CLINICAL PROTOCOL

A PHASE 2B RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL, MULTICENTER, DOSE-RANGING, STUDY TO EVALUATE THE EFFICACY AND SAFETY PROFILE OF PF-04965842 IN SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Compound:	PF-04965842
Compound Name:	Not applicable (N/A)
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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 the quality of life. The lifetime prevalence of AD in children is 10-20% with 70% of cases occurring in children <5 years of age. Most cases (approximately 75%) improve by adulthood, while approximately 25% of AD patients have symptoms throughout their life.

There are a limited number of treatments available for AD. Current treatments for mild to moderate AD include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. 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).[15] 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 to reduce pruritus and the resulting sleep disturbance.[9,13]

Key cytokines implicated in the pathophysiology of AD including IL-4, IL-5, IL-13, IL-31, and IFN-γ, require janus kinase 1 (JAK1) for signal transduction, suggesting that selective JAK1 inhibitors, that modulate the activity of these cytokines, represent a compelling approach to the treatment of inflammatory skin diseases such as AD.[1]

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 in the human genome: 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 IFNγ.

Objectives and Endpoints:

Primary Objectives

- The primary objective of this study is to evaluate the efficacy of 4 QD dose levels (10, 30, 100, and 200 mg) of PF-04965842 relative to placebo in adult subjects with moderate to severe atopic dermatitis, using the Investigator's Global Assessment (IGA).

Secondary Objectives

- To evaluate the effect of PF-0465842 on additional efficacy endpoints and patient reported outcomes over time in adult subjects with moderate to severe atopic dermatitis.

- To evaluate the safety and tolerability of PF-0465842 over time in adult subjects with moderate to severe atopic dermatitis.

Exploratory Objectives

- To assess pharmacodynamic and disease-related biomarkers over time.

- To characterize pharmacokinetics of PF-04965842 over 12 weeks.

Endpoints

Primary Endpoints

- Proportion of subjects achieving the IGA for clear (0) or almost clear (1) and ≥2 points improvement from baseline at Week 12. The baseline will be defined as the IGA score on Day 1 pre-dose.

Secondary Endpoints

Efficacy Endpoints

Baseline is defined as the score for each assessment on Day 1 pre-dose.

Key Secondary Efficacy Endpoint

- Percent change from baseline in the eczema area and severity index (EASI) total score at Week 12.

Secondary Efficacy Endpoints

- Proportion of subjects achieving the IGA for clear (0) or almost clear (1) and ≥2 points improvement from baseline at all scheduled time points except Week 12.

- Percent change from baseline in the EASI total score at all scheduled time points except Week 12.

- Proportion of subjects achieving ≥3 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points.

- Percent change from baseline in the pruritus NRS from baseline at all scheduled time points.

- Proportion of subjects achieving ≥2 points improvement in the IGA from baseline at all scheduled time points.

- Proportion of subjects achieving a ≥50%, 75% and 90% improvement in the EASI Total score (EASI50, EASI75, EASI90) at all scheduled time points.

- Change from baseline in affected body surface area (BSA) at all scheduled time points.

- Change from baseline in SCORing atopic dermatitis (SCORAD) at all scheduled time points.

- Proportion of subjects achieving a ≥50% and 75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points.

Safety Endpoints

- Incidence of treatment-emergent adverse events.

- Incidence of specific clinical laboratory abnormalities (anemia, neutropenia, thrombocytopenia, lymphopenia, lipid profile, liver function tests [LFTs]).

Patient-Reported Outcome (PRO) Endpoints

Baseline is defined as the score for each assessment on Day 1 pre-dose.

- Change from baseline in Pruritus NRS score at all scheduled time points.

- Proportion of subjects with patient global assessment (PtGA) of AD of clear (0) or almost clear (1) and ≥2 points improvement from baseline at all scheduled time points.

- Change from baseline in dermatology life quality index (DLQI) total score at all scheduled time points.

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

- Change from baseline in the hospital and anxiety depression scale (HADS) at all scheduled time points.

[redacted]

[redacted]

Study Design:

This Phase 2b, multi-center, randomized, double-blind, 5-arm, parallel group study will enroll a total of approximately 250 subjects (providing approximately 200 completers, 40 subjects per treatment group). The study will be conducted at approximately 60 sites.

Subjects who have chronic AD that has been present for at least 1 year (prior to screening visit) and affected BSA of ≥10%, EASI ≥12 and IGA ≥3 at the screening and baseline visits will be included in the study. Subjects must also have a documented history of inadequate response to treatment with topical medications given for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks) within 12 months of the first dose of study drug. Subjects will be randomized to 1 of 4 treatment groups or placebo in the ratio of 1:1:1:1:1. Investigators, subjects, and the sponsor study team will be blinded as to treatment group.

Subjects will be screened within 35 days prior to the first dose of study drug to confirm that they meet the subject selection criteria for the study. There will be a 12-week double-blind treatment period as well as a 4-week follow up period.

An interim analysis may be performed when a total of approximately 110 randomized subjects complete 6 weeks of study or discontinue prematurely from study in order to assess the percent change of EASI score from baseline as well as other efficacy and safety endpoints such as IGA response, pruritus NRS response and hematological parameters as appropriate. Modifications to the design such as adjustments to the final sample size or termination of enrollment of subjects in a treatment arm or stopping a treatment arm may be made upon review of the data. Unless a safety concern arises, no decisions to stop the trial will be made based on this interim analysis. Please refer to Section 9.4 for details.

Study Treatments:

PF-04965842 will be administered orally at one of the following 4 doses: 10, 30, 100, or 200 mg administered QD for 12 weeks. In addition, one cohort will receive PF-04965842-matching placebo.

Statistical Methods:

Sample Size Determination

The sample size is based on the primary efficacy endpoint, IGA response rate of clear or almost clear and ≥2 points improvement at Week 12. For IGA response rate at Week 12, a total of 250 randomized subjects from the 5 treatment groups (providing approximately 200 completers, 40 completers per treatment group assuming 20% dropout rate) will provide approximately 95% power to detect a 33% difference between PF-04965842 and placebo assuming placebo response rate is approximately 10%, and significance level is 0.0125 (Bonferroni adjusted with 4 comparisons).

Efficacy Analysis

Analysis of the Primary Endpoint

When the 12 week treatment period is completed, the analysis of the primary endpoint will be conducted. The primary endpoint is the proportion of IGA responders at Week 12 and the corresponding primary analysis will be based on the normal approximation for the difference in binomial proportions (such as IGA response rates) to test the superiority of each dose of PF-04965842 to placebo at Week 12. Subjects who receive at least one treatment and discontinue from the study before Week 12 will be considered non-responders for the primary endpoint (IGA) for all subsequent visits during the treatment phase until Week 12.

Sensitivity analysis will be performed with a generalized linear mixed model if there are no convergence issues. The modified intention-to-treat (mITT) population will be the subjects who receive at least one dose of randomized investigational product (PF-04965842 or placebo). In addition, dose-response analysis using an E_{max} model may be provided for the primary endpoint.

Analysis of the Secondary Endpoints

The key secondary endpoint is the percent change from baseline in EASI score at Week 12. The estimates for treatment effect will be obtained by fitting the mixed-effect models repeated measures (MMRM) assuming missing at random if there is no convergence issue to the percent change of EASI score from baseline score. MMRM will also be employed for other continuous secondary endpoints.

In addition to the primary analysis based on the pairwise evaluation of the treatment effects, we will explore the modeling of dose-response relationship for the key secondary endpoint.

The binary secondary endpoints will be analyzed using the same method specified for the primary endpoint.

Analysis of Other Endpoints

Other continuous endpoints such as change from baseline in PSAAD, PtGA, DLQI, POEM, and HADS over 12 weeks and change from baseline in the pruritus severity and frequency over time will be analyzed with the same method used for the continuous endpoints in Section 9.2.2. For the binary endpoint such as proportion of subjects with PtGA of AD of clear (0) or almost clear (1) and ≥2 points improvement from baseline over 12 weeks, the same method used for the binary endpoint in Section 9.2.1 will be employed.

Safety Analysis

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. Safety endpoints for the study include:

- On-treatment adverse events (AEs) and serious adverse events (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, anemia, neutropenia, thrombocytopenia, lymphopenia, lipid profile, LFTs).
- Vital signs.
- Electrocardiography (ECG) parameters if applicable.

Safety data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. The safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. The safety analyses will be carried out in the safety population, detailed analyses will be described in the SAP.

Interim Analysis

An interim analysis may be performed when approximately a total of 110 randomized subjects complete 6 weeks of study or discontinue prematurely from study in order to assess the percent change of EASI score from baseline as well as other efficacy and safety endpoints such as IGA response, NRS response and hematological parameters as appropriate. A non-binding futility analysis may be performed on the efficacy endpoints. Modifications to the design such as adjustments to the final sample size or termination of enrollment of subjects in a treatment arm or stopping a treatment arm may be made upon review of the data. Unless a safety concern arises, no decisions to stop the trial will be made based on this interim analysis. An unblinded support team will perform the interim analysis. The study team and investigators will remain blinded to the results of the interim analysis.

Analysis of Pharmacokinetics Endpoints

Pharmacokinetic concentrations will be summarized and presented by treatment group with summary statistics and, where appropriate, non-compartmental PK parameters estimates will be provided. A population PK model may be developed for the purpose of estimating PK parameters. Population PK data for PF-04965842 will be summarized through appropriate data tabulations, descriptive statistics, and graphical presentation and will be reported separately. Data permitting, the relationship between exposure and clinical responses (efficacy and safety) during 12 weeks of treatment in subjects with moderate to severe atopic dermatitis may be explored using either observed or modeled exposures.

Data Monitoring Committee

This study will use an internal review committee (IRC) to monitor the safety of the subjects throughout the study and to make recommendations to the study team. Composition of the IRC and processes under which the IRC operates will be documented in an IRC charter.

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, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Protocol Activity	Screening	Treatment Period							Follow-up Period		
Visit Identifier	1	2	3	4	5	6	7	8	9	10	11
Visit Day/Week	Days -35 to -1	Day 1/ W 0	Day 8/ W 1	Day 15/ W 2	Day 29/ W 4	Day 43/ W 6	Day 57/ W 8	Day 85/ W 12	Day 92/ W 13	Day 99/ W 14	Day 113/W 16 ET/EOS
Visit Window[a]	None	None	±1 Day based on Day 1 visit				±3 Days based on Day 1 visit		±3 Day based on Day 1 visit		
Enrollment Procedure											
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Demographics, Medical History, Atopic Dermatitis Disease History[b]	X										
Medical Procedures											
Complete Physical Exam[c]	X	X						X			X
Targeted Physical Exam[c]			X	X	X	X	X		X	X	
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X									X
Height	X										
Chest X-ray[e]	X										
ECG (12 lead)	X	X						X			X
Laboratory Assessments											
Blood Chemistry[f]	X	X		X		X		X		X	X
Urinalysis	X	X				X		X			X
Hematology	X	X	X	X	X	X	X	X	X	X	X
Serum FSH (WONCBP only) or Pregnancy Test[g]	X										
Urine Pregnancy Test (conducted at study site)[h]		X	X	X	X	X	X	X	X	X	X

Protocol Activity	Screening	Treatment Period							Follow-up Period		
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit Day/Week	**Days -35 to -1**	**Day 1/ W 0**	**Day 8/ W 1**	**Day 15/ W 2**	**Day 29/ W 4**	**Day 43/ W 6**	**Day 57/ W 8**	**Day 85/ W 12**	**Day 92/ W 13**	**Day 99/ W 14**	**Day 113/W 16 ET/EOS**
Visit Window[a]	**None**	**None**	**±1 Day based on Day 1 visit**				**±3 Days based on Day 1 visit**		**±3 Day based on Day 1 visit**		
HIV Testing (per local regulations)[i]	X										
HBsAg, HBcAb, and HCVAb (HepB reflex testing)[j]	X										
Tuberculosis test[k]	X										
Viral Surveillance: EBV, CMV, HSV1, HSV2, and VZV		X				X		X			X
Laboratory Pharmacodynamics											
Total IgE		X		X	X	X	X	X			X
hsCRP		X		X	X	X	X	X			X
IP-10 (CXCL10)		X		X	X	X	X	X			X
IL-31		X		X	X	X	X	X			X
CCL17 (TARC)		X		X	X	X	X	X			X
FACS-TBNK and T cell Subsets		X		X	X	X	X	X			X
Blood for mRNA exploratory analysis		X			X		X	X			X
Serum for exploratory analysis		X			X		X	X			X
Cell-free plasma for exploratory analysis		X			X		X	X			X
Pharmacokinetic											
Pharmacokinetic Sampling (Pre-dose only)[l]				X	X		X				
Pharmacokinetic Sampling[m]						X		X			
Trial Treatment											
Impala Registration	X										
Randomize Subjects in IWRS		X									
Drug Dispensing		X	X	X	X	X	X				
Drug Accountability			X	X	X	X	X	X			
Investigational Treatment Administration[n]		**X----------X**									
Emollient and Sunscreen Dispensing[o]	X										

Protocol Activity	Screening	Treatment Period							Follow-up Period		
Visit Identifier	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Visit Day/Week	**Days -35 to -1**	**Day 1/ W 0**	**Day 8/ W 1**	**Day 15/ W 2**	**Day 29/ W 4**	**Day 43/ W 6**	**Day 57/ W 8**	**Day 85/ W 12**	**Day 92/ W 13**	**Day 99/ W 14**	**Day 113/W 16 ET/EOS**
Visit Window[a]	**None**	**None**	**±1 Day based on Day 1 visit**				**±3 Days based on Day 1 visit**		**±3 Day based on Day 1 visit**		
Review Prior/concomitant Medications & Treatments	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X
Review Contraception Method	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessments											
Fitzpatrick Skin Type Assessment		X									
Investigator's Global Assessment (IGA)	X	X	X	X	X	X	X	X	X	X	X
SCORing Atopic Dermatitis (SCORAD)	X	X	X	X	X	X	X	X	X	X	X
Eczema Area and Severity Index (EASI)	X	X	X	X	X	X	X	X	X	X	X
Body Surface Area (BSA)	X	X	X	X	X	X	X	X	X	X	X
Photography[p]		X				X	X	X			
Patient Reported Outcome											
Pruritus Numerical Rating Scale (NRS)[q]		X	X	X	X	X	X	X		X	X
Patient Global Assessment (PtGA)		X	X	X	X	X	X	X		X	X
Dermatology Life Quality Index (DLQI)		X	X	X	X	X	X	X		X	X
Patient Oriented Eczema Measure (POEM)		X	X	X	X	X	X	X		X	X
[redacted]		[redacted]									
Hospital and Anxiety Depression Scale (HADS)		X	X	X	X		X	X		X	X
Banked Biospecimens											
Prep D1 (DNA)		X									

Abbreviations: BSA = body surface area; CCL17 = Chemokine ligand 17; CMV = Cytomegalovirus; CXCL-10 = C-X-C motif chemokine 10; DLQI = Dermatology Life Quality Index; DNA = Deoxyribonucleic acid; EASI = Eczema Area and Severity Index; EBV = Epstein-Barr virus; ECG = electrocardiogram; FACS = fluorescence-activated cell sorting; FSH = follicle stimulating hormone; HADS= Hospital and Anxiety Depression Scale; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCVAb = hepatitis C antibody; Hep B = Hepatitis B; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; HSV1 = herpes simplex virus type 1; HSV 2 = herpes simplex virus type 2; IGA = Investigator Global Assessment; IgE = Immunoglobulin E; IL-31 = Interleukin-31; IP10 = Interferon gamma-induced protein 10; IWRS = Interactive Web-based Response System; NRS = numerical rating scale; POEM= Patient Oriented Eczema Measure; [redacted] PtGA = Patient Global Assessment; RNA = Ribonucleic acid; SCORAD = SCORing Atopic Dermatitis; TBNK = T, B, and NK cell; TARC = thymus and activation regulated chemokine; VZV = varicella zoster virus; 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, the use of topical treatments, systemic treatments and other treatments for AD.

c. 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 should include skin, heart, lung, and abdomen and examination of body systems where there are symptom complaints by the subject.

d. Vital Signs include sitting blood pressure, pulse, respiratory rates, and temperature measured after approximately 5 minutes of rest.

e. Chest X-ray or other appropriate diagnostic image (ie, CT or MRI) may be performed up to 12 weeks prior to Day 1. Official reading must be located in the source documentation.

f. Blood Chemistry consists of blood urea nitrogen (BUN), serum creatinine, creatine phosphokinase, glucose, Ca++, Na+, K+, Cl-, total CO2, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin, alkaline phosphatase, uric acid, albumin, total protein, and lipid profile panel. 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, W 6, W 12, and EOS. **Laboratory tests may be repeated once during the screening period**; the last value will be used to determine eligibility.

