol Oncol 2007;29(7):471-9.

Appendix 1. Abbreviations

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

Abbreviation	Term
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	Area under the curve
AUC_{inf}	area under the curve from time zero extrapolated to infinity
AUC_{last}	area under the curve from time zero to last quantifiable
AUC_{tau}	area under the curve over dosing interval tau
BBS	Biospecimen Banking System
BCG	Bacille Calmette Guérin
BID	twice a day
BP	blood pressure
BSA	body surface area
C_{max}	maximum concentration
CD	cluster of differentiation
CCI	[redacted]
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	cyclosporine A
CS	clinically significant
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DILI	drug-induced liver injury
CCI	[redacted]
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index

Abbreviation	Term
EASI-75	Eczema Area and Severity Index 75% improvement from baseline
EBV	Epstein Barr virus
EC	ethics committee
ECG	electrocardiogram
e-Diary	electronic diary
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
ePRO	electronic Patient Reported Outcome
CCI [redacted]	[redacted]
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
CCI [redacted]	[redacted]
FACs	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GM-CSF	granulocyte-macrophage colony-stimulating factor
CCI [redacted]	[redacted]
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
HIV	human immunodeficiency virus
HRQL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
HSV	herpes simplex virus
HTA	health technologies assessment

Abbreviation	Term
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
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
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
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
NRS	numerical rating scale
PCD	primary completion date
PCP	primary care physician
PD	Pharmacodynamics
PEER Study	Pediatric Eczema Elective Registry Study
CCI [redacted]	[redacted]

Abbreviation	Term
	CCI [redacted]
PFS	prefilled syringe
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGx	Pharmacogenomics
PHQ8	Patient Health Questionnaire - 8 items
PI	principal investigator
PK	Pharmacokinetics
POC	proof of concept
CCI [redacted]	[redacted]
PPAS	per-protocol analysis set
PPD	purified protein derivative test
CCI [redacted]	[redacted]
PT	prothrombin time
CCI [redacted]	[redacted]
QD	once daily
QFT-G	QuantiFERON®-TB Gold
QT	Q wave interval
QTc	corrected Q wave interval
QTcF	Fridericia corrected Q wave interval
R_{ac}	accumulation ratio
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBQ-R	Suicide Behaviors Questionnaire-Revised
SCORAD	Scoring Atopic Dermatitis
CCI [redacted]	[redacted]
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	Half-life
T_{max}	time to maximum absorption
TARC	thymus and activation regulated chemokine
TB	tuberculosis
TBili	total bilirubin
TdP	Torsade de Pointes
TH1	type 1 helper T cell
TH2	type 2 helper T cell
TYK2	tyrosine kinase 2

Abbreviation	Term
ULN	upper limit of normal
US	United States
UVA	ultraviolet A light
UVB	ultraviolet B light
VAS	visual analog scale
V/F	volume of distribution/fraction absorbed
VHP	Voluntary Harmonisation Procedure
VZV	varicella zoster virus
WBC	white blood cell
WONCBP	women of non-childbearing potential
CCI [redacted]	[redacted]

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.[16]

Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

Must have three or more basic features described below:

Pruritus

Typical morphology and distribution:

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

Chronic or chronically-relapsing dermatitis

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

Must have three or more following minor features:

Xerosis

Ichthyosis/palmar hyperlinearity, keratosis pilaris

Immediate (type 1) skin test reaction

Elevated serum IgE

Early age of onset

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

Tendency toward non-specific hand or foot dermatitis

Nipple eczema

Cheilitis

Recurrent conjunctivitis

Dennie-Morgan infraorbital fold

Keratoconus

Anterior subcapsular cataracts

Orbital darkening

Facial pallor, facial erythema

Pityriasis alba

Anterior neck folds

Itch when sweating

Intolerance to wool and lipid solvents

Periofollicular accentuation

Food intolerance

Course influenced by environmental and emotional factors

White dermographism, delayed blanch

Appendix 3. Prohibited Concomitant Medications

CYP2C19 Inhibitors

Amitriptyline (Elavil)
Clomipramine (Anafranil)
Fluconazole (Diflucan)
Fluvoxamine (Luvox)
Imipramine (Tofranil)
Ticlopidine (Ticlid)
Esomeprazole (Nexium)
Fluoxetine (Prozac)
Moclobemide
Omeprazole (Prilosec)
Voriconazole (Vfend)

CYP2C19 Inducers

Enzalutamide (Xtandi)
Rifampin

CYP2C9 Inhibitors

Fluconazole (Diflucan)
Amiodarone (Cordarone)
Fluvoxamine (Luvox)
Miconazole
Oxandrolone (Oxandrin)
Voriconazole (Vfend)

CYP2C9 Inducers

Carbamazepine (Tegretol)
Enzalutamide (Xtandi)
Rifampin

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

Discontinuation Criteria

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

- Marked prolongation of the QTcF interval to >500 ms or >60 ms change from screening ECG.

Note: any quoted lab value below must be confirmed by re-test, preferably within 48 hours.

- Serious infection (see definition for Serious Adverse Events in Section 8.2.3).
- Two sequential platelet counts <50,000/mm^3. If the subject has a platelet count <25,000/mm^3, investigational product should be discontinued pending the confirmatory retest. If the subject has a platelet count <50,000/mm^3 and the confirmatory retest cannot be obtained within 48 hours, investigational product should be discontinued pending the confirmatory retest.
- Any platelet count reduction thought to be associated with a bleeding event per the judgement of the investigator (or, if necessary/desired, following discussion with sponsor).
- Two sequential neutrophil counts <500/mm^3.

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

- Two sequential hemoglobin assessments <8.0 g/dL or a decrease of more than 30% from baseline value (either criteria or both).

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.

- 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.

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

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. Night Time Itch Scale

Severity of Night Time Itch

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 your most recent night's sleep? (select one number only)

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

Frequency of Night Time Itch

On a scale of 0 to 10, with 0 being "no itching" and 10 being "constant itching", how would you rate the frequency of itching during your most recent night's sleep (select one number only)

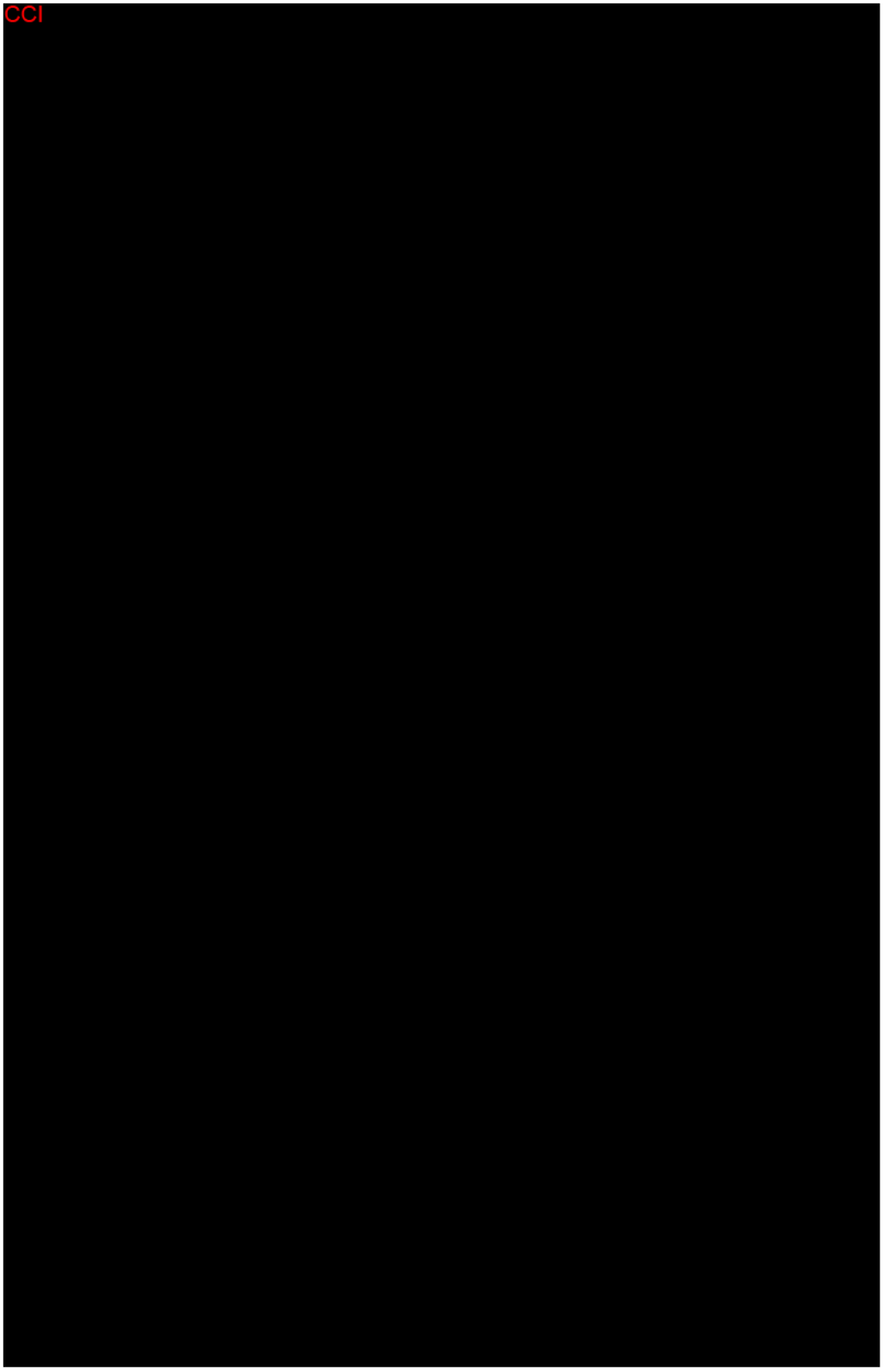
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Never/No itching										Always/Constant itching