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

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

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

j. All subjects will be screened for HBsAg and HBcAb; subjects who are HBsAg positive will be screen-failed. Subjects who are HBsAg negative but HBcAb positive will be reflex-tested for HBsAb and, if HBsAb positive, may enroll; if HBsAb negative, they will be screen-failed. Subjects who are positive for HCVAb will be screen-failed.

k. A documented TB test performed within 12 weeks prior to Day 1 is acceptable. IGRA official reading and method, or test as per country specific guidelines, must be located in source documentation. Subjects with a history of tuberculosis may not require TB testing as per the protocol Section 4.2.

l. Pharmacokinetic samples will be collected at the following visits prior to dosing at the study site on: Week 2, 4 and 8.

m. On Week 6, PK samples will be collected at 2 hour (±30 min) pre-dose, immediately prior to dosing, and 0.5 hour (±15 min) post dose. On Week 12, PK samples will be collected at 2 hour (±30 min) pre-dose, immediately prior to dosing, and 1 hour (±30 min), 2 hour (±30 min) and 4 hour (±30 min) post dose.

n. Subjects should take the medication from study Days 1 to 85. Subjects will be encouraged to take the medication after breakfast whenever it is possible. However, at study visit days, subjects are to be instructed to refrain from dosing at home, and are to take the dose in the clinic.

o. Non-medicated study emollient and sunscreen will be provided to subjects at the Screening visit and re-supplied during the study as applicable. Subjects will start the study provided emollient 7 days prior to Day 1 through to the End of Study visit.

p. For subjects at a selected study site(s), photographs of treatment-eligible atopic dermatitis will be obtained at Day 1 and Week 6. Areas photographed should be recorded in study documents so that the same atopic dermatitis body region(s) will be photographed at Week 6. Additional photographs may also be taken at Week 8 and/or Week 12 at the investigator's discretion.

q. Pruritus Numerical Rating Scale (NRS) will be assessed daily from Day 1 to 15 and then at study site at every study visits.

[redacted]

1. INTRODUCTION

1.1. Indication

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

1.2. Mechanism of Action

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 (IFNγ), and interferon alfa (IFNα). 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.[11] 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.[12]

Key cytokines implicated in the pathophysiology of AD including IL-4, IL-5, IL-13, IL-31, and IFN-γ, require JAK1 for signal transduction, suggesting that selective JAK1 inhibitors, that modulate the activity of these cytokines, represent a compelling approach to the treatment of inflammatory skin diseases such as AD.[1]

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 in the human genome: 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 IFNγ.

The Phase 1 study with the JAK1 selective inhibitor PF-04965842 in adult healthy volunteers has demonstrated an acceptable pharmacokinetic (PK) and pharmacodynamic (PD) profile with no safety issues to date. The PF-04965842 proof-of-concept (POC) study in patients with moderate to severe psoriasis (B7451005) was terminated early due to a clinical development strategy change. Preliminary data showed that PF-04965842 appeared generally well tolerated in this 4 week study.

This study B7451006 is a Phase 2b POC study which is planned to assess four PF-04965842 once daily (QD) doses (10, 30, 100, 200 mg) relative to placebo over 12 weeks to characterize the efficacy and safety of PF-04965842 in subjects with moderate to severe AD. The objectives of the study are to demonstrate the efficacy of PF-04965842 by showing improvement in disease severity in patients with moderate to severe AD as measured by the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) scores, and safety to support further clinical development of PF-04965842.

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

1.3. Background and Rationale

1.3.1. Drug Development and Rationale

PF-04965842 is being developed for several indications. The clinical development program for PF-04965842 includes healthy volunteers, patients with psoriasis, and under this protocol, patients with AD. Information on clinical safety for all doses of PF-04965842 from the completed studies is provided in the current version of the IB.

1.3.2. 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. The lifetime prevalence of AD in children is 10-20% with 70% of cases occurring in children <5 years of age. Most cases (approximately 75%) improve by adulthood, while approximately 25% of AD patients have symptoms throughout their life. The majority of studies conducted across multiple age groups suggest a continued decrease in prevalence with older age.[5] Adult-onset AD does also occur, though it is less common. The prevalence of AD in adults is estimated to be 10%.[14] 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.[8]

Although great strides have been made in understanding the causes, the complex pathophysiology of AD is still not completely understood. However, 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.[7]

Acute AD lesions have been associated with the Type 2 helper T cell (T_H2) phenotype, showing dominance of IL-4, -5, -13, and -31 secretion.[7,3,1] Recent research showed that a small increase of Type 1 helper T cell (T_H1)-associated genes has been also detected in acute phase.[6] While IL-4-producing T_H2 cells may drive the development of atopic skin lesions, chronic lesions show either the coexistence of both IL-4-producing T_H2 and IFN-γ-producing T_H1 cells or T_H1 dominance.[7] This coexistence of T_H2 and T_H1 responses or T_H1 dominance is more likely to be the underlying immunopathology in adult patients who have had AD chronically or intermittently since childhood. Recent evidence supports IL-31's role in pruritus and inflammation in AD.[3,1]

Atopic dermatitis can be categorized into extrinsic and intrinsic types. The extrinsic or allergic AD is characterized by high total serum immunoglobulin E (IgE) levels, and the presence of specific IgE for environmental and food allergens. While the extrinsic AD is the classical type and has higher prevalence, the incidence of intrinsic AD is approximately 20% and is associated with female predominance.[16] The clinical features of intrinsic AD include relative late onset, milder severity, and Dennie-Morgan folds, but no ichthyosis vulgaris or palmar hyperlinearity observed in the extrinsic AD. Compared to the extrinsic AD, the intrinsic type is immunologically characterized by the lower expression of IL-4, IL-5 and IL-13, and the higher expression of IFNγ.

There are a limited number of treatments available for AD. Current treatments for mild to moderate AD include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. 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.[15] 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 to reduce pruritus and the resulting sleep disturbance.[9,13]

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 both oral corticosteroids and 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. Therefore, the predominant unmet medical need in the treatment of AD is an effective therapeutic agent without restrictions on long-term or continuous use without significant side effects.

As mentioned above, a variety of pro-inflammatory cytokines such as IL-4, IL-13, IL-17, IL-22, IL-31 and IFNγ, 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.

[redacted]

[redacted]

1.4.2.3. B7451005 Study Safety Data

B7451005 was a Phase 2, randomized, double-blind, placebo controlled study to evaluate safety and efficacy of PF-04965842 in patients with moderate to severe psoriasis. There were 59 subjects enrolled and randomized to one of three treatment groups (200 mg QD, 400 mg QD, and 200 mg BID) or placebo.

Preliminary data showed that PF-04965842 appeared generally well tolerated in this 4 week study. The only serious adverse event reported in the study occurred in the placebo group. However, the AEs occurred at a higher frequency among subjects receiving PF-04965842 than those receiving placebo. The AEs were more frequent in the 400 mg QD and 200 mg BID dose groups than in the 200 mg QD group. The most common AEs were those affecting the hematological and gastrointestinal system. The majority of the hematological lab abnormalities occurred in the 200 mg BID group. There were a greater number of events in the infections and infestations category in the active treatment groups compared to the placebo group.

[redacted]

[redacted]

1.6.2. B7451005 Study Data

Preliminary results of biomarkers (IP-10 and hsCRP) showed rapid reduction in all active treatment groups. The effect was more pronounced in the BID than the QD groups.

1.7. Summary of Benefits and Risks

The anticipated risks associated with PF-04965842 in relation to anemia are minimal because erythropoietin signals through the JAK2 dimers. Thus, in comparison to pan-JAK inhibitors, PF-04965842's selectivity to erythropoietin may provide clear advantage in regard to anemia. However, the 10-day dosing duration in the Phase 1 study B7451001 was not long enough to test for anemia. Also, PF-04965842's lesser effect on IL-15 which is linked to non-killer (NK) cells may provide further differentiation from pan-JAK inhibitors and may prove to be beneficial in terms of lesser effect on immune functions related to viral infections and tumor surveillance.

Overall, the safety profile observed during the Phase 1 program for PF-04965842 appears to be acceptable at dosages of up to 800 mg administered as a single dose and up 400 mg when administered as repeat doses of either 400 mg QD or 200 mg BID. The preliminary data from the 4 week POC Pso study showed that PF-04965842 appeared generally well tolerated up to 400 mg QD or 200 mg BID. The data generated in the development program to date support the further development of PF-04965842 and its advancement to a POC study in AD.

1.8. Rationale

1.8.1. Study Rationale

PF-04965842 is a selective inhibitor of JAK1. The selective inhibition of JAK1 will lead to modulation of multiple cytokines which play a critical role in the pathogenesis of AD (eg, IL-4, IL-13, IL-17, IL-22, IL-31, and IFNγ). Dupilumab, a fully human monoclonal antibody that blocks the activity of IL-4 and IL-13 signaling, has shown efficacy in patients with AD.[2] Systemic treatment with dupilumab in adults with moderate to severe AD resulted in marked reductions in signs and symptoms of AD, and associated biomarker levels. Topical tofacitinib, a pan JAK inhibitor, recently completed a 4 week Phase 2a trial that demonstrated the efficacy of JAK inhibition in mild to moderate AD (study A3921214). In this study, significantly greater efficacy was observed with topical tofacitinib vs. vehicle in reducing the signs and symptoms of AD, with a suitable safety and local tolerability profile. In addition, oral tofacitinib has shown therapeutic effect in 6 patients with recalcitrant AD.[10]

JAK1-selective inhibitors such as PF-04965842, spare dose-limiting effects of pan-JAK inhibition by preserving JAK2 homodimer signaling and thus provide the potential for safer and efficacious oral treatments for AD. Oclacitinib, a JAK1 inhibitor, has already demonstrated efficacy and is approved for the treatment of canine atopic dermatitis.[4]

B7451006 is a Phase 2b study to evaluate the efficacy and safety of PF-04965842 in comparison to placebo in patients with moderate to severe atopic dermatitis using the Investigator Global Assessment.

Clinical evaluations of AD in this study will include Investigator Global Assessment (IGA), Eczema Area and Severity Index (EASI), Body Surface Area (BSA) involvement, and SCORing Atopic Dermatitis (SCORAD).

PF-04965842 efficacy will also be evaluated via patient reported outcomes (PROs): Pruritus numerical rating scale (NRS) score, Patient Global Assessment (PtGA), Dermatology Life Quality Index (DLQI), Patient Oriented Eczema Measure (POEM), [redacted] and Hospital and Anxiety Depression Scale (HADS).

The study will provide samples for exploratory analysis of pharmacodynamic biomarkers for JAK1 inhibition such as IP-10 (CXCL10), hsCRP, CCL17 (TARC), IL-31, total IgE. Samples will also be collected for flow-cytometric (fluorescence-activated cell sorting [FACS]) assessment of lymphocyte subsets.

1.8.2. Dose Selection Rationale

This Phase 2b study will evaluate the efficacy and safety of PF-04965842 in patients with moderate to severe AD. The study will assess 4 PF-04965842 doses of 10 mg, 30 mg, 100 mg and 200 mg administered orally once daily (QD) for 12 weeks. [redacted]

[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As previously described there are multiple cytokines involved in the manifestation of AD, thus, the main driver of disease or the relative contribution of the cytokines to efficacy is not understood. However, Dupilumab an antibody to the receptors for IL-4 and IL-13 has demonstrated efficacy in AD. In study B7451005, in subjects with psoriasis, which evaluated 200 mg and 400 mg QD and 200 mg BID of PF-04965842 for 28 days, all active treatments decreased itch severity score at 7 days post dose, the first evaluation timepoint. [redacted]

Preliminary assessment of safety data from study B7541005 showed that the majority of the hematological laboratory abnormalities occurred in the 200 mg BID group. Based on this finding a BID regimen will not be evaluated in AD. [redacted]

[redacted] There were platelet reductions in all active treatment groups. Platelet counts <100,000/mm^3 were observed in the 400 mg QD and 200 mg BID cohorts, with the majority of cases occurring in the BID cohort. There were no cases of platelet counts <100,000/mm^3 in the 200 mg QD group. No bleeding events relative to thrombocytopenia were reported during the clinical trial.

The projected reductions suggest that at least 1 dose should be active with acceptable safety and tolerability appropriate for the long term treatment of adult subjects with moderate to severe AD.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives

- The primary objective of this study is to evaluate the efficacy of 4 QD dose levels (10, 30, 100, and 200 mg) of PF-04965842 relative to placebo in adult subjects with moderate to severe atopic dermatitis, using the Investigator's Global Assessment (IGA).

2.2. Secondary Objectives

- To evaluate the effect of PF-0465842 on additional efficacy endpoints and patient reported outcomes over time in adult subjects with moderate to severe atopic dermatitis.

- To evaluate the safety and tolerability of PF-0465842 over time in adult subjects with moderate to severe atopic dermatitis.

2.3. Exploratory Objectives

- To assess pharmacodynamic and disease-related biomarkers over time.

- To characterize pharmacokinetics of PF-04965842 over 12 weeks.

2.4. Endpoints

2.4.1. Primary Endpoints

- Proportion of subjects achieving the IGA for clear (0) or almost clear (1) and ≥2 points improvement from baseline at Week 12. The baseline will be defined as the IGA score on Day 1 pre-dose.

2.4.2. Secondary Endpoints

2.4.2.1. Efficacy Endpoints

Baseline is defined as the score for each assessment on Day 1 pre-dose.

2.4.2.1.1. Key Secondary Efficacy Endpoint

- Percent change from baseline in the eczema area and severity index (EASI) Total score at Week 12.

2.4.2.1.2. Secondary Efficacy Endpoints

- Proportion of subjects achieving the IGA for clear (0) or almost clear (1) and ≥2 points improvement from baseline at all scheduled time points except Week 12.
- Percent change from baseline in the EASI total score at all scheduled time points except Week 12.
- Proportion of subjects achieving ≥3 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points.
- Percent change from baseline in the pruritus NRS from baseline at all scheduled time points.
- Proportion of subjects achieving ≥2 points improvement in the IGA from baseline at all scheduled time points.
- Proportion of subjects achieving a ≥50%, 75% and 90% improvement in the EASI Total score (EASI50, EASI75, EASI90) at all scheduled time points.
- Change from baseline in affected body surface area (BSA) at all scheduled time points.
- Change from baseline in SCORing atopic dermatitis (SCORAD) at all scheduled time points.
- Proportion of subjects achieving a ≥50% and 75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points.

2.4.2.2. Safety Endpoints

- Incidence of treatment-emergent adverse events.
- Incidence of specific clinical laboratory abnormalities (anemia, neutropenia, thrombocytopenia, lymphopenia, lipid profile, liver function tests [LFTs]).

2.4.2.3. Patient-Reported Outcome (PRO) Endpoints

Baseline is defined as the score for each assessment on Day 1 pre-dose.

- Change from baseline in Pruritus NRS score at all scheduled time points.

- Proportion of subjects with patient global assessment (PtGA) of AD of clear (0) or almost clear (1) and ≥2 points improvement from baseline at all scheduled time points.

- Change from baseline in dermatology life quality index (DLQI) total score at all scheduled time points.

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

- Change from baseline in the hospital and anxiety depression scale (HADS) at all scheduled time points.

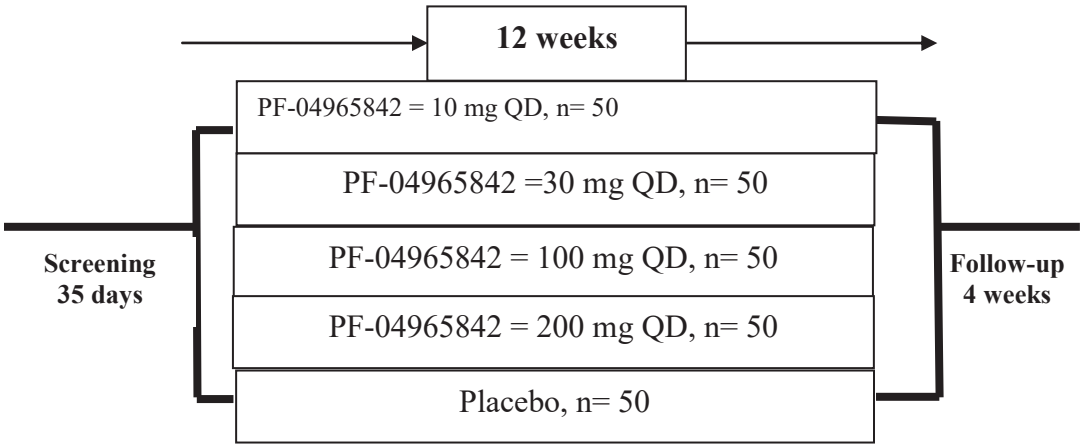
2.4.3. Exploratory Endpoints

[redacted]

3. STUDY DESIGN

This Phase 2b, multi-center, randomized, double-blind, 5-arm, parallel group study will enroll a total of approximately 250 subjects (providing approximately 200 completers, 40 subjects per treatment group). The study will be conducted at approximately 60 sites.

Figure 1. Study Design Schematic



Subjects who have chronic AD that has been present for at least 1 year (prior to screening visit) and affected BSA of ≥10%, EASI ≥12 and IGA ≥3 at the screening and baseline visits will be included in the study. Subjects must also have a documented history of inadequate response to treatment with topical medications given for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks) within 12 months of the first dose of study drug. Subjects will be randomized to 1 of 4 treatment groups or placebo in the ratio of 1:1:1:1:1. Investigators, subjects, and the sponsor study team will be blinded as to treatment group.