CCI [redacted]

[redacted]

- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]
- ☐ [redacted]

CCI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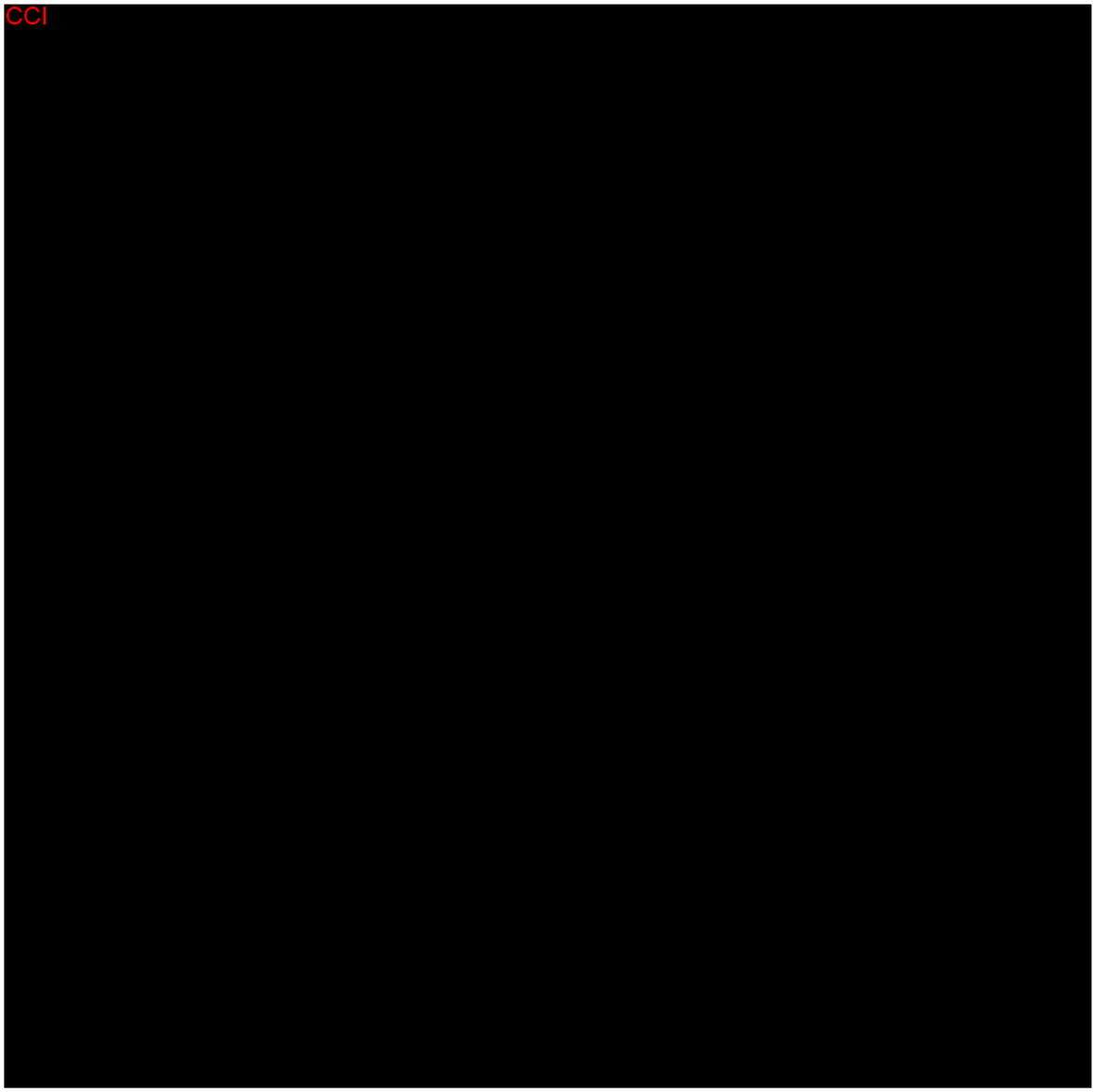