Subjects will be screened within 35 days prior to the first dose of study drug to confirm that they meet the subject selection criteria for the study. There will be a 12-week double-blind treatment period as well as a 4-week follow up period.

An interim analysis may be performed when approximately a total of 110 randomized subjects complete 6 weeks of study or discontinue prematurely from study in order to assess the percent change of EASI score from baseline as well as other safety and efficacy endpoints such as IGA response as appropriate. Please refer to Section 9.4 for details.

4. SUBJECT SELECTION

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.

4.1. Inclusion Criteria

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

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

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

2. Male or female subjects between 18-75 years of age, inclusive, at time of informed consent.

3. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

4. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception (per Section 4.4.2) throughout the study and for at least 28 days after the last dose of assigned treatment.

Female subjects who are not of childbearing potential (eg, 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; status may be confirmed by having a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

5. Must have the following atopic dermatitis criteria:

   a. Have a 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 (Hanifin and Rajka criteria of AD refer to Appendix 2) at the Screening visit.

   b. Have inadequate response to treatment with topical medications given for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks) within 12 months of the first dose of study drug.

   c. Moderate to severe AD (affected BSA ≥10 %, IGA >3, and EASI >12 at the screening and baseline visits).

6. 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.

7. 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. Subject must be willing to stay on a stable regimen during 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. Severe acute or chronic medical or psychiatric condition 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 or Pfizer (or designee), would make the subject inappropriate for entry into this study.

2. Currently have active forms of other inflammatory skin diseases.

3. 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.

4. Have received any of the following treatment regiments specified in the timeframes outlined below:

   Within 6 months of first dose of study drug:

   - Any cell-depleting agents including but not limited to rituximab: within 6 months of first dose of study drug or 5 half-lives (if known), whichever is longer, or until lymphocyte count returns to normal, whichever is longer.

   Within 12 weeks of first dose of study drug:

   - Any studies with JAK inhibitors.

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

   Within 8 weeks of first dose of study drug:

   - Participation in other studies involving investigational drug(s) within 8 weeks of first dose of study drug or within 5 half-lives (if known), whichever is longer

     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.

   Within 6 weeks of first dose of study drug:

   - Have been vaccinated with live or attenuated live vaccine.

   Within 4 weeks of first dose of study drug:

   - Use of oral immune suppressants (eg, cyclosporine A [CsA], azathioprine, MTX, Celcept, systemic corticosteroids, mycophenolate-mofetil, IFN-γ) within 4 weeks of first dose of study drug or within 5 half-lives (if known), whichever is longer.

   - Phototherapy (NB-UVB) or broad band phototherapy.

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

Within 1 week of first dose of study drug:

- 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.

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

5. Pregnant female subjects, breastfeeding female subjects, or male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol (per Section 4.4.2) for the duration of the study and for at least 28 days after last dose of investigational product.

6. Have current or recent history of clinically significant severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, psychiatric, immunologic/rheumatologic or neurologic disease; or have any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration, or interfere with the interpretation of study results; or in the opinion of the investigator or Pfizer (or designee), the subject is inappropriate for entry into this study, or unwilling/unable to comply with STUDY PROCEDURES and Lifestyle Guidelines.

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

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

9. Have a 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 (for exception regarding latent Tuberculosis (TB) infection see Exclusion Criterion 19 or skin infections that lead to hospitalizations see Exclusion Criterion 10).

10. Have active chronic or acute skin infection (except latent TB infection see Exclusion Criterion 20) 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. NOTE: patients may be rescreened after infection resolves.

11. 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.

12. 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).

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

14. 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.

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

16. Require treatment with prohibited concomitant medication(s) (Section 5.8 and Appendix 3) or have received a prohibited concomitant medication within 7 days or 5 half-lives (whichever is longer) prior to Day 1.

17. History of human immunodeficiency virus (HIV) or positive HIV serology at screening,

18. Infected with hepatitis B or hepatitis C viruses. For Hepatitis B, all subjects will undergo testing for Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb). Subjects who are HBsAg positive are not eligible for the study. Subjects who are HBsAg negative and HBcAb positive will be reflex tested for Hepatitis B Surface Antibody (HBsAb) and if HBsAb is positive, may be enrolled in the study; if HBsAb is negative, the subject is not eligible for the study.

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

    a. A positive QuantiFERON®-TB Gold (QFT-G) In-Tube test or positive Mantoux/Purified Protein Derivative (PPD) tuberculin skin test performed at or within the 12 weeks prior to Day 1 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 7.3.5 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 or is currently receiving a documented adequate treatment for latent TB infection;

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

c. 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 nor a Mantoux/PPD tuberculin skin test is needed, but a chest radiograph(s) (per local standard/guidelines) must be obtained 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;

d. A subject who is currently being treated for active TB infection is to be excluded.

20. **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:

- Absolute neutrophil count of $<2.5 \times 10^9$/L ($<2500/mm^3$).
- Hemoglobin <10.0 g/dL or hematocrit <30%;
- Platelet count below the lower limit of normal (LLN) at Screening;
- Absolute lymphocyte count of <0.5 x 109 /L ($<500/mm^3$);
- Estimated Creatinine Clearance <40 mL/min based on the age appropriate calculation, or serum creatinine >1.5 times the upper limit of normal (ULN);
- AST or 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;
- 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. Subjects who are investigational 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 directly involved in the conduct of the study.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have signed an informed consent document to participate in the study, have undergone all screening procedures, 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 and Interactive Voice Response System (IVRS).

4.4. Lifestyle Guidelines

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

- On study visit days (Day 1, Week 6, Week 12, and End of Study [EOS]), comply with fasting requirement for at least 8 hours prior to the visit.
- On study visit days, do not smoke or ingest caffeine during the 30 minutes prior to blood pressure and heart rate measurements.
- On study visit days, do not take the dose of study drug 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 do not apply emollient Discontinue and avoid using certain medications and treatments (Section 4.2, Section 5.8.2, and Appendix 3).
- Agree to use proper contraception methods (Section 4.4.2).

4.4.1. 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 study drug prior to the surgical procedure. In general, planned surgical procedures should not be performed unless the study drug 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.

4.4.2. Contraception

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy 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 his or her partner) from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart. In addition, the investigator or his or her 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 subject's 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 or 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 spermicide (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).

6. Female partner who meets the criteria for non-childbearing potential, as described below:

   Female subjects of non-childbearing potential must meet at least one 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; status may be confirmed by having a serum FSH level confirming the post-menopausal state.

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

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 compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational 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 investigational 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 investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

4.6. 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 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.

5. STUDY TREATMENTS

PF-04965842 will be administered orally at one of the following 4 doses: 10, 30, 100, or 200 mg administered QD for 12 weeks. In addition, one cohort will receive PF-04965842-matching placebo.

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference 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 (Interactive Web Response (IWR)/Interactive Voice Response (IVR) 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 drug 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 helpdesk 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

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 either a manual or 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.

Unblinding plan for interim analysis will be specified in Section 9.4.

5.3. Subject Compliance

Subject compliance will be verified by the accounting of investigational product at each visit. When investigational product is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the investigational product will be monitored by delegated site personnel by the accounting of unused medication returned by the subject at the study visits. Compliance will be documented on the CRF and source document. If compliance is <80%, the investigator or designee is to counsel the subject and ensure steps are taken to improve compliance. Subjects interrupting investigational product for more than 4 consecutive days or for a total of more than 7 days between visits are to be discussed with the Sponsor for possible withdrawal from the study.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Blinded PF-04965842 and its matched placebo will be provided as tablets for oral administration. The 10-mg and 50-mg tablets and their matching placebos will be supplied in separate blister cards 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 blisters (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 blister cards provided, in quantities appropriate for the study visit schedule. The subject/caregiver should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

5.5. Administration

Subjects should take the medication orally for 12 weeks; **Subjects will be encouraged to take the medication after breakfast whenever it is possible;** 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.

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. The exception will be on study visit

days when subjects will be instructed to refrain from dosing at home, and will take the dose at the clinic.

5.6. Investigational Product Storage

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

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

Storage conditions stated in the SRSD (ie, IB) will be superseded by the storage conditions stated in the labeling.

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 study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor 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.

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

5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. 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.

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 study 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. All bottles must be returned to the investigator by the subject.

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 study 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 the Inclusion and Exclusion Criteria sections of the protocol.

Medications that are taken in the Screening/Washout period (after informed consent is obtained and before the first dose of study drug) will be documented as prior medications. Medications taken after the first dose of study drug has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in study records with indication, daily 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.

The start date, stop date, and indication for all therapies will be recorded on the CRF.

5.8.1. Permitted Concomitant Medications

The following concomitant AD therapies are permitted during the study:

- Oral antihistamines.
- Subjects will be provided a non-medicated study emollient and a sunscreen at the Screening visit. Subjects will start the emollient 7 days prior to Day 1 through to the follow up visit and use the sunscreen as needed. The non-medicated study emollient

and sunscreen are the only topical products permitted to be used on atopic dermatitis skin during the study. If a subject has a history of intolerability or currently does not tolerate the non-medicated study emollient or sunscreen or if the product is unavailable, the investigator should contact the Pfizer clinician or designee for approval to use an alternative topical treatment; the approved alternative non-medicated emollient and sunscreen should be documented in study records.

A subject who is receiving a permitted concomitant medication for any reason must be on a locally-approved medication and dose for the treated indication, 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.

Acetaminophen 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 hypervitaminosis).

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.

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.

5.8.2. Prohibited Medications and Treatments

Subjects are required to discontinue and avoid using certain medications and treatments (see Inclusion/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 avoid the use of tanning booths, sun lamps or other ultraviolet light sources during the study.

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

Herbals supplements are only allowed on a case by case basis; please contact the Pfizer staff. Herbal medications with unknown properties or known beneficial effects for AD or that are known to have an effect on drug metabolism (eg St. John's Wort) must be discontinued at least 1 week or 5 half-lives (whichever is longer) before the first dose of investigational product.

Restrictions on certain vaccinations are described in Section 5.8.3.

5.8.3. Vaccinations

Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within the 6 weeks prior to the first dose of study drug, during the study, and for 6 weeks after the last dose of investigational product. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and for 6 weeks following completion of treatment.

Such vaccines include: FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR (measles, mumps, rubella) vaccine and vaccinia (smallpox) 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.

6. STUDY PROCEDURES

Refer to the Schedule of Activity for a detailed list of a detailed list of study procedures as they should be conducted at each respective visit. Visit windows are based on Day 1 visit.

Subjects are required to fast for at least 8 hours prior to all visits that include lipid profile panel testing (Day 1, Week 6, Week 12, and EOS). During the fasting period, subjects should refrain from all food and liquids (water and non-study medications are permitted).

Due to possible need for PPD testing and chest radiograph, screening procedures may be performed over more than 1 visit in the 35 days prior to the Day 1 visit.

Visits should occur in the morning and prior to the subject's dose on Day 1, Week 6, Week 12, and EOS. 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 their study visit.

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

Non-medicated study emollient and sunscreen will be provided to subjects at the Screening Visit and re-supplied during the study as applicable. Prior to attending a study visit, subjects are allowed to shower but should not moisturize. However, they may apply study provided emollient upon completion of all clinic visit study procedures. Subjects will start the study provided emollient 7 days prior to Day 1 through to the EOS visit.

Refer to Appendix 11 for guidelines on subject safety monitoring and discontinuation.

6.1. Visit 1, Screening

Subjects will be screened within 35 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section.

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 5-week screening period, the subject may enter the study. Sites will be permitted to re-screen subjects (with a new screening number) who initially do not meet eligibility criteria once.

The following procedures will be completed:

- Obtain written informed consent.
- Review Inclusion and Exclusion criteria.
- Register subject in Impala.
- Demography.
- Complete medical history, including history of drug, 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 (a glass) of wine, 12 oz of beer, or 1.5 oz of 90 proof of spirits.
- Complete AD disease history includes collection of details of AD: AD diagnosis, 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 35 days prior to the planned first dose.

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

  - 2 years: Lipid-lowering medications;
  - 3 years: Previous drug treatments for AD includes use of topical treatments, systemic treatments and other any treatments.

- Conduct complete physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain weight
- Obtain height.
- Chest X-ray (if previous chest X-ray has not been performed within 12 weeks of Day 1, may require a visit to a different location).
- Perform single 12-lead electrocardiogram (ECG).
- Obtain samples for laboratory testing: Blood chemistry, hematology, urinalysis, serum FSH or pregnancy test, HIV, HBsAg, HBcAb, and HCVAb.
- Mantoux Purified Protein Derivative (PPD) skin test or QuantiFERON® – TB Gold test (unless performed within 12 weeks of Day 1). If Mantoux PPD tuberculin skin test is performed, the subject must return between 48-72 hours post-injection for evaluation of induration.
- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Dispense ePRO handheld device. PSAAD will be collected daily in selected country/ies daily starting 3 days prior to Day 1 through to the End of Study visit.
- Dispense study emollient and sunscreen. Subjects will start the emollient 7 days prior to Day 1 through to the end of study visit.
- Assess for occurrence of Adverse Events: The SAE reporting period starts with the signing of the informed consent.

6.2. Study Period

6.2.1. Visit 2, Day 1/Week 0

- Review of Inclusion/Exclusion Criteria.
- If subject meets all Inclusion/Exclusion criteria, officially randomize subject into the study.
- Review any changes in the subject's prior and concomitant treatment information.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain weight.

- Conduct complete physical examination.
- Obtain **fasting** samples for blood chemistry including lipid profile.
- Obtain samples for other laboratory testing: hematology, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, CMV, HSV1, HSV2, VZV, IgE, hsCRP, IP-10, IL-31, CCL17, TBNK, T cell subsets, and exploratory biomarker samples.
- Perform Fitzpatrick skin type assessment.
- Photography (at selected sites).
- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Administer PROs including Pruritus NRS, PtGA, DLQI, POEM, and HADS.

  Note: The Pruritus NRS will be assessed daily from Day 1 to 15.
- Review PSAAD (in selected country/ies) as necessary.
- Perform single 12-lead ECG.
- Obtain Prep D1 sample for banked biospecimen pharmacogenomics testing.
- Confirm proper contraception is being used.
- Administer first dose of study drug to subject.
- Dispense study drug supply to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

6.2.2. Visit 3, Day 8/Week 1 (±1 day)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology and urine pregnancy test (female subjects of childbearing potential only).
- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.

- Administer PROs including Pruritus NRS, PtGA, DLQI, POEM, and HADS.

  Note: The Pruritus NRS will be assessed daily from Day 1 to 15.

- Review PSAAD (in selected country/ies) as necessary.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

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

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: blood chemistry, hematology, urine pregnancy test (female subjects of childbearing potential only), IgE, hsCRP, CXCL-10, IL-31, CCL17, TBNK, and T cell subsets.
- Obtain samples for PK analysis prior to dosing.
- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Administer PROs including Pruritus NRS, PtGA, DLQI, POEM, and HADS.
- Review PSAAD (in selected country/ies) as necessary.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject.

- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.2.4. Visit 5, Day 29/Week 4 (±1 day)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology, urine pregnancy test (female subjects of childbearing potential only), IgE, hsCRP, IP-10, IL-31, CCL17, TBNK, T cell subsets, and exploratory biomarker samples.
- Obtain samples for PK analysis prior to dosing.
- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Administer PROs including Pruritus NRS, PtGA, DLQI, POEM, and HADS.
- Review PSAAD (in selected country/ies) as necessary.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.2.5. Visit 6, Day 43/Week 6 (±1 day)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain **fasting** samples for blood chemistry including lipid profile.

- Obtain samples for laboratory testing: hematology, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, CMV, HSV1, HSV2, VZV, IgE, hsCRP, IP-10, IL-31, CCL17, TBNK, and T cell subsets.
- **Prior to dosing**, obtain samples for PK analysis (the first PK sample is to be collected 2 hours (±30 minutes) prior to dosing; the second PK sample is to be collected immediately prior to dosing).
- Photography (at selected sites).
- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Administer PROs including Pruritus NRS, PtGA, DLQI, POEM, and HADS.
- Review PSAAD (in selected country/ies) as necessary.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject.
- Obtain samples for PK analysis at 0.5 hour (±15 minutes) after dosing.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

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

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology and urine pregnancy test (female subjects of childbearing potential only), IgE, hsCRP, IP-10, IL-31, CCL17, TBNK, T cell subsets, and exploratory biomarker samples.
- Obtain samples for PK analysis prior to dosing.
- Photography at selected sites (at PI's discretion).

- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Administer PROs including Pruritus NRS, PtGA, DLQI, POEM, and HADS.
- Review PSAAD (in selected country/ies) as necessary.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject.
- Dispense study drug to the subject.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.2.7. Visit 8, Day 85/Week 12 (±3 day)

- Conduct complete physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain **fasting** samples for blood chemistry including lipid profile.
- Obtain samples for laboratory testing: hematology, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, CMV, HSV1, HSV2, VZV, IgE, hsCRP, IP-10, IL-31, CCL17, TBNK, T cell subsets, and exploratory biomarker samples.
- **Prior to dosing**, obtain samples for PK analysis (the first PK sample is to be collected 2 hours (±30 minutes) prior to dosing; the second PK sample is to be collected immediately prior to dosing).
- Photography at selected sites (at PI's discretion).
- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Administer PROs including Pruritus NRS, PtGA, DLQI, POEM, and HADS.
- Review PSAAD (in selected country/ies) as necessary.
- Perform single 12-lead ECG.

- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Perform drug accountability procedures.
- Administer study drug to the subject.
- Obtain samples for PK analysis at 1 hour (±30 minutes), 2 hour (±30 minutes), and 4 hour (±30 minutes), after dosing.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.3. Follow-up Visits

6.3.1. Visit 9, Day 92/Week 13 (±3 day)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: hematology and urine pregnancy test (female subjects of childbearing potential only).
- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Review PSAAD (in selected country/ies) as necessary.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.3.2. Visit 10, Day 99/Week 14 (±3 day)

- Conduct targeted physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain samples for laboratory testing: blood chemistry, hematology and urine pregnancy test (female subjects of childbearing potential only).

- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Administer PROs including Pruritus NRS, PtGA, DLQI, POEM, and HADS.
- Review PSAAD (in selected country/ies) as necessary.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.3.3. Visit 11, End of Study Visit, Day 113/Week 16 (±3 day) or Early Termination Visit

The following procedures will be completed:

- Conduct complete physical examination.
- Obtain vital signs including pulse rate, blood pressure, respiratory rate (after at least 5 minutes of rest) and oral or tympanic temperature.
- Obtain weight.
- Perform single 12-lead ECG.
- Obtain **fasting** samples for blood chemistry including lipid profile.
- Obtain samples for laboratory testing: hematology, urinalysis, urine pregnancy test (female subjects of childbearing potential only), EBV, CMV, HSV1, HSV2, VZV, IgE, hsCRP, IP-10, IL-31, CCL17, TBNK, T cell subsets, and exploratory biomarker samples.
- Conduct clinical evaluations including IGA, EASI, BSA, and SCORAD.
- Administer PROs including Pruritus NRS, PtGA, DLQI, POEM, and HADS.
- Review PSAAD (in selected country/ies) as necessary.
- Confirm proper contraception is being used.
- Review any changes in the subject's concomitant treatments information.
- If early termination visit, perform drug accountability procedures.

- Assess for occurrence of Adverse Events by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.4. Subject Withdrawal

Withdrawal of consent: Subjects who request to discontinue study treatment will remain in the study and must enter into the Follow-up Period with their **first follow-up visit occurring 1 week after their last dose** to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post treatment 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 permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety 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 who are requested to discontinue study treatment will remain in the study and must enter into the Follow-up Period with their first follow-up visit occurring 1 week after their last dose.

See Appendix 11 for guidelines on subject safety monitoring and discontinuation. The early termination visit only applies to subjects who are randomized and then are prematurely withdrawn from the study treatment.

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 fashion.

7.1. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, and a urine pregnancy test will be performed at every visit including the end of treatment (EOT/ET) and follow-up visits. A negative pregnancy 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), and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will discontinue use of investigational product and be withdrawn from the study.

7.2. Banked Biospecimens

7.2.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens

for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study ID number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also postmarketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 4-mL blood biospecimen **Prep D1 (K_2 edetic acid [ethylenediaminetetraacetic acid] [EDTA] whole blood collection optimized for DNA analysis)** will be collected at the baseline visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. The banked biospecimens will be collected from all subjects **unless prohibited by local regulations or ethics committee decision**. Detailed collection, processing, storage, and shipment instructions are provided in the laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/subject information sheet that they will not be compensated in this event.

7.2.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation among people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimen specified in the Markers of Drug Response section will be used. Subjects may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.3. Safety Assessments

Safety will be assessed by the spontaneous reporting of AEs, physical examinations 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 (blood pressure, pulse, respiratory rates and temperature) will be measured after 5 minutes of rest as indicated in the Schedule of Activities.

It is preferred that body temperature be collected using the tympanic or oral methods and that the same method 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 Exam, 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 and extent of disease, cardiac history and smoking history will be collected at Screening. 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 timepoints, see Schedules of Activities.

Complete physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines. Complete physical examinations consist of assessments of general appearance; skin; head, eyes, ears, nose and throat (HEENT); mouth, heart; lungs; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; and lymph nodes.

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

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

7.3.3. Chest X-Ray

Chest radiograph (posterior-anterior and lateral views are recommended, however local guidelines should be followed) 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, general infections, heart failure or malignancy 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. Electrocardiogram

Single 12-lead ECGs should be collected at times specified in the Schedule of Activities.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position and prior to any blood collection.

The screening ECG values will serve as each subject's baseline values. To ensure safety of the subjects, a qualified individual (eg sub-investigator) at the investigator site will make comparisons to baseline measurements. A paper or digital copy of the ECG should be filed

in the subject's chart and must be available to the Sponsor upon request. Any clinically significant changes will be recorded and evaluated further, as clinically warranted. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

7.3.5. QuantiFERON® - TB Gold In-Tube Test and Mantoux/Purified Protein Derivative (PPD) Tuberculin Skin Test

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.

Test results will be reported as positive, negative or indeterminate. In the case of an indeterminate result, repeat tests may be permitted for the purpose of determining eligibility of subjects to enroll in this study. It is recommended that subjects with a history of BCG vaccination be tested with the QFT-G test since the Mantoux/PPD tuberculin skin test may be positive due to vaccination. A positive QFT-G test is exclusionary. The procedure for using this test and interpreting the results will be described fully in the laboratory manual, which will be provided to investigators.

Subjects can be TB screened using the Mantoux/PPD Tuberculin Skin Test. Mantoux/PPD testing can also be performed if there are indeterminate QFT-G test results. Subjects must have a Mantoux/PPD tuberculin skin test administered and then evaluated by a health care professional 48 to 72 hours later. A positive Mantoux/PPD tuberculin skin test is exclusionary.

The Mantoux/PPD Tuberculin Skin Test consists of an intracutaneous injection of 5 Tuberculin Units (5 TU) PPD in 0.1 mL of solution (according to local standard) on the volar aspect of the forearm, using a short beveled 26-or 27-gauge needle. The test is read according to local standard 48 to 72 hours after injection.

7.3.6. Special Safety Assessment

In case of a suspected viral skin infection (eg, herpes zoster and herpes simplex), a specimen for viral DNA should be obtained for confirmation. Details for such collection will be provided in the laboratory manual.

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 Phototype assessment (Appendix 4). This is used to classify a person's skin type by their response to sun exposure (ie, burning or tanning).

7.5. Clinical Laboratory Tests

7.5.1. Blood Volume

Total blood sampling volume planned for this study is approximately 439 mL. Further details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the lab manual.

7.5.2. 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 6, Week 12, and EOS. All other labs (including PK sample collections) 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	Glucose	Protein (qual)	HBcAb[a]
Reticulocyte count	Na+, K+, Cl- ,Ca++	Blood (qual)	HbsAB[b]
Platelet count	Total CO2 (Bicarbonate)	Ketones	HCVAb[a]
WBC count with differential	AST, ALT	Nitrites	Serum pregnancy test [a, c]
Total neutrophils (%, Abs)	Total Indirect & Direct Bilirubin	Leukocyte esterase	Urine pregnancy test [c]
Eosinophils (%, Abs)	Alkaline phosphatase	Microscopy and/or culture[d]	FSH[a, g]
Monocytes (%, Abs)	Uric acid		QFT-G or other IGRA, or PPD[e]
Basophils (%, Abs)	Albumin		EBV, CMV, HSV1, HSV2, VZV
Lymphocytes (%, Abs)	Total protein		Total IgE
	Lipid Profile Panel [f]:		hsCRP
	Total cholesterol		IP10 (CXCL10)
	LDL		IL-31
	HDL		CCL17(TARC)
	Triglycerides		TBNK
			T cell subtypes

[a] At Screening only.
[b] HepB reflex testing only if HBsAg negative but HBcAb positive.
[c] Females of childbearing potential.
[d] Only if urine analysis is positive for blood, protein, nitrites, or leukocyte esterase.
[e] PPD results should be read within 48 to 72 hours.
[f] Lipid Profile Panel requires at least an 8 hour fast. Lipid profile panel will be completed at Day 1, Week 6, Week 12, and EOS, and will include total cholesterol, LDL, HDL, and triglycerides.
[g] Females of non-child bearing potential.

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 11 for laboratory discontinuation criteria.

7.5.2.1. Viral Surveillance

Blood sample (8 mL) for the analysis of CMV, EBV, HSV-1, HSV-2 and VZV will be collected according to the times outlined in the Schedule of Activities. Additional sample collection instructions will be provided in the lab manual.

7.6. Efficacy Assessments

7.6.1. Investigator Global Assessment (IGA)

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 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..

7.6.2. 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 Region 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.

7.6.2.1. Body Surface Area – Efficacy (BSA Efficacy)

BSA Efficacy will be derived from the sum of the BSA in handprints across 4 body regions assessed as part of the EASI assessment (Table 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%.

7.6.3. Scoring Atopic Dermatitis (SCORAD)

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

Extent (A, maximum 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 of 100%.

Severity (B, maximum 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);
- 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 of 18).

Subjective Symptoms (C, maximum of 20)

Subjective symptom (ie. itch and sleeplessness) are each scored by the subject or caregiver using a numeric rating scale (NRS) where “0” is no itch (or no sleeplessness) and “10” is the worst imaginable itch (or sleeplessness). These scores are added to give 'C' (maximum 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. Patient-Reported Outcomes (PROs)

Subjects will complete the PROs at the clinic prior to other clinical activities and study drug administration except for PSAAD. The PROs should be checked for completeness by the study site staff before the subject leaves the clinic at the end of their visit. For selected country/ies in which subjects are given a handheld device to complete the PSAAD on a daily basis, delegated site staff will review compliance with subjects at each visit and counsel as appropriate. If a subject has repeated non-compliance, the subject should be re-trained on the device. If a subject is unable to complete the PSAAD due to documented technical disability or other limitation, the subject will be permitted to enter or remain in the study. As the PSAAD is an exploratory endpoint, no deviations will be recorded in regards to ePRO compliance.

7.7.1. Pruritus Numeric Rating Scale (NRS)

Severity of Pruritus

The severity of itch (pruritus) due to atopic dermatitis will be assessed using a horizontal NRS (Appendix 6). Subjects will be asked to assess their "worst itching due to atopic dermatitis over the past 24 hours" on a NRS anchored by the terms "no itching" (0) and "worst possible itching" (10).

Frequency of Pruritus

The frequency of itch (pruritus) due to atopic dermatitis will be assessed using a horizontal NRS (Appendix 6). Subjects will be asked to assess "frequency of itching due to atopic dermatitis over the past 24 hours" on a NRS anchored by the terms "never/no itching" (0) and "always/constant itching" (10).

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

7.7.2. Patient Global Assessment (PtGA)

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

7.7.3. Dermatology Life Quality Index (DLQI)

The DLQI is a general dermatology questionnaire that consists of 10 items that assess subject health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment) (Appendix 7). It has been extensively used in

clinical trials for AD. The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to be responsive to change. The minimally important difference for the DLQI has been estimated as a 2 to 5 point change from baseline. The DLQI should be completed as per Schedule of Activities.

7.7.4. Patient-Oriented Eczema Measure (POEM)

The POEM is a 7-item PRO measure used to assess the impact of AD over the past week (Appendix 8). The POEM should be completed as per Schedule of Activities.

7.7.5. Hospital and Anxiety Depression Scale (HADS)

The HADS is a 14-item PRO measure used to detect states of anxiety and depression over the past week (Appendix 9). The HADS should be completed as per Schedule of Activities.

[redacted]

7.8. Photography of Atopic Dermatitis Treated with Study Drug

For subjects at a selected study site(s), photographs of treatment-eligible atopic dermatitis will be obtained (according to the separately provided Photography Instructions) at Day 1 and Week 6. Areas photographed should be recorded in study documents so that the same atopic dermatitis body region(s) will be photographed at Week 6. Additional photographs may also be taken at Week 8 and/or Week 12 at the investigator's discretion.

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

7.9. Pharmacokinetics

7.9.1. Plasma for Analysis of PF-04965842

During all study periods, blood samples (4 mL) to provide approximately 1.2-1.5 mL of plasma for PK analysis will be collected into appropriately labeled tubes containing K_2EDTA at times specified in the STUDY PROCEDURES section of the protocol.

Blood will be collected at the time points identified in the Schedule of Activities section of the protocol. All efforts will be made to obtain the pharmacokinetic 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 Schedule of Activities will be considered a protocol deviation.

- 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 pharmacokinetics of the study drug, 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 shipment address and assay lab contact information will be provided to the Investigator site prior to initiation of the study. 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.

7.10. Pharmacodynamics Markers

The pharmacodynamics (PD) samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PD 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. Depending on sampling and transport constraints, it is possible that not all biomarker samples will be collected in all study regions.

All efforts will be made to obtain the PD samples at the exact nominal time relative to dosing. Please consult the laboratory manual(s) for final instructions on sample collection, storage, and shipping requirements. These manual(s) supersede the instructions listed in the applicable protocol sections. Samples that are handled according to the respective manual guidance are considered "per protocol".

Samples will be analyzed using fit for purpose or validated analytical methods in compliance with Pfizer standard operating procedures.

As part of understanding the pharmacodynamics of the study drug and the disease under study, samples may be used for evaluation of the bioanalytical method. These data will be used for internal (ie, Pfizer) exploratory purposes and will not be included in the clinical report.

7.10.1. Samples for IP-10 Analysis

Blood samples (3 mL) to provide approximately 1.2 mL serum for the analysis of IP-10 will be collected into appropriately labeled tubes containing no preservative, anticoagulant or serum separator according to the times outlined in the Schedule of Activities.

The blood will be allowed to clot in an upright position at ambient temperature for approximately 30 min. Place the clotted samples into an ice bath for approximately 10 min prior to centrifugation. The serum will be transferred to appropriately labeled screw-capped polypropylene tubes and stored according to the laboratory manual.

Note: During all steps after the sample is clotted, the sample will be kept on ice until transferred to frozen storage.

7.10.2. Samples for hs-CRP Analysis

Blood samples (3.5 mL) to provide approximately 1.2 mL serum for the analysis of hs-CRP will be collected into appropriately labeled 3.5 mL Goldtop tubes according to the times outlined in the Schedule of Activities.

Samples will be allowed to clot at room temperature for 30 minutes. The serum will be transferred to an appropriately labeled screw-capped polypropylene tube and stored according to the laboratory manual.

7.10.3. Samples for Immunoglobulin E (IgE) Analysis

Blood sample (4 mL) to provide approximately 1.5 mL serum for the analysis of immunoglobulin (IgE) will be collected into a serum tube according to the times outlined in the Schedule of Activities.

Samples will be allowed to clot at room temperature for at least 30 minutes. The serum will be transferred to appropriately labeled screw-capped polypropylene tubes and stored according to the laboratory manual.

7.10.4. Samples for FACS analysis (T cell, B cell, and NK cell subsets)

Blood samples (5 mL) for the assessment of percent and absolute lymphocyte subsets will be collected and will be analyzed by FACS to identify T cell, B cell, and NK cell subsets according to the times outlined in the Schedule of Activities. Sample tube should be completely filled to ensure correct final preservative concentration. Immediately after the sample is drawn, gently invert the tube 180° and back, for **at least 1 minute** to thoroughly mix the blood with the anti-coagulant. The samples should be appropriately labeled (ie, date and time of collection, subject ID, sample ID, and protocol number). All samples must be immediately shipped to the FACS lab at ambient temperature (18°C - 25°C).

7.10.5. Samples for FACS Analysis: T-cell subtype profiling

Blood samples (4 mL) for the assessment of T cell subsets will be collected in appropriately labeled tubes, and will be analyzed by FACS to measure the frequency of Th1, Th2, Th9, Th22, Th17 and Th17/Th1 cell subsets according to the times outlined in the Schedule of Activities.

Sample tube should be completely filled to ensure correct final preservative concentration. Immediately after the sample is drawn, gently invert the tube 180° and back, for **at least 1 minute** to thoroughly mix the blood with the anticoagulant. Samples must be immediately shipped to the FACS lab at ambient temperature (18°C-25°C).

7.10.6. Samples for IL-31 Analysis

Blood samples (2 mL) to provide approximately 0.6 mL plasma for the analysis of IL-31 will be collected into appropriately labeled tubes, pre-chilled in a wet ice bath for at least 5 minutes prior to blood collection. Samples will be collected according to the times outlined in the Schedule of Activities.

Immediately after allowing the tube to completely fill, gently invert the tube 8 times, and return the tube to the wet ice bath. Within 30 minutes of collection, centrifuge at 1,500-2,000 x g for approximately 10 minutes at 4°C. The plasma will be transferred to appropriately labeled screw-capped polypropylene tubes and stored according to the laboratory manual.