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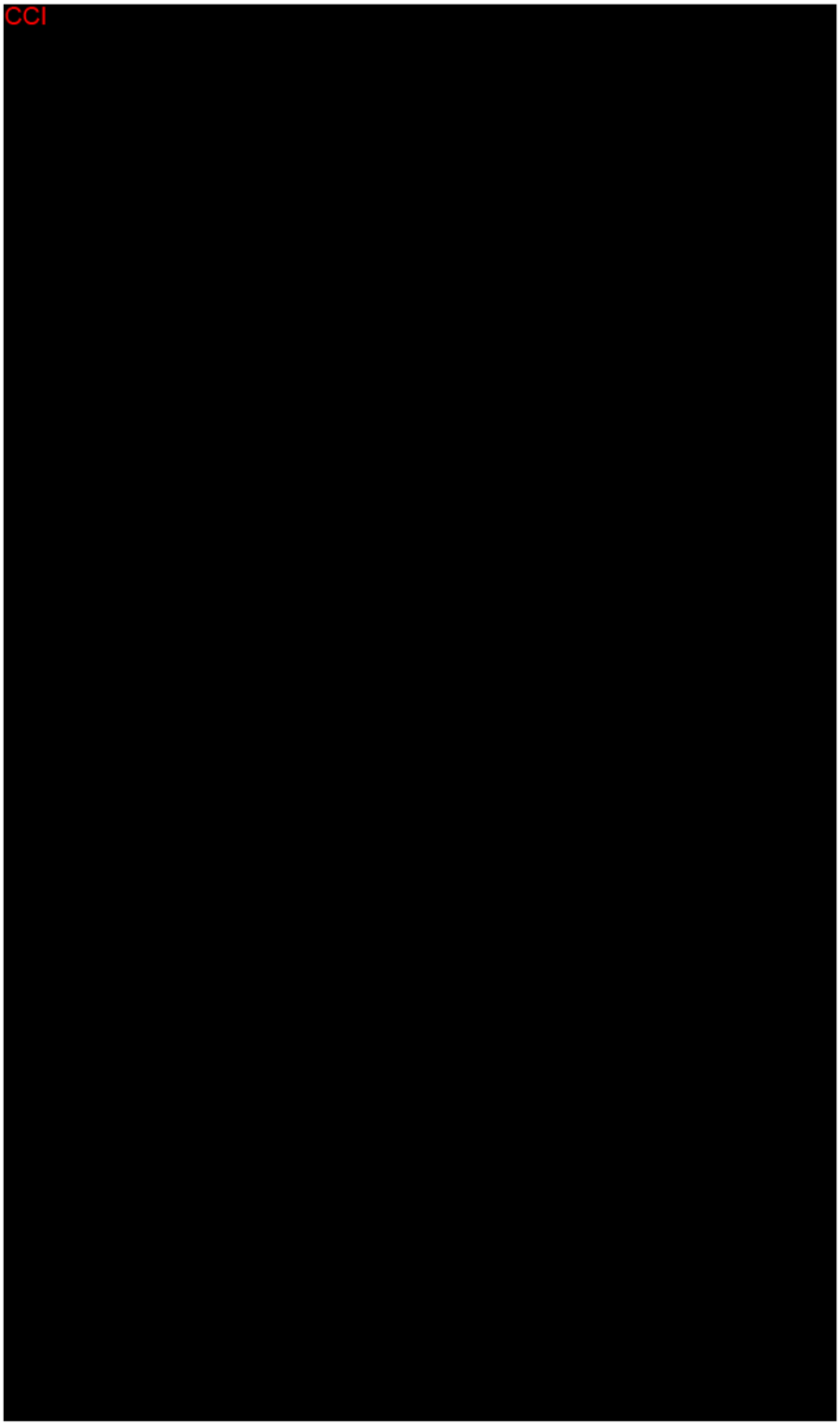
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CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

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.

CCI

[redacted]

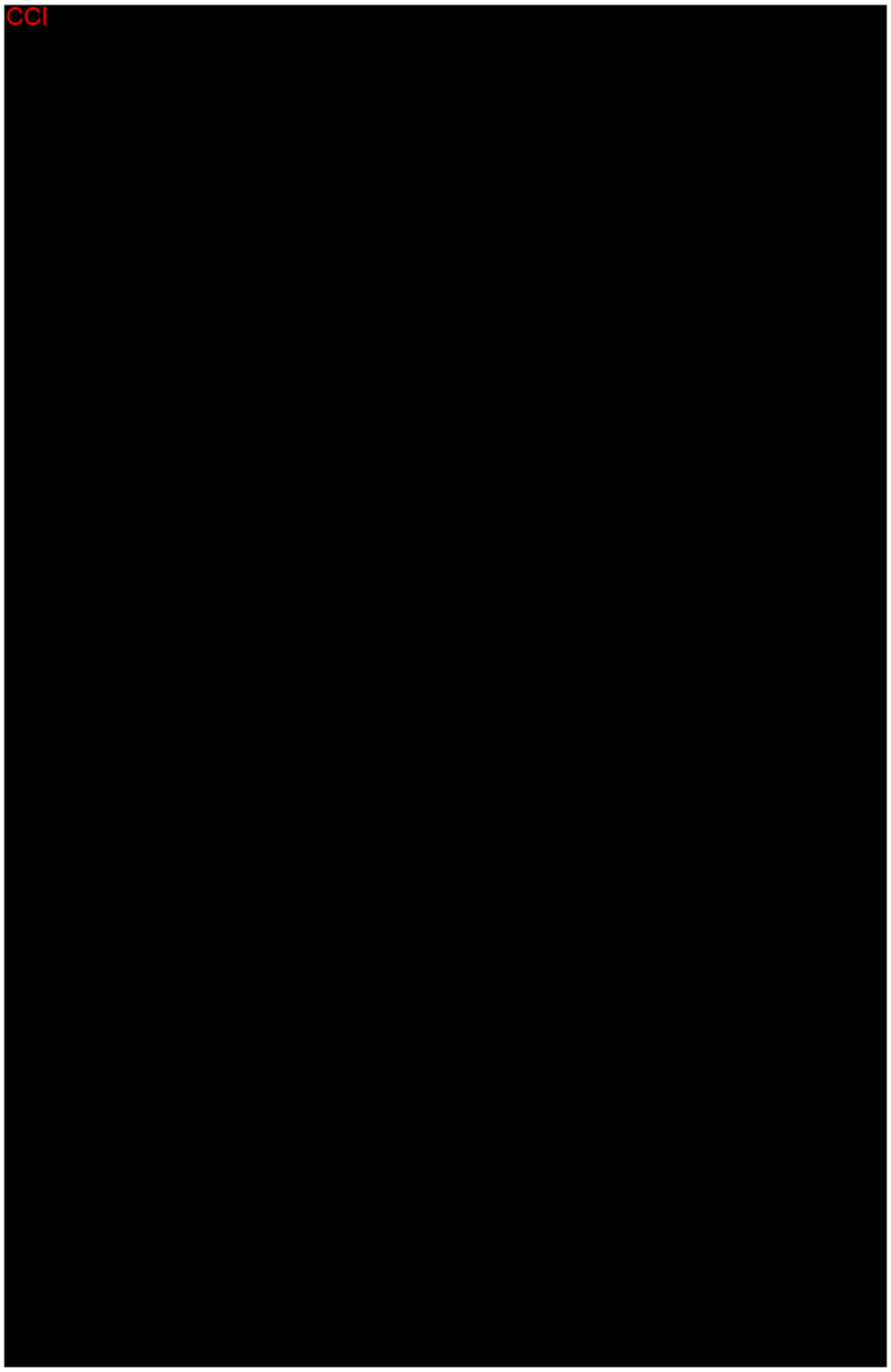
CCI

[redacted]