7.10.7. Samples for CCL17 (TARC) Analysis

Blood samples (4 mL) to provide approximately 1.2 mL serum for the analysis of CCL17 (TARC) will be collected into appropriately labeled tubes according to the times outlined in the Schedule of Activities.

Samples will be allowed to clot at room temperature for 30 minutes. The serum will be transferred to an appropriately labeled screw-capped polypropylene tube and stored according to the laboratory manual.

7.10.8. Serum for Exploratory Analysis

Blood samples (10 mL) to provide approximately 3 mL serum will be collected into appropriately labeled tubes according to the times outlined in the Schedule of Activities. These samples may be used for the evaluation of exploratory biomarkers that may include markers related to atopic dermatitis and/or other inflammatory conditions and/or the mechanism of action of PF-04965842. These samples are for biomarker analysis and will not be used for genetic testing.

Detailed processing, storage and shipment instructions will be provided in the lab manual.

7.10.9. Cell-free Plasma for Exploratory Analysis

Blood samples (10 mL) will be collected into appropriately labeled tubes according to the times outlined in the Schedule of Activities. These samples may be used for the evaluation of exploratory biomarkers from cell-free plasma that may include markers related to atopic dermatitis and/or other inflammatory conditions and/or the mechanism of action of PF-04965842. These samples are for biomarker analysis and will not be used for genetic testing.

Detailed processing, storage and shipment instructions will be provided in the lab manual.

7.10.10. Gene Expression Analysis

Blood samples (2.5 mL) for the assessment of gene expression (mRNA analysis) will be collected in appropriately labeled PAXgene Blood RNA Tubes. Samples will be collected according to the times outlined in the Schedule of Activities. These samples may be used for the evaluation of exploratory biomarkers that may include markers related to atopic dermatitis and/or other inflammatory conditions and/or the mechanism of action of PF-04965842. These samples are for biomarker analysis and will not be used for genetic testing.

Detailed Processing, Storage and Shipment Instructions will be provided in the Lab Manual.

7.10.11. Shipment of Pharmacodynamic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated

representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. 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.

As part of ongoing safety reviews conducted by the sponsor, any nonserious 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.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor 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 are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation 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 symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

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

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- 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.

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

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- 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 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 reporting as an AE.

8.6. 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.

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.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the ULN concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with 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).

    Concurrent with

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The subject should return to the investigational 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, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. 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 should be 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 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 AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, 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.

8.9. 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 in the CRF, as appropriate, 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 (see the section on Reporting Requirements). 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, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

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

1. 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).

2. 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 study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an 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) 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 of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

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 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 investigator. 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 study 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.

8.11. 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 the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

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

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or 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 or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. 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.

9. DATA ANALYSIS/STATISTICAL METHODS

This section outlines the key planned statistical summaries and analyses for the data collected in this study. A comprehensive overall Statistical Analysis Plan (SAP) will be provided prior to the un-blinding of the trial. The SAP may modify the plans outlined in the protocol; however, any major modifications of planned analyses will be reflected in a protocol amendment if it is modified before data un-blinding. If, after the trial is un-blinded, changes are made to the SAP, then these deviations to the plan will be documented, along with an explanation as to why they occurred, in the Clinical Study Report (CSR).

9.1. Sample Size Determination

The sample size is based on the primary efficacy endpoint, IGA response rate of clear or almost clear and ≥2 points improvement at Week 12. For IGA response rate at Week 12, a total of 250 randomized subjects in the 5 treatment groups (providing approximately 200 completers, 40 completers per treatment group assuming 20% dropout rate) will provide approximately 95% power to detect a 33% difference between PF-04965842 and placebo assuming placebo response rate is approximately10%, and significance level is 0.0125 (Bonferroni adjusted with 4 comparisons).

9.2. Efficacy Analysis

9.2.1. Analysis of the Primary Endpoint

When the 12 week treatment period is completed, the analysis of the primary endpoint will be conducted. The primary endpoint is the proportion of IGA responders at Week 12 and the corresponding primary analysis will be based on the normal approximation for the difference in binomial proportions (such as IGA response rates) to test the superiority of each dose of PF-04965842 to placebo at Week 12. Subjects who receive at least one investigational product and discontinue from the study before Week 12 will be considered as non-responders for the primary endpoint (IGA) for all subsequent visits during the treatment phase until Week 12. Bayesian analysis using a non-informative prior (such as Jeffery's prior) may be employed if the normality assumption does not hold.

Sensitivity analysis will be performed with a generalized linear mixed model utilizing the data from all scheduled visits if there is no convergence issue. This model will have fixed effects for time, treatment, time by treatment interaction and other potential covariates. The dependent variable will be logit of the probability of "response". An unstructured correlation may be used to model the association between observations within a subject. The modified intention-to-treat (mITT) population will be the subjects who receive at least one dose of randomized investigational product (PF-04965842 or placebo). In addition, dose-response analysis using an Emax model may be provided for the primary endpoint.

9.2.2. Analysis of the Secondary Endpoints

The key secondary endpoint is the percent change from baseline in EASI score at Week 12. The treatment effect in each of the active treatment groups is the difference (mean percent change from baseline at Week 12 in the active treatment group minus the mean percent change from baseline at Week 12 in the placebo group) in the mean percent change from baseline of a EASI score at Week 12.

The estimates for treatment effect will be obtained by fitting the mixed-effect models repeated measures (MMRM) assuming missing at random to the percent change of EASI score from baseline score if there is no convergence issue. The model will include time , treatment (active doses and placebo), treatment by time interaction as fixed effects and baseline value as a covariate. We will allow an unstructured variance-covariance matrix. Covariance matrices with other structure will be considered in sensitivity analysis. Estimates and the appropriate confidence intervals will be presented.

In addition to the primary analysis based on the pairwise evaluation of the treatment effects, we will explore the modeling of dose-response relationship for the key secondary endpoint.

MMRM will also be employed for other continuous endpoints such as percent change from baseline in the EASI total score at all scheduled time points, percent change from baseline in the pruritus NRS from baseline at all scheduled time points, change from baseline in affected BSA at all scheduled time points, and change from baseline in SCORAD at all scheduled time points. Estimates of mean values and the mean differences from placebo at each week

(along with 90% confidence intervals) will be reported. Descriptive statistics of the actual and change from baseline values will be calculated.

The binary secondary endpoints such as proportion of subjects achieving the IGA for clear (0) or almost clear (1) and ≥2 points improvement from baseline at all scheduled time points except Week 12, proportion of subjects with the IGA response of ≥2 points improvement from baseline at all scheduled time points, proportions of subjects achieving 50%, 75% and 90% reduction in EASI total score from baseline at all scheduled time points , proportion of subjects with improvement (reduction) of the pruritus NRS ≥3 from baseline at all scheduled time points and Proportion of subjects achieving a 50% and 75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points will be analyzed using the same method specified for the primary endpoint in Section 9.2.1. We will calculate estimate and 90% confidence interval for the difference of proportions (each of the active doses against placebo) using normal approximation to the distribution of the observed difference in proportions.

9.2.3. Analysis of Other Endpoints

Other continuous endpoints such as change from baseline in PSAAD, PtGA, DLQI, POEM, and HADS at all scheduled time points and change from baseline in the pruritus severity and frequency at all scheduled time points will be analyzed with the same method used for the continuous endpoints in Section 9.2.2. For the binary endpoint such as proportion of subjects with PtGA of AD of clear (0) or almost clear (1) and ≥2 points improvement from baseline over 12 weeks, the same method used for the binary endpoint in Section 9.2.1 will be employed.

Descriptive statistics will be generated for other endpoints such as incidence of treatment-emergent AEs (TEAE) and incidence of specific clinical laboratory abnormalities.

9.3. Safety Analysis

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. Safety endpoints for the study include:

- On-treatment 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, anemia, neutropenia, thrombocytopenia, lymphopenia, lipid profile, LFTs).
- Vital signs.

- ECG parameters if applicable.

Safety data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. A set of safety summary tables by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering the investigational product, continuous outcomes (eg, blood pressure, heart rate etc.) will be summarized using N, Mean, Median, Standard Deviation etc. Categorical outcomes (eg, occurrence of any adverse event) will be summarized by subject counts and percentage. Change from baseline on laboratory data and vital signs will be additionally summarized. Subject listings will also be produced for these safety endpoints. The safety endpoints will be listed and summarized in accordance with Pfizer Data Standards. The safety analyses will be carried out in the safety population, detailed analyses will be described in the SAP.

9.4. Interim Analysis

An interim analysis may be performed when approximately 110 randomized subjects complete 6 weeks of study or discontinue prematurely from study in order to assess the percent change of EASI score from baseline as well as other efficacy and safety endpoints such as IGA response, itch response measured by NRS and hematological parameters as appropriate. The actual interim analysis data cutoff date may vary slightly depending on the actual patient recruitment. A non-binding futility analysis may be performed on the efficacy endpoints. Modifications to the design such as adjustments to the final sample size or termination of enrollment of subjects in a treatment arm or stopping a treatment arm may be made upon review of the data. Unless a safety concern arises, no decisions to stop the trial will be made based on this interim analysis. Further information about the interim analysis will be specified in an Internal Review Committee (IRC) charter.

The study team and investigators will remain blinded to the results of the interim analysis. It is expected that all interim analysis data from the treatment phase of the study will be as clean as possible and that all clinical relevant queries will have been addressed. Access to the database containing individual treatment group assignments will be restricted to the unblinded support team including programmer, statistician, clinician and clinical pharmacologist. Paper copies of the treatment assignments will not be kept and any copies printed for temporary checks of the data will be destroyed.

9.5. PK/PD Unblinding Plan

A PK/PD unblinding plan approved by the clinical lead, clinical pharmacology lead and statistical lead will be in place to describe the procedures to be employed in safeguarding the study blind for members of the PF-04965842 study team. These procedures will be in accordance with applicable Pfizer SOPs for releasing randomization codes and breaking the study blind. Under this plan a group of statisticians, PK/PD data provider, PK/PD analyst and PK/PD support would be unblinded in order to initiate the building of statistical models of the PK, dose/response as well as exposure/response analysis models and conduct associated simulations. The aim of this work would be to facilitate a comprehensive interpretation of the study upon completion (at appropriate interim milestone). This group will not serve on the study team during the period of early unblinding. The unblinding may

occur after the last subject has been randomized. The details of the procedures will be described in the PK/PD Unblinding Plan for Modelling and Simulation for study B7451006. In order to expedite the analyses of the exploratory biomarkers, an unblinded team may review the exploratory (ie, any data not explicitly stated as primary or secondary endpoint) and exposure data on an ongoing basis. This group will minimally be comprised of bioanalyst and statistician, but may also include clinicians/precision medicine personnel, clinical pharmacologist and PK/PD analyst/support staff. This group will be unblinded throughout the study in order to conduct the analyses of the exploratory biomarkers in accordance with an exploratory biomarker data analysis plan, and will be independent of the study team. This unblinding process will not have any impact on the conduct of the study. The exploratory biomarker plan will be approved by the clinical lead, clinical pharmacology lead and statistical lead, and will be in place to describe the procedures to be employed in safeguarding the study blind for members of the study team. These procedures will be in accordance with Pfizer SOPs related to Releasing Randomization Codes and Breaking the Blind. The exploratory biomarker plan will outline the range of possible analyses and provide details of the decision-making process.

9.6. Analysis of Pharmacokinetics Endpoints

PK concentrations will be summarized and presented by treatment group with summary statistics and, where appropriate, non-compartmental PK parameters estimates will be provided. A population PK model may be developed for the purpose of estimating PK parameters. Population PK data for PF-04965842 will be summarized through appropriate data tabulations, descriptive statistics, and graphical presentation. Data permitting, the relationship between exposure and clinical responses (efficacy and safety) and disease and mechanism related PD biomarkers during treatment of subjects with moderate to severe AD may be explored using either observed or modeled exposures. Any population analyses conducted will not be part of the clinical study report and may be reported separately.

9.7. Data Monitoring Committee

This study will use an IRC to monitor the safety of the subjects throughout the study and to make recommendations to the study team. Composition of the IRC and processes under which the IRC operates will be documented in an IRC charter.

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 study site may be subject to review by the institutional review board (IRB)/ethics committee (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 study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. 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's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

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

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

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki. Note: The Declaration of Helsinki (World Medical Association 2013, as mandated by local law) will be followed except that the investigational product PF-04965842 will not be made available to subjects after they have finished the study.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

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 a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study 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 documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

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

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject, before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees (or institutional review boards) and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. 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 competent 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 a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as 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 or discontinued, 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 for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date 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 prespecified 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 primary completion date for studies in adult populations or within 6 months of the primary completion date 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 principal investigator of the results of the study based on information collected or generated by principal investigator, 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 they are 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 study sites, and that any subsequent publications by the principal investigator will reference that primary publication.. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical

Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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

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

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Appendix 1. Abbreviations

This 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 concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
AUC_{last}	area under the plasma concentration time curve from time zero extrapolated to the last quantifiable concentration
AUC_{tau}	area under the plasma concentration-time curve from time zero to 24 hours
BA	bioavailability
BCG	bacille calmette guérin
BP	blood pressure
BSA	body surface area
CDS	core data sheet
CL	clearance
C_{max}	maximum plasma concentration
CMV	cytomegalovirus
CRF	case report form
CSA	clinical study agreement
CsA	cyclosporine A
CSF	cerebrospinal fluid
CT	computed tomography
CTA	clinical trial application
CTCAE	common terminology criteria for adverse events
DAI	dosage and administration instructions
DDI	drug-drug interaction
DLQI	dermatology life quality index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	eczema area and severity index
EBV	epstein barr virus
EC	ethics committee
ECG	electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy

Abbreviation	Term
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EFD	embryo-fetal development
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
EPO	erythropoietin
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	good clinical practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HADS	hospital and anxiety depression scale
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HEENT	head, eyes, ears, nose and throat
HIV	human immunodeficiency virus
HRQL	health-related quality of life
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IFNα	interferon alfa
IFNγ	interferon gamma
IGA	investigator's global assessment
IgE	immunoglobulin E
IL	interleukin
IND	investigational new drug application
INR	international normalized ratio
IOBU-SDMC	Internal Oncology Business Unit-Safety Data Monitoring Committee
IP-10	interferon gamma-induced protein 10
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IVRS	interactive voice response system
IWR	interactive web response
JAK	janus kinase

Abbreviation	Term
LFT	liver function test
LLN	lower limit of normal
LPD	local product document
LSLV	last subject last visit
MAD	multiple ascending dose
MDCK/MDR1	Madin Darby canine kidney cell line/multidrug resistance 1 gene
mITT	modified intention-to-treat
MMRM	mixed-effect models repeated measures
MRI	magnetic resonance imaging
MTX	methotrexate
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NK	non-killer cells
NOAEL	no observed adverse effect level
NRS	numerical rating scale
OBU	oncology business unit
PCD	primary completion date
PD	pharmacodynamic
PFS	pre-filled syringe
P-gp	P-glycoprotein
PK	pharmacokinetic
POC	proof-of-concept
POEM	patient Oriented Eczema Measure
POM	proof of mechanism
PPD	purified protein derivative
PRO	patient reported outcomes
[redacted]	[redacted]
PT	prothrombin time
PtGA	patient global assessment
QD	once daily
QFT-G	QuantiFERON®-TB Gold
R_{ac}	accumulation ratio
RNA	ribonucleic acid
RRCK	ralph russ canine kidney cells
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCL	supply chain lead
SCORAD	SCORing atopic dermatitis
SIB	suicidal ideation and behavior
SOC	system organ class
SOP	standard operating procedure

Abbreviation	Term
SPC	summary of product characteristics
SRSD	single reference safety document
STATs	signal transducers and activators of transcription
$t_{½}$	half life
TB	tuberculosis
TDAR	T cell-dependent antibody response
TEAE	treatment-emergent adverse event
T_H1	type 1 helper T cell
T_H2	type 2 helper T cell
T_{max}	the time after administration of a drug when the maximum plasma concentration is reached
TYK2	tyrosine kinase 2
ULN	upper limit of normal
US	United States
USPI	United States package insert
UVA	ultraviolet A light
UVB	ultraviolet B light
UVR	ultraviolet radiation
VAS	visual analogue scale
VZV	varicella zoster virus

Appendix 2. Diagnostic Criteria for Atopic Dermatitis

A subject is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.

Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

Major Criteria (must have at least three)
Pruritus
Typical morphology and distribution:
Adults: flexural lichenification or linearity
Children and infants: involvement of facial and extensor surfaces
Chronic or relapsing dermatitis
Personal or family history of atopy
Minor Criteria (must have at least three)
Xerosis
Icthyosis/keratosis pilaris/palmer hyperlinearity
Immediate (type 1) skin test reactivity
Elevated serum IgE
Early age at onset
Tendency to skin infections (Staphylococcus aureus, herpes simplex)/impaired cellular immunity
Hand/foot dermatitis
Nipple eczema
Conjunctivitis
Dennie-Morgan fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor/erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Perifollicular accentuation
Food intolerance
Course influenced by environmental/emotional factors
White demographic/delayed blanch

Appendix 3. Prohibited Concomitant Medications

CYP3A4, 5,7 Inhibitors

HIV antivirals:
-delavirdine (Rescriptor)
-indinavir (Crixivan)
-nelfinavir (Viracept)
-ritonavir (Kaletra, Norvir)
-saquinavir (Fortovase)
amiodarone (Cordarone, Pacerone)
cimetidine (Tagamet)
ciprofloxacin (Cipro)
clarithromycin (Biaxin, Prevpac)
diethyl-dithiocarbamate
diltiazem (Cardizem, Tiazac)
erythromycin
fluconazole (Diflucan)
fluvoxamine (Luvox)
gestodene (Femodene, Melodene, Minulette, Mirelle, Triodene ED)
grapefruit juice and marmalade
itraconazole (Sporanox)
ketoconazole (Nizoral)
mifepristone (Mifeprex, RU486)
nefazodone (Serzone)
norfloxacin (Shibroxin, Noroxin)
Norflouxetine
Mibefradil
verapamil (Calan SR,Covera HS, Isoptin SR, Tarka, Verelan)

CYP3A Inducers

efavirenz (Sustiva)
nevirapine (Viramune)
barbiturates
carbamazepine (Carbatrol, Tegretol)
modafinil (Provigil)
phenobarbital
Phenytoin (Dilantin, Phenytek)
rifampin (Rifadin, Rifamate, Rifater)
St. John's wort
troglitazone (Rezulin)
pioglitazone (Actos)
rifabutin (Mycobutin)

Appendix 4. 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 5. Patient Global Assessment (PtGA)

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

Choose only ONE response.

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

Appendix 6. Pruritus Severity and Frequency

Severity of Pruritus

Select he number that best describes your 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
No itching										Worst possible itching

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. Dermatology Life Quality Index (DLQI)

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

Appendix 8. Patient-Oriented Eczema Measure (POEM)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 9. Hospital and Anxiety Depression Scale (HADS)

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

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

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

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

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

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

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

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

9. I get a sort of frightened feeling like 'butterflies' in the stomach
- ☐ 0 Not at all
- ☐ 1 Occasionally
- ☐ 2 Quite often
- ☐ 3 Very often

10. I have lost interest in my appearance
- ☐ 3 Definitely
- ☐ 2 I don't take as much care as I should
- ☐ 1 I may not take quite as much care
- ☐ 0 I take just as much care as ever

11. I feel restless as if I have to be on the move
- ☐ 3 Very much indeed
- ☐ 2 Quite a lot
- ☐ 1 Not very much
- ☐ 0 Not at all

12. I look forward with enjoyment to things
- ☐ 0 As much as I ever did
- ☐ 1 Rather less than I used to
- ☐ 2 Definitely less than I used to
- ☐ 3 Hardly at all

13. I get sudden feelings of panic
- ☐ 3 Very often indeed
- ☐ 2 Quite often
- ☐ 1 Not very often
- ☐ 0 Not at all

14. I can enjoy a good book or radio or television program
- ☐ 0 Often
- ☐ 1 Sometimes
- ☐ 2 Not often
- ☐ 3 Very seldom

[redacted]


[redacted]

Appendix 11. Guidelines for Subject Safety Monitoring and Discontinuation

These guidelines for subject safety monitoring and discontinuation are to be applied to all subjects in study B7451006. Additional individual subject monitoring is at the discretion of the investigator and dependent on any perceived safety concerns. Unscheduled clinical labs may be obtained at any time during the study to assess such concerns, and a subject may be withdrawn at any time at the discretion of the investigator.

Appendix 11.1. Monitoring

The following laboratory abnormalities require re-testing within 1 week:

- Absolute neutrophil count <2000/mm^3;
- Hemoglobin <11.0 g/dL;
- Platelet count below <100,000/mm^3;
- Serum creatinine >upper limit of normal (ULN).

Appendix 11.2. Discontinuation

Treatment with PF-04965842 will be discontinued and the subject withdrawn from this study for:

Adverse Events:

- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring parenteral antimicrobial therapy or hospitalization;
- Other serious or severe AEs, after consultation with the Pfizer clinician.

Laboratory Abnormalities:

All the following laboratory abnormalities **require discontinuation** if they are confirmed. Confirmation through re-testing should occur within 1 week:

Laboratory Variable	Laboratory Value
Hematology	
Absolute Neutrophil Count	<1000/mm^3; <1.0 x10^9/L
Hemoglobin	<10.0 g/dL; <6.2 mmol/L; <100 g/L
Platelet count	<75,000/mm^3; <75.0x10^9/L
Lymphocytes	<500/mm^3; <0.8x10^9/L
Chemistry	
AST	>2.5x ULN
ALT	>2.5x ULN
Creatinine (serum)	>1.5x ULN
Total bilirubin[a]	>1.5x ULN

[a] Total bilirubin ≥1.5 x 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

The following vital sign abnormality will **require discontinuation** if it is confirmed. Confirmation through re-testing should occur within 1 week:

- Diastolic: recurrent or persistent (≥24 hrs) or symptomatic increase from baseline, in same posture, by >20 mmHg.

Discontinuation/End of Treatment Monitoring for Adverse Events, Laboratory, and Vital Signs:

Any subject meeting discontinuation criteria must enter into the Follow-up Period with their first follow-up visit occurring 1 week after their last dose, until the event has returned to normal or baseline levels or is deemed clinically stable. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Additional follow-up visits may occur as needed until any clinically relevant abnormalities or adverse events have resolved, returned to a baseline state, or are deemed clinically stable.

PROTOCOL B7451006

A PHASE 2B RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL, MULTICENTER, DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY PROFILE OF PF-04965842 IN SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

STATISTICAL ANALYSIS PLAN (SAP)

Version: 2.0

Author: [redacted]

Date: May 2, 2017

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Date	Author(s)	Summary of Changes/Comments
2.0	May 02, 2017	[redacted]	• Section 3 interim analysis re-written to clarify goals and time of IA • Section 7.1 re-written to clarify the missing value imputation proposal on efficacy data • Section 8.1.1 removed summary statistics for NR and LOCF imputation. Summary stats will only be generated for FAS with OC except a few key efficacy endpoints • Section 8.1.1.1 removed sensitivity analyses using GLMM on FAS with NR and LOCF. Logistic regression with NR imputation will be performed regardless of GLMM convergence • Section 8.1.1.3 changed Santner and Snell method to Chan and Zhang method • Section 8.1.2 added ANCOVA analysis for percent change from baseline in EASI with LOCF imputation • Section 8.1.3 added statistical methods for time-to-event variables • Section 8.2.2.1 removed sensitivity analyses using GLMM on FAS with NR and LOCF • Section 8.2.2.2.1 clarified that sensitivity analysis will be performed using ANCOVA on FAS with LOCF imputation • Section 8.2.2.2.2 changed logistic regression analysis at each time point with LOCF imputation to NR imputation • Section 6.1.2.3 added four more secondary endpoints:1) proportion of subjects achieving ≥ 4 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points 2) Percent change from baseline in SCORing atopic dermatitis (SCORAD) at all scheduled time points 3) Time to achieving ≥ 3 points improvement in NRS 4) Time to achieving ≥ 4 points improvement in NRS • Section 8.2.2.2.2 added survival analysis for time to NRS response • Section 8.2.2.2.2 added: "For endpoint "Proportion of subjects achieving ≥ 3 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points", subjects with baseline NRS ≤ 2 will be considered as

			non-responders." And "For endpoint "Proportion of subjects achieving ≥ 4 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points", only subjects with baseline NRS ≥ 4 will be analyzed". • Section 8.2.2.4 sensitivity analysis was removed • Section 8.2.3 Santner and Snell changed to Chan and Zhang method • Section 8.2.5 summary table of statistical analysis updated
1.0	March 09, 2016	[redacted]	First version

[redacted]

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicised***.
This study B7451006 is a phase 2b POC study which is planned to assess four PF-04965842 once daily (QD) doses (10, 30, 100, 200 mg) relative to placebo over 12 weeks to characterize the efficacy and safety of PF-04965842 in subjects with moderate to severe Atopic Dermatitis AD. *The objectives of the study are to demonstrate the efficacy of PF-04965842 by showing improvement in disease severity in patients with moderate to severe AD as measured by the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) scores, and safety to support further clinical development of PF-04965842.*

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

2.1. Study Design

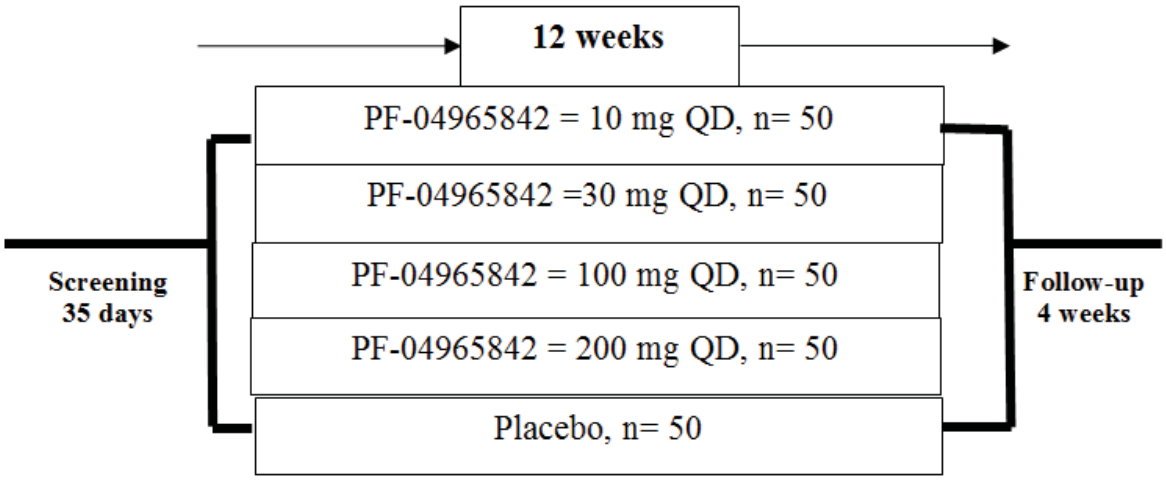
This Phase 2b, multi-center, randomized, double-blind, 5-arm, parallel group study will enroll a total of approximately 250 subjects (providing approximately 200 completers, 40 subjects per treatment group). The study will be conducted at approximately 60 sites.

Subjects who have chronic AD that has been present for at least 1 year (prior to screening visit) and affected BSA of $\geq$ 10%, EASI $\geq$ 12 and IGA $\geq$ 3 at the screening and baseline visits will be included in the study. Subjects must also have a documented history of inadequate response to treatment with topical medications given for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks) within 12 months of the first dose of study drug. Subjects will be randomized to 1 of 4 treatment groups or placebo in the ratio of 1:1:1:1:1. Investigators, subjects, and the sponsor study team will be blinded as to treatment group.

Subjects will be screened within 35 days prior to the first dose of study drug to confirm that they meet the subject selection criteria for the study. There will be a 12-week double-blind treatment period as well as a 4-week follow up period.

An interim analysis may be performed when approximately a total of 110 randomized subjects complete 6 weeks of study or discontinue prematurely from study in order to assess the percent change of EASI score from baseline as well as other safety and efficacy endpoints such as IGA response as appropriate.

Figure 1. Study Design Schematic



2.2. Study Objectives

2.2.1. Primary Objective

- *The primary objective of this study is to evaluate the efficacy of 4 QD dose levels (10, 30, 100, and 200 mg) of PF-04965842 relative to placebo in adult subjects with moderate to severe atopic dermatitis, using the Investigator's Global Assessment (IGA).*

2.2.2. Secondary Objectives

- *To evaluate the effect of PF-0465842 on additional efficacy endpoints and patient reported outcomes over time in adult subjects with moderate to severe atopic dermatitis.*

- *To evaluate the safety and tolerability of PF-0465842 over time in adult subjects with moderate to severe atopic dermatitis.*

2.2.3. Exploratory Objectives

- *To assess pharmacodynamic and disease-related biomarkers over time.*

- *To characterize pharmacokinetics of PF-04965842 over 12 weeks.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

An interim analysis (IA) will be performed when approximately 50% subjects complete 6 weeks of study or discontinue prematurely from study in order to assess the percent change of EASI score from baseline (primary endpoint for IA) as well as other efficacy and safety endpoints such as IGA response, itch response measured by Pruritus Numeric Rating Scale (NRS) and hematological parameters as appropriate. *The study team and investigators will*

remain blinded to the results of the interim analysis. It is expected that all interim analysis data from the treatment phase of the study will be as clean as possible and that all clinical relevant queries will have been addressed. Access to the database containing individual treatment group assignments will be restricted to the unblinded support team including programmer, statistician, clinician and clinical pharmacologist. Paper copies of the treatment assignments will not be kept and any copies printed for temporary checks of the data will be destroyed.

Interim analysis results will be used for internal business decision regarding future study planning. The results will have no impact on the ongoing study. Additional logistical details will also be provided in the Internal Review Committee (IRC) Charter.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Statistical inference will be made on the primary endpoint: Proportion of subjects achieving the IGA for clear (0) or almost clear (1) and ≥ 2 points improvement from baseline at Week 12. The null hypothesis is that there is no difference between any dose of PF-04965842 (200mg, 100mg, 30mg and 10mg) and placebo on the primary endpoint. The alternative hypothesis is that at least one dose of *PF-04965842* is superior to placebo on the primary endpoint.

4.2. Decision Rules

4.2.1. Dose Response Modeling

A three-parameter Emax model will be employed for dose-response fitting for the primary endpoint (IGA response at Week 12). If a monotonic dose-response curve is detected, then model estimates and the corresponding treatment effect along with 95% confidence intervals will be reported.

If the data do not support an Emax model, the decision rule may be based on pairwise comparison analysis.

4.2.2. Multiplicity Adjustment

The multiplicity adjustments are considered only in the analysis of the primary endpoint when the Emax model does not fit. Hochberg method (Hochberg, 1988) is used to account for that the null hypothesis will be rejected if a treatment effect is detected at Week 12. The overall Type I family-wise error rate (FWER) is controlled at 0.05 (one-sided).

4.2.3. Decision Rules for the Interim Analysis

This study will not stop irrespective of whether statistical significance has been reached at the interim analysis for any efficacy endpoint. However the results from interim analysis may be used for internal planning purpose.

4.2.4. Efficacy Analysis and Sample Size Justification

The sample size is based on the primary efficacy endpoint, IGA response rate of clear or almost clear and ≥2 points improvement at Week 12. For IGA response rate at Week 12, a total of 250 randomized subjects in the 5 treatment groups (providing approximately 200 completers, 40 completers per treatment group assuming 20% dropout rate) will provide approximately 95% power to detect a 33% difference between PF-04965842 and placebo assuming placebo response rate is approximately 10%, and significance level is 0.0125 (Bonferroni adjusted with 4 comparisons).

5. ANALYSIS SETS

5.1. Full Analysis Set

As specified in the protocol, the analysis of the efficacy, health outcome and biomarker endpoints will be performed for the modified intent-to-treat (mITT) population, defined as all randomized subjects who receive at least 1 dose of investigational product. This population is also called as the Full Analysis Set (FAS).

5.2. Safety Analysis Set

The safety analysis set (SAS) will be all subjects who receive at least 1 dose of investigational product. The safety analysis set will include the follow-up period. The safety analysis set excluding follow-up period data may be conducted as a sensitivity analysis.

The final safety database will include all reported safety data at the time of database release.

5.3. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) will be the subset of subjects from the safety analysis set who provide at least one pharmacokinetic concentration.

5.4. Treatment Misallocations

If a subject was:

- Randomized but not treated: the subject will appear on the subject evaluation table as randomized but not treated; this is the extent of how much the subject will be reported;
- Treated but not randomized: the subject will be reported under the treatment they actually received for all safety analyses, but will not be included in the efficacy analyses;
- Randomized but took incorrect treatment: If a subject received the incorrect treatment for the whole duration of the study, then the subject will be reported under their randomized treatment group for all efficacy analysis, but will be summarized under the treatment they actually received for all safety analyses; if a subject received the incorrect treatment at only some dosing occasions then the subject will be reported under their randomized treatment group for both efficacy and safety analyses. If sufficient doses were incorrect and therefore deemed a major protocol deviation, the subjects may be excluded as sensitivity analysis.

5.5. Protocol Deviations

The following sections describe any protocol deviations that relate to the statistical analyses. It is possible that unexpected deviations will arise, becoming known only after the study has been active for a long period of time; hence more deviations may be added. A full list of protocol deviations for the study report will be compiled prior to database closure.

5.5.1. Deviations Assessed Prior to Randomization

At screening phase prior to randomization, the investigator will assess and document subjects against the inclusion and exclusion criteria as set out in sections 4.1 and 4.2 of the protocol.

5.5.2. Deviations Assessed Post-Randomization

Post-randomization deviations include:

- Subjects who receive excluded concomitant medications or rescue medications during the treatment period as described in Section 5.8 of the Protocol;
- Subjects who were randomized but took incorrect treatment;
- Subjects not satisfying the eligibility criteria, although, not identified until after randomization occurred.

Any significant deviation or violations from the protocol will be reviewed by the clinical team during the course of the study and prior to database closure and a decision taken regarding evaluation for each analysis set.