CCI

CCI

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

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

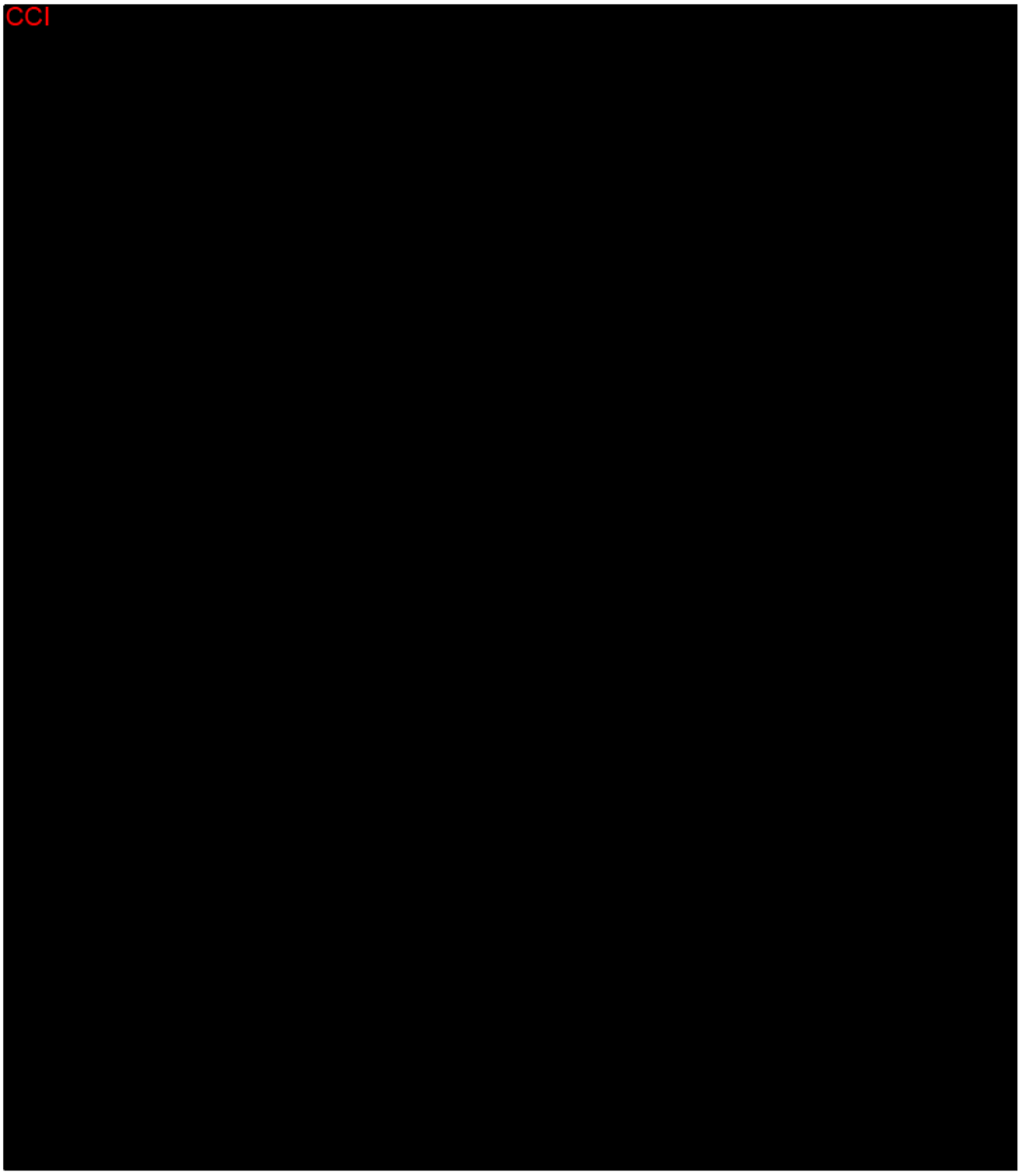
- ☐ Not present
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Moderately Severe
- ☐ Severe
- ☐ Extremely Severe

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

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

CCI

[redacted]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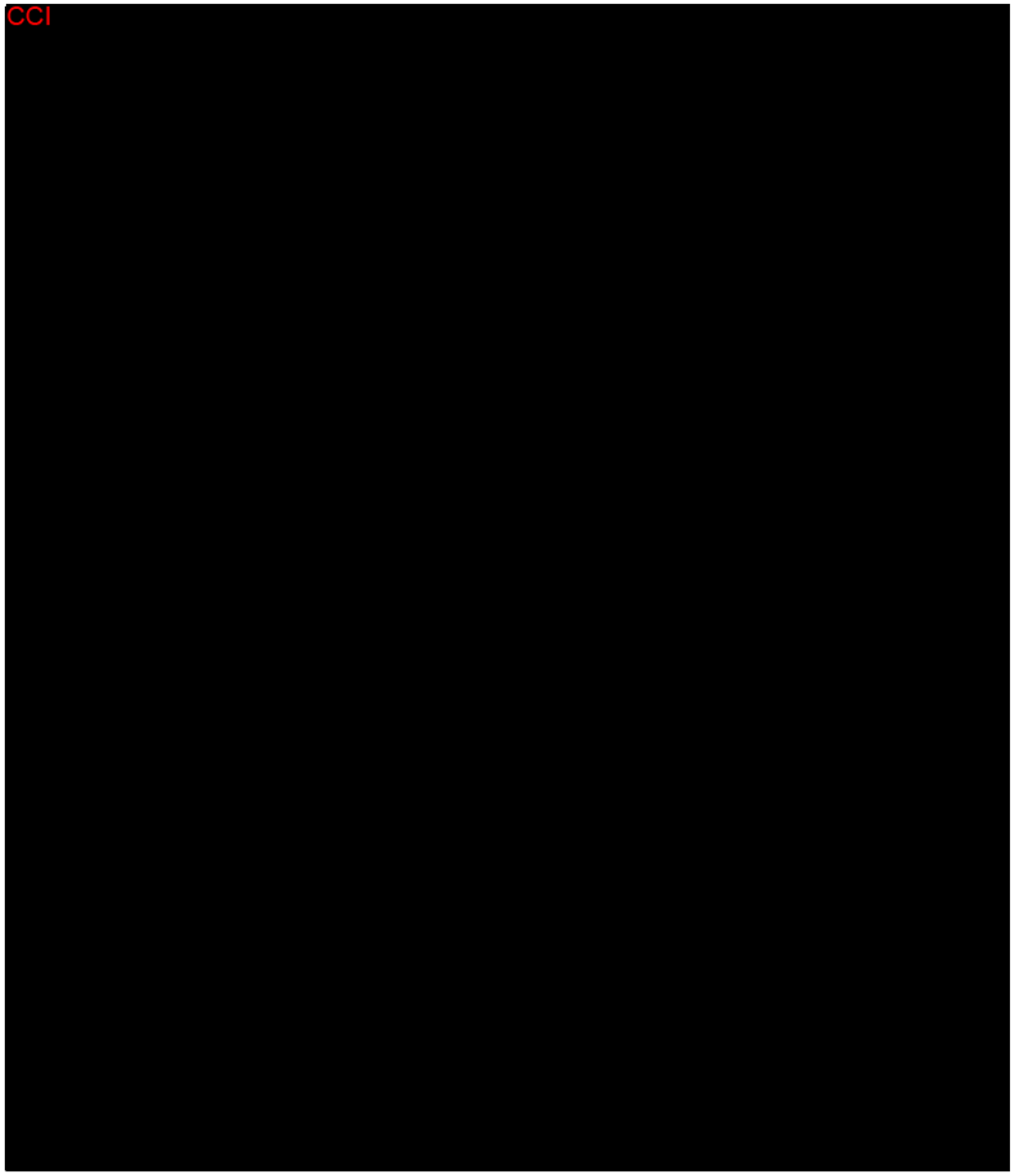
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SF36V2™ HEALTH SURVEY - Page 4 of 6