6. ENDPOINTS AND COVARIATES

For all clinically planned measures, visits should occur within a window of the scheduled visit, which can be found in Appendix 1.

6.1. Efficacy Endpoint(s), Health Outcome and Biomarkers

6.1.1. Primary Endpoint

- *Proportion of subjects achieving the IGA for clear (0) or almost clear (1) and 2 points improvement from baseline at Week 12. The baseline will be defined as the IGA score on Day 1 pre-dose.*

6.1.2. Secondary Endpoints

6.1.2.1. Efficacy Endpoints

6.1.2.2. Key Secondary Efficacy Endpoints

- *Percent change from baseline in the eczema area and severity index (EASI) Total score at Week 12.*

6.1.2.3. Secondary Efficacy Endpoints

- *Proportion of subjects achieving the IGA for clear (0) or almost clear (1) and ≥ 2 points improvement from baseline at all scheduled time points except Week 12.*

- *Percent change from baseline in the EASI total score at all scheduled time points except Week 12.*

- *Proportion of subjects achieving ≥ 3 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points.*

- Proportion of subjects achieving ≥ 4 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points

- Time to achieving ≥ 3 points improvement in NRS

- Time to achieving ≥ 4 points improvement in NRS

- *Percent change from baseline in the pruritus NRS from baseline at all scheduled time points.*

- *Proportion of subjects achieving ≥ 2 points improvement in the IGA from baseline at all scheduled time points.*

- *Proportion of subjects achieving a ≥ 50%, 75% and 90% improvement in the EASI Total score (EASI50, EASI75, EASI90) at all scheduled time points.*

- *Change from baseline in affected body surface area (BSA) at all scheduled time points.*

- *Change from baseline in SCORing atopic dermatitis (SCORAD) at all scheduled time points.*

- Percent change from baseline in SCORing atopic dermatitis (SCORAD) at all scheduled time points.

- *Proportion of subjects achieving a ≥ 50% and 75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points.*

6.1.2.4. Safety Endpoints

- *Incidence of treatment emergent adverse events.*

- *Incidence of specific clinical laboratory abnormalities (anemia, neutropenia, thrombocytopenia, lymphopenia, lipid profile, liver function tests [LFTs]).*

6.1.2.5. Patient Reported Outcome (PRO) Endpoints

- *Change from baseline in Pruritus NRS score at all scheduled time points.*

- *Proportion of subjects with patient global assessment (PtGA) of AD of clear (0) or almost clear (1) and ≥ 2 points improvement from baseline at all scheduled time points.*

- *Change from baseline in dermatology life quality index (DLQI) total score at all scheduled time points.*

- *Change from baseline in patient Oriented Eczema Measure (POEM) at all scheduled time points.*

- *Change from baseline in the hospital and anxiety depression scale (HADS) at all scheduled time points.*

[redacted]

6.3. Covariates

For variables expressed as change from baseline, the baseline value will also be included in the analysis model as a covariate.

7. HANDLING OF MISSING VALUES

In general missing values will not be imputed for descriptive statistics.

7.1. Efficacy Data

For the binary efficacy data such as IGA response, subjects who receive at least one investigational product and discontinue from the study before Week 12 will be considered as non-responders (NR) for all subsequent visits during the treatment phase until Week 12.

For the continuous efficacy endpoints such as percent change from baseline in EASI score at Week 12, the observed case (OC) approach and the last efficacy observation carrying forward (LOCF) missing value imputation will both be considered. The efficacy endpoints will be set to missing after rescue treatment is used. The LOCF method will then be used to impute missing values.

7.2. Pharmacokinetic Concentrations and Biomarker Data

- **Concentrations outside the limit of quantification**

  In summary statistics for pharmacokinetic and biomarker data, assayed values below the lower limit of quantification (LLOQ) will be set to zero. Other imputations (eg, ½ LLOQ) may also be considered in other analyses (eg, Pop-PK and PK/PD analyses), if deemed appropriate. In listings values below LLOQ will be reported as "<LLOQ"

[redacted]

where LLOQ will be replaced with the numerical value for the lower limit of quantification. The LLOQ for various PK and biomarker concentrations will be noted in all tables and listings.

- **Missing concentrations**

  If a concentration value is not collected or cannot be analyzed due to bad samples, it will be considered as missing data and will not be imputed.

- **Missing actual sampling time**

  If actual sampling time (date or hour) value is missing, the protocol-stated nominal time will be used.

7.3. Patient Reported Outcomes (PRO) Data

Some of the analyses of PRO endpoints will be based on the OC data. If missing values happen at the item level within a PRO, the developer's guideline on missing value imputation will be considered.

7.4. Safety Endpoints

Missing data for safety endpoints will not be imputed and will be left as missing. The follow-up period will be included for the safety endpoint. A sensitivity analysis maybe carried out excluding the follow-up period.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

All efficacy analyses described in this section will only apply to the data in the treatment period to the end of week 16 (Week 0 to 16).

Percentages will be presented to one decimal place in all summaries. Minimum and maximum values will be presented to the same number of decimal places as collected on the CRF or within the laboratory screening panel; mean and median will be presented to one further decimal place; standard deviation will be presented to two further places.

Whilst every effort has been made to pre-specify all analyses in this statistical analysis plan, should any additional exploratory analyses be found to be required after unblinding, the analyses and the reasons for them will be fully detailed in the clinical study report.

In all data presentations, results will be sorted by increasing dose level, starting with Placebo.

8.1. Statistical Methods

The following sub-sections contain the descriptions of the methods that will be used in the analysis of the various endpoints in this study. The choice of analysis method will be dependent on the endpoint of interest (eg whether the endpoint is a primary, key secondary or exploratory endpoint or whether the endpoint is efficacy or safety). The analysis methods to be used for each endpoint will be covered in Section 8.2.5.

8.1.1. Statistical Methods for Binary Variables

For all binary endpoints, a summary of the number of responders based on FAS with OC in each treatment arm at each time point will be produced and the response rate will also be plotted against time, by treatment group. In addition, similar tables and figures will be generated based on FAS with NR imputation for IGA response, EASI50/75/90 and NRS response.

8.1.1.1. Primary Analysis

The primary analysis is the analysis of the primary endpoint, IGA clear (0) or almost clear (1) and ≥ 2 points improvements at Week 12, based on the FAS population. NR approach will be used to handle missing values as described in Section 7.1.

IGA response at Week 12 will be analyzed using the Emax dose-response model. The estimation of E0, Emax and ED50 will be reported in mean, standard deviation and 95% CI. These can be implemented by using PROC NLMIXED in SAS.

The three parameter Emax model is a non-linear equation such that the expected response E with or without baseline disease severity in the model can be written as:

$$E = E_0 + \frac{E_{max} Dose}{ED_{50} + Dose}$$

Where:

E is the logit function for the log odds of response *Logit(p)*.

E_0 is in placebo IGA response.

E_{max} is the difference between maximum achievable response (at infinite dose) and baseline.

ED_{50} is the dose that produces half maximal effect ($E_0 + E_{max}/2$).

The 3-parameter Emax model describes a dose response that starts at E_0 and smoothly increases to an asymptote. The fitted curve will be graphically displayed with 95% confidence band. Model based estimation of treatment effect for each dose compared to placebo will be presented with 95% confidence interval.

Sensitivity analyses for IGA will be performed with generalized linear mixed models (GLMM) on FAS population with OC. Fixed factors include treatment, covariates (baseline disease severity such as EASI score), visit and treatment by visit interaction. Random effect includes random intercept for each subject. These can be implemented with SAS PROC GLIMMIX. P-values and inference for odds ratios between treatments will be provided based on the link function of logit. A delta method will be used to obtain 90% confidence intervals for the risk differences. The overall p-value for treatment effect at each time point may be also presented. In addition, logistic regression analysis including treatment, covariates (baseline disease severity) at each time point will be performed on FAS with NR missing value imputation.

When an Emax model does not adequately capture the dose-response relationship or the Emax model does not converge, analysis from GLMM on FAS with OC and/or logistic regression on FAS with NR imputation may be considered for decision making to characterize the dose-response with dose being considered as a continuous variable.

8.1.1.2. Other Analysis of Binary Data

The analyses for other binary endpoints will be performed using GLMM on the FAS population with OC as described in Section 8.1.1.1. Logistic regression analysis may be performed on FAS with NR imputation in case of convergence issues from GLMM.

8.1.1.3. Safety Data

An unconditional exact method for risk difference proposed by Chan and Zhang (1999) will be used to compare each active dose to placebo. P-values and 90% confidence intervals will be formed for tier 1 events and 90% confidence intervals will be formed for tier 2 events.

The exposure adjusted summaries for the Tier 1 and Tier 2 events will also be conducted. See Section 8.2.1 for the calculation of exposure.

8.1.2. Statistical Methods for Continuous Variables

Unless stated otherwise, descriptive summary statistics for continuous variables will be presented on FAS with OC by treatment group and will include the following: n, mean, median, standard deviation, minimum and maximum. In addition, similar tables will be generated on FAS with LOCF imputation for EASI, NRS, SCORAD scores and BSA.For longitudinal continuous variables, such as the percent changes from baseline of EASI score, percent changes from baseline of pruritus NRS score etc., the primary analysis will be conducted using a mixed model repeated measures (MMRM) analysis on FAS with OC. Each analysis will be performed with a restricted maximum likelihood (REML) MMRM analysis. The model will include treatment and visit as fixed factors, along with the interaction of treatment and visit. Baseline measurement such as baseline disease severity will be used as a covariate. An unstructured covariance structure will be used to model the within-subject variability. In the event there are difficulties with initially fitting an unstructured covariance matrix, a variety of methods will be used to facilitate the computations. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The model will be fit using SAS PROC MIXED. Least squares (LS) means of the treatment groups at each available visit along with 90% CIs will be presented. LS mean difference between treatment and placebo for each visit will be presented along with 90% confidence intervals. Least squares means and confidence intervals will be back transformed to an appropriate scale when necessary. In addition, ANCOVA including treatment and baseline disease severity on FAS with LOCF imputation will be performed.

For the key secondary endpoint (percent change of EASI score from baseline to Week 12), a dose-response relationship will be characterized by a three-parameter Emax model described in Section 8.1.1.1, in which case E denotes the percent change of EASI at Week12 and E_0 denotes the percent change of EASI at Week12 in placebo group.

8.1.3. Statistical Methods for Time_to_Event Variables

For time to event variables such as time to achieve NRS response, Kaplan-Meier analyses will be used to account for any right censoring, i.e., event not observed. Kaplan-Meier survival estimates and the number and percentage of subjects experiencing the relevant event or being censored will be summarized and plotted by treatment group. 90% CIs will be generated for the estimate of time to NRS response.

8.2. Statistical Analyses

8.2.1. Standard Analyses

Study conduct and subject disposition

The number of subjects randomized, treated, completing and discontinuing from the study, as well as the number of subjects in each analysis population will be summarized by treatment group. For subjects who did not complete the study, the reasons for withdrawal from the study will be presented.

Demography and baseline characteristics

Demographic and baseline characteristics will be summarized by randomized treatment group for all randomized and treated subjects. Continuous variables will be summarized using mean and standard deviation. Categorical variables will be summarized using relative frequency. Key demographic and baseline variables to be summarized include: geographic region, age, gender, race, ethnicity, height, weight, body mass index, disease duration, baseline EASI score, baseline IGA, baseline NRS score etc.

Exposure and compliance

Exposure to the study therapy is defined as the number of days the subject is known to be on study drug. The exposure is roughly calculated as the date of the last visit (including the follow up visits) of the subject in this study minus the date of the first administration of the study therapy plus one. Summary statistics will be provided for exposure by treatment group.

For each subject, percent will then be calculated using the following formula:

Percent Compliance = # doses actually administrated / # doses planned * 100%.

The number of doses planned or actually administrated is counted up to the conclusion date of the treatment period. Summary statistics will be provided to percent compliance by treatment group.

Descriptive Statistics

Descriptive statistics for all primary, secondary and exploratory endpoints presented in Section 6 will be tabulated.

8.2.2. Statistical Analyses for Efficacy, Health Outcomes and Biomarkers

Unless stated otherwise, the analyses for efficacy, health outcomes and biomarkers will be based on the FAS population, as defined in Section 5.1. A summary table of the analysis strategy for all the efficacy and health outcome is shown in Section 8.2.5.

8.2.2.1. Analysis for the Primary Endpoint

The primary efficacy endpoint is the IGA response at Week 12. The primary analysis data will be based on FAS population with NR as missing value imputation method. Baseline is defined as the score for each assessment prior to the first dosing. .

The objective for the analysis of primary endpoint is to characterize the dose response in inducing clinical IGA reduction in subjects with moderate to severe atopic dermatitis. To achieve this objective, a three parameter Emax dose response model specified in Section 8.1.1.1 will be used as the primary analysis approach to characterize the dose response relationship.

As sensitivity analyses, GLMM will be employed on IGA response from all visits including follow-up. These analyses will be carried out on the FAS population with OC as described in Section 8.1.1.1. P-values and 90% confidence intervals for odds ratios between treatments and placebo will be computed at each visit. Logistic regression will be performed at each visit on FAS with NR as additional sensitivity analysis.

8.2.2.2. Analyses for the Secondary Endpoints

8.2.2.2.1. Analysis of continuous secondary endpoints

All primary analyses for the continuous secondary endpoints are based on the FAS population with OC. Baseline is defined as the score for each assessment prior to the first dosing. These endpoints include:

- *Percent change from baseline in the EASI total score at all scheduled time points*
- *Percent change from baseline in the pruritus NRS at all scheduled time points*
- *Change from baseline in affected body surface area (BSA) at all scheduled time points*
- *Change from baseline in SCORing atopic dermatitis (SCORAD) at all scheduled time points*
- Percent change from baseline in SCORing atopic dermatitis (SCORAD) at all scheduled time points

All continuous secondary endpoints including all time points will be analyzed using MMRM as described in Section 8.1.2. LS means at each time point will be computed. P values and 90% confidence intervals will also be computed for placebo adjusted effect (LS mean difference between treatment and placebo) at each time point. Sensitivity analysis will be performed using ANCOVA on FAS with LOCF imputation as described in Section 8.1.2.

Dose response analysis on the percent change from baseline in the EASI total score at Week 12 will be performed using a 3-parameter Emax model as described in Section 8.1.2.

8.2.2.2.2. Analysis of binary secondary endpoints

Unless otherwise stated, all primary analyses for the binary secondary endpoints are based on the FAS population with OC missing value imputation. Baseline is defined as the score for each assessment prior to the first dosing. These endpoints include:

Binary secondary endpoints include:

- *Proportion of subjects achieving the IGA for clear (0) or almost clear (1) and ≥2 points improvement from baseline at all scheduled time points except Week 12*
- *Proportion of subjects achieving ≥3 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points*
- Proportion of subjects achieving ≥ 4 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points
- *Proportion of subjects achieving ≥2 points improvement in the IGA from baseline at all scheduled time points*
- *Proportion of subjects achieving a ≥50%, 75% and 90% improvement in the EASI total score (EASI50, EASI75, EASI90) at all scheduled time points*
- *Proportion of subjects achieving a ≥50% and 75% improvement in SCORAD (SCORAD50, SCORAD75) from baseline at all scheduled time points*

All binary secondary endpoints at each visit (except Week 12 for IGA response) will be analyzed in the same fashion as the primary endpoint using GLMM. In the case of convergence issues, logistic regression analysis at each time point with NR imputation will be performed.

For endpoint "Proportion of subjects achieving ≥ 3 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points", subjects with baseline NRS ≤ 2 will be considered as non-responders.

For endpoint "Proportion of subjects achieving ≥ 4 points improvement in the pruritus numerical rating scale (NRS) from baseline at all scheduled time points", only subjects with baseline NRS ≥ 4 will be analyzed.

Survival analysis will be performed for time-to-event data such as time to achieving ≥ 3 points improvement in NRS and time to achieving ≥ 4 points improvement in NRS as described in section 8.1.3.

[redacted]

8.2.2.4. Analyses for the Patient-Reported Outcome (PRO) Endpoints

Unless otherwise stated, all primary analyses for the PRO endpoints are based on the FAS population with OC missing value imputation. Baseline is defined as the score for each assessment prior to the first dosing.

PRO endpoints include:

- *Change from baseline in pruritus NRS score at all scheduled time points*
- *Proportion of subjects with patient global assessment (PtGA) of AD of clear (0) or almost clear (1) and ≥2 points improvement from baseline at all scheduled time points*
- *Change from baseline in dermatology life quality index (DLQI) total score at all scheduled time points*
- *Change from baseline in patient Oriented Eczema Measure (POEM) at all scheduled time points*
- *Change from baseline in the hospital and anxiety depression scale (HADS) at all scheduled time points*

The binary PRO endpoint such as PtGA response will be analyzed in the same fashion as the primary endpoint using GLMM as described in Section 8.1.1.1. In the case of convergence issues, logistic regression analysis at each time point will be performed with NR imputation. All continuous PRO endpoints will be analyzed using MMRM as described in Section 8.1.2. LS means at each time point will be computed. P values and 90% confidence intervals will also be computed for placebo adjusted effect (LS mean difference between treatment and placebo) at each time point. In case of convergence issues, ANCOVA with LOCF may be performed at each time point.

[redacted]

[redacted]

8.2.3. Statistical Analyses for Safety

The analysis population for safety is described in Section 0. Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs) and laboratory tests. A complete list of laboratory parameters can be obtained in Section 7.3 of the protocol.

All the tables, listings and graphs for adverse events, lab parameters and vital sign will follow Pfizer standards.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers.

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan.

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA Preferred Term (PT) is defined as a tier-2 event if there are at least 4 in any treatment group.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events.

There will be no adjustment for multiple comparisons or stratification factors in the analyses unless specified. For tier-1 and tier-2 events, the proportion of AEs observed in each treatment groups will be presented along with the point estimates and associated 90% confidence intervals of the risk difference for each active treatment compared with placebo. The exact methods (Chan and Zhang, 1999) and asymptotic approach will be employed for analysis of tier-1 and tier-2 events . For tier-1 events p-values may be included in the presentations. AEs will be arranged in the output sorted in descending point estimate of the risk difference within system organ class. Footnotes in the outputs will include the methods used to derive any p-values and confidence intervals as per Pfizer standards. The exposure adjusted summaries for the Tier 1 and Tier 2 events will also be conducted.

8.2.4. PK and PK/PD Analyses

PK concentrations will be summarized and presented by treatment group with summary statistics and, where appropriate, non-compartmental PK parameters estimates will be provided. A population PK model may be developed for the purpose of estimating PK parameters. Population PK data for PF-04965842 will be summarized through appropriate data tabulations, descriptive statistics, and graphical presentation. Data permitting, the relationship between exposure and clinical responses (efficacy and safety) and disease and mechanism related PD biomarkers during treatment of subjects with moderate to severe AD may be explored using either observed or modeled exposures. Any population analyses conducted will not be part of the clinical study report and may be reported separately.

The PK/PD analysis plan will be detailed in another document.

8.2.5. Brief Summary of Major Efficacy, Health Outcome and Biomarker Analyses

Endpoints	Primary, Secondary, or Exploratory Endpoint	Analysis	Including Follow-UP	Missing Data Imputation	Primary or Sensitivity Approach
IGA Response	Primary/Secondary	Emax	Yes	NR	Primary
IGA Response	Primary/Secondary	GLMM	Yes	OC	Sensitivity
IGA Response	Primary/Secondary	Logistic regression	Yes	NR	Sensitivity
Percent change of EASI	Secondary	MMRM	Yes	OC	Primary
Change of EASI	Secondary	MMRM	Yes	OC	Sensitivity
Percent change of NRS	Secondary	MMRM	Yes	OC	Primary
Change of BSA	Secondary	MMRM	Yes	OC	Primary
Change of SCORAD	Secondary	MMRM	Yes	OC	Primary
Percent change of SCORAD	Secondary	MMRM	Yes	OC	Primary
Proportion of subjects achieving ≥ 3 NRS improvement	Secondary	GLMM	Yes	OC	Primary
Proportion of subjects achieving ≥ 4 NRS improvement	New endpoint	GLMM	Yes	OC	Primary
Proportion of subjects achieving ≥ 2 IGA improvement	Secondary	GLMM	Yes	OC	Primary
EASI50/EASI75/EASI90	Secondary	GLMM	Yes	OC	Primary
SCORAD50/SCORAD75	Secondary	GLMM	Yes	OC	Primary
Change of NRS	PRO	MMRM	Yes	OC	Primary
Change of DLQI	PRO	MMRM	Yes	OC	Primary
Change of POEM	PRO	MMRM	Yes	OC	Primary
Change of HADS	PRO	MMRM	Yes	OC	Primary

9. REFERENCES

1. Pfizer Clinical Protocol B7451006: A Phase 2B Randomized, Double-blind, Placebo-controlled, Parallel, Multicenter, Dose-ranging Study to Evaluate the Efficacy and Safety Profile of PF-04965842 in Subjects with Moderate to Severe Atopic Dermatitis.

2. Hochberg, Y, A sharpened Bonferroni procedure for multiple tests of significance, Biometrica, 1988, 75, 4: 800-802.

3. Chan, I. S. F. and Zhang, Z. (1999), "Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions," Biometrics, 55, 1202–1209.

10. APPENDICES

Appendix 1. DEFINITION AND USE OF VISIT WINDOWS IN REPORTING

Note Day 1 in the table below is taken as the first day of dosing with study drug. It may not be the same as the first study date which is the randomization date. Also note that Day 0 does not exist, so Day -1 is the day before Day 1. Also the relative days (rel_day) from Day 1 are defined as the visit date minus first dosing date plus one.

Visit windows will be used for efficacy variables, and for any safety displays that display by week.

Table 1. Visit Window Definition for Analysis (update wider visit windows)

Visit No.	Visit Label	Target Day	Visit Window
1	Screening	N/A	-35≤rel_day≤-1
2	Baseline*	1	Rel_day= 1
3	Week 1	8	2≤rel_day≤11
4	Week 2	15	12≤rel_day≤22
5	Week 4	29	23≤rel_day≤36
6	Week 6	43	37≤rel_day≤50
7	Week 8	57	51≤rel_day≤71
8	Week 12	85	72≤rel_day≤88
9	Week 13	92	89≤rel_day≤95
10	Week 14	99	96≤rel_day≤106
11	Week 16	113	107≤rel_day≤120
* Baseline analysis visit window may be considered as Rel_day≤1 in some analyses (eg, those involving change from baseline). That is, in case that Day 1 observation is missing, the last observation by the first dosing date may be considered as the baseline.			

Appendix 2. Investigator's Global Assessment (IGA)

A subject is said to have achieved the IGA response when all the following are true:

- IGA score is 0 (clear) or 1 (almost clear)
- IGA score improvement ≥ 2

Appendix 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.

[redacted]

Table 5. Handprint Determination of Body Region 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.

Appendix 4. Body Surface Area (BSA)

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%.

Appendix 5. 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 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 of 100%.

Severity (B, maximum 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);*

[redacted]

- *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 of 18).

Subjective Symptoms (C, maximum of 20)

Subjective symptom (ie. itch and sleeplessness) are each scored by the subject or caregiver using a numeric rating scale (NRS) where "0" is no itch (or no sleeplessness) and "10" is the worst imaginable itch (or sleeplessness). These scores are added to give "C" (maximum of 20).

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

Appendix 6. Pruritus Numeric Rating Scale (NRS)

Severity of Pruritus

The severity of itch (pruritus) due to atopic dermatitis will be assessed using a horizontal NRS (Appendix 6). Subjects will be asked to assess their "worst itching due to atopic dermatitis over the past 24 hours" on a NRS anchored by the terms "no itching" (0) and "worst possible itching" (10).

Frequency of Pruritus

The frequency of itch (pruritus) due to atopic dermatitis will be assessed using a horizontal NRS (Appendix 6). Subjects will be asked to assess "frequency of itching due to atopic dermatitis over the past 24 hours" on a NRS anchored by the terms "never/no itching" (0) and "always/constant itching" (10). The pruritus NRS should be completed as per Schedule of Activities.

[redacted]

Severity of Pruritus

Select he number that best describes your 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

No itching — Worst possible itching

Frequency of Pruritus

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

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

Never /No itching — Always/constant itching

Appendix 7. Patient Global Assessment (PtGA)

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

Appendix 8. Dermatology Life Quality Index (DLQI)

The DLQI is a general dermatology questionnaire that consists of 10 items that assess subject health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment) (Appendix 7). It has been extensively used inclinical trials for AD. The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to be responsive to change. The minimally important difference for the DLQI has been estimated as a 2 to 5 point change from baseline. The DLQI should be completed as per Schedule of Activities.

[redacted]

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

Appendix 9. Patient-Oriented Eczema Measure (POEM)

The POEM is a 7-item PRO measure used to assess the impact of AD over the past week (Appendix 8). The POEM should be completed as per Schedule of Activities.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 10. Hospital and Anxiety Depression Scale (HADS)

The HADS is a 14-item PRO measure used to detect states of anxiety and depression over the past week (Appendix 9). The HADS should be completed as per Schedule of Activities.

[redacted]

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

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

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

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

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

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

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

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

9. I get a sort of frightened feeling like 'butterflies' in the stomach
- ☐ 0 Not at all
- ☐ 1 Occasionally
- ☐ 2 Quite often
- ☐ 3 Very often

10. I have lost interest in my appearance
- ☐ 3 Definitely
- ☐ 2 I don't take as much care as I should
- ☐ 1 I may not take quite as much care
- ☐ 0 I take just as much care as ever

11. I feel restless as if I have to be on the move
- ☐ 3 Very much indeed
- ☐ 2 Quite a lot
- ☐ 1 Not very much
- ☐ 0 Not at all

12. I look forward with enjoyment to things
- ☐ 0 As much as I ever did
- ☐ 1 Rather less than I used to
- ☐ 2 Definitely less than I used to
- ☐ 3 Hardly at all

13. I get sudden feelings of panic
- ☐ 3 Very often indeed
- ☐ 2 Quite often
- ☐ 1 Not very often
- ☐ 0 Not at all

14. I can enjoy a good book or radio or television program
- ☐ 0 Often
- ☐ 1 Sometimes
- ☐ 2 Not often
- ☐ 3 Very seldom

[redacted]

Appendix 11. Example SAS Code for Generalized Linear Mixed model for IGA

This code has been included as an example of generalized linear mixed model in SAS. The actual code may be adjusted, depending on the testing of programming and the data. No SAP amendment is needed if the actual code is different from the example code in this section. The common procedure of PROC GLIMMIX has been used. As our decision criteria are based on differences in proportions this procedure allows us to back transform and express the data in this format. The following code was written assuming the format of the input dataset is of the form:

DOSE	id	week	IGA Response
0	1	4	0
10	2	6	0
30	3	8	0
100	4	12	1
…….			

```
/* SAS example code */
*** Model: GLIMMIX MODEL ***;

/* random trend logistic regression via GLIMMIX */
PROC GLIMMIX DATA=one METHOD= RSPLNOCLPRINT;
CLASS id week;
MODEL IGA = dose week dose*week / SOLUTION DIST=BINARY LINK=LOGIT;
RANDOM INTERCEPT / SUBJECT=id TYPE=UN GCORR SOLUTION;
RUN;
```

Appendix 12. Example SAS Code for Analyses OF Dose-Response Models

This code has been included as an example to show possible ways of fitting an Emax model and in SAS. The actual code may be adjusted, depending on the testing of programming and the data. No SAP amendment is needed if the actual code is different from the example code in this section. The common procedure of PROC NLMIXED has been used. Therefore, PROC NLMIXED has also been used as the ESTIMATE statement allows you to specify the contrast of interest. As our decision criteria are based on differences in proportions this procedure allows us to back transform and express the data in this format. The following code was written assuming the format of the input dataset is of the form:

DOSE	LNDOSE	COUNT	N
0	-9.2103	5	30
10	2.3025	9	30
303.4012	11	30	
100	4.6052	18	30
200	5.2983	21	30

where

DOSE=DOSE in mg,
LNDOSE=log(DOSE+0.0001)
COUNT=number of responses,
N=number of subjects

/* SAS example code */

```
*** Model 1: EMAX MODEL without covariate ***;

**Degrees of freedom is number of subjects-number of parameters (3);
proc nlmixed data=resp alpha=0.1 df=&df;


** specify that ed50 must be positive;
  bounds ed50>0;

  eta = e0 + ((emax*dose)/(ed50+dose));
  expeta = exp(eta);
  p = expeta/(1+expeta);

  model count ~ binomial(n,p);


** LOG(ODDS RATIOS) - TAKE EXP(ESIMATE) and EXP(CI) TO CALCULATE PARAMETER AND
60% CI FOR MAIN BODY TABLE;

** ACTUAL ESTIMATED PROPORTIONS ;

  estimate 'Model 1: Actual proportions 200mg'
        exp(e0 + (emax*200/(ed50+200)))/ (1 + exp(e0_int + (emax*200/(ed50+200))));

  estimate 'Model 1: Actual proportions 100mg'
```


[redacted]

```
        exp(e0 + (emax*100/(ed50+100)))/ (1 + exp(e0_int + (emax*100/(ed50+100))));

  estimate 'Model 1: Actual proportions 30mg'
        exp(e0 + (emax*30/(ed50+30)))/(1 + exp(e0_int + (emax*30/(ed50+30))));
  estimate 'Model 1: Actual proportions 10mg'
        exp(e0 + (emax*10/(ed50+10)))/(1 + exp(e0_int + (emax*10/(ed50+10))));
  estimate 'Model 1: Actual proportions 0mg'
        exp(e0)/(1 + exp(e0_int));

** Differences among ACTUAL ESTIMATED PROPORTIONS ;

  estimate 'Model 1: proportion difference 200mg vs. placebo'
        exp(e0 + (emax*200/(ed50+200)))/ (1 + exp(e0_int + (emax*200/(ed50+200))))- exp(e0)/(1 +
exp(e0_int));
  estimate 'Model 1: proportion difference 100mg vs. placebo'
        exp(e0 + (emax*100/(ed50+100)))/ (1 + exp(e0_int + (emax*100/(ed50+100))))- exp(e0)/(1 +
exp(e0_int));

  estimate 'Model 1: proportions difference 30mg vs. placebo'
        exp(e0 + (emax*30/(ed50+30)))/(1 + exp(e0_int + (emax*30/(ed50+30)))) - exp(e0)/(1 + exp(e0_int));
  estimate 'Model 1: proportion difference 10mg vs. placebo'
        exp(e0 + (emax*10/(ed50+10)))/(1 + exp(e0_int + (emax*10/(ed50+10))))- exp(e0)/(1 + exp(e0_int));

  ods output AdditionalEstimates=est
         FitStatistics=loglike
         ParameterEstimates=parms;

run;
```


[redacted]

Appendix 13. Estimate and Confidence Interval for Risk Difference (Proportion Difference) Using GLIMMIX Procedure with link=logit

It is known that the estimate and CI on the logit scale can be obtained using GLIMMIX procedure with dist=binary and link=logit; and using link option in GLIMMIX will generate the estimate for proportions. The variance of risk difference (proportion difference) cannot be directly obtained by GLIMMIX procedure using link=logit. This appendix describes how to obtain the estimate and the confidence interval (CI) for risk difference (proportion difference) by delta method.

Suppose that π_1 and π_2 are the two proportions of interest. $\lambda_1 = \text{logit}(\pi_1) = \log(\frac{\pi_1}{1-\pi_1})$ and $\lambda_2 = \text{logit}(\pi_2) = \log(\frac{\pi_2}{1-\pi_2})$ are the logit for the two proportions. Note that the λ_1, λ_2, π_1 and π_2 can be obtained by GLIMMIX procedure, and so are the covariance matrix for λ_1 and λ_2. Our interest is to derive the variance of π_1 - π_2.

Denote that $f(\lambda_1,\lambda_2) = \frac{e^{\lambda_1}}{1+e^{\lambda_1}} - \frac{e^{\lambda_2}}{1+e^{\lambda_2}} = \pi_1 - \pi_2$. A Taylor series expansion of $f(\lambda_1,\lambda_2)$ about the values $(\lambda_{10},\lambda_{20})$ is given by:

$$f(\lambda_1,\lambda_2) = f(\lambda_{10},\lambda_{20}) + \frac{\partial f(\lambda_1,\lambda_2)}{\partial \lambda_1}|_{(\lambda_{10},\lambda_{20})}(\lambda_1-\lambda_{10}) + \frac{\partial f(\lambda_1,\lambda_2)}{\partial \lambda_2}|_{(\lambda_{10},\lambda_{20})}(\lambda_2-\lambda_{20}) + (\text{2nd or higher order terms}).$$

Therefore

$$Var(f(\lambda_1,\lambda_2)) \approx \left[\frac{\partial f(\lambda_1,\lambda_2)}{\partial \lambda_1}|_{(\lambda_{10},\lambda_{20})}\right]^2 Var(\lambda_1) + \left[\frac{\partial f(\lambda_1,\lambda_2)}{\partial \lambda_2}|_{(\lambda_{10},\lambda_{20})}\right]^2 Var(\lambda_2) + 2\left[\frac{\partial f(\lambda_1,\lambda_2)}{\partial \lambda_1}|_{(\lambda_{10},\lambda_{20})}\right]\left[\frac{\partial f(\lambda_1,\lambda_2)}{\partial \lambda_2}|_{(\lambda_{10},\lambda_{20})}\right] Cov(\lambda_1,\lambda_2) \quad (1)$$

Since

$$\frac{\partial f(\lambda_1,\lambda_2)}{\partial \lambda_1} = \frac{e^{\lambda_1}}{(1+e^{\lambda_1})^2} \text{ and } \frac{\partial f(\lambda_1,\lambda_2)}{\partial \lambda_2} = -\frac{e^{\lambda_2}}{(1+e^{\lambda_2})^2},$$

$$Var(f(\lambda_1,\lambda_2)) \approx \left[\frac{e^{\lambda