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

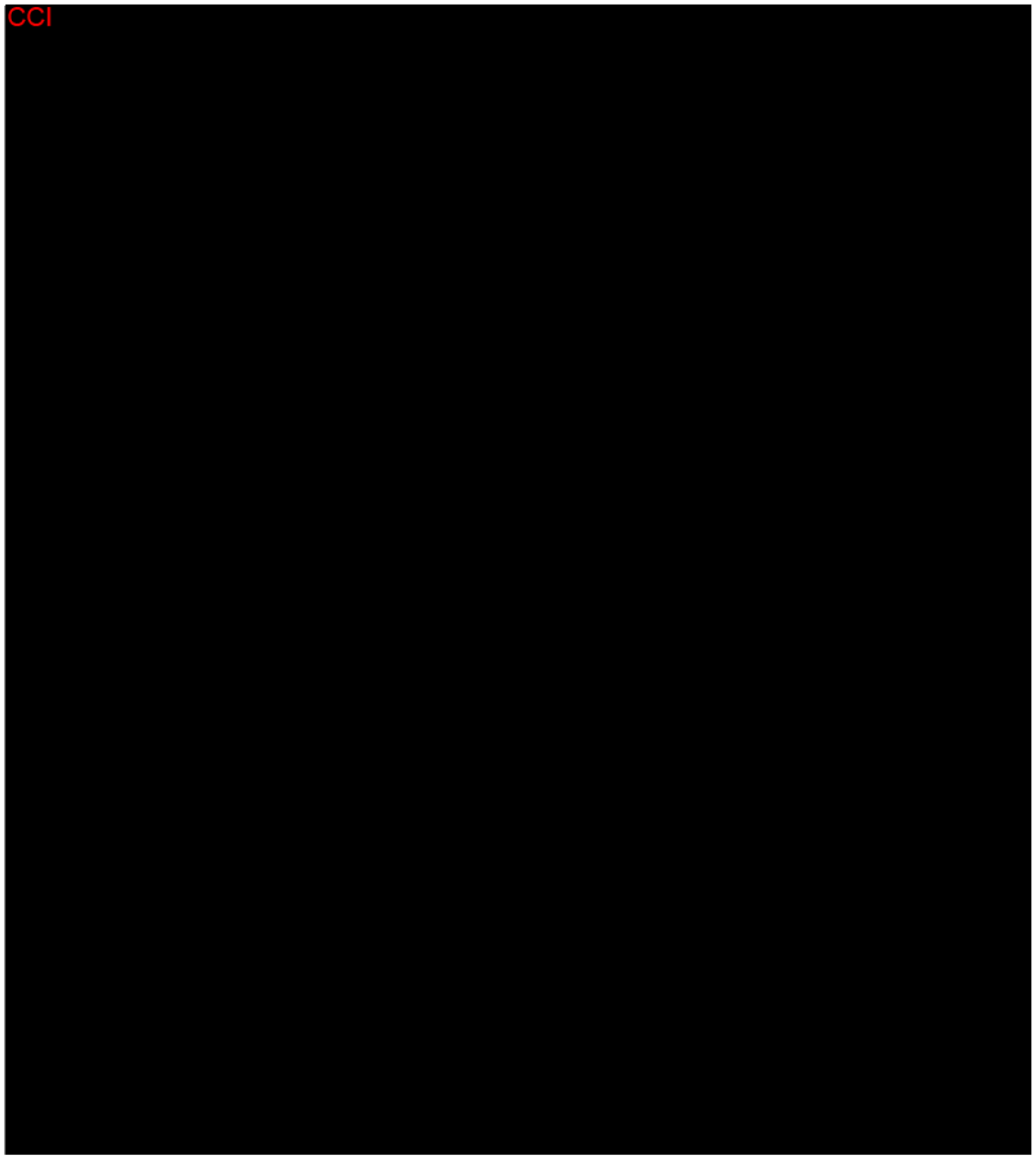
SF36V2™ HEALTH SURVEY - Page 5 of 6

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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Appendix 17. C-SSRS – Columbia Suicide Severity Rating Scale

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT dd - MMM - yyyy

Visit: _____

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

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

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past ____ Months**
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. Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***	Most Severe	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 a week (4) Daily or almost daily (5) Many times each day	____	____

Protocol ID: _____

CENTER | SUBJECT ID

DATE OF VISIT: dd - MMM - yyyy

Visit: _____

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

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

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

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT
dd - MMM - yyyy

Visit: _____

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

	Yes	No	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:	☐	☐	☐	☐
	Total # of interrupted _____		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	Yes	No
	☐	☐	☐	☐
	Total # of aborted _____		Total # of aborted _____	
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempted or preparing to kill yourself (such as collection pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes	No	Yes	No
	☐	☐	☐	☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes	No	Yes	No
	☐	☐	☐	☐

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

Appendix 18. SBQ-R – Suicide Behaviors Questionnaire – Revised

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 19. Patient Health Questionnaire – 8 items

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

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

Visit: _____

PATIENT HEALTH QUESTIONNAIRE (PHQ-8)

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

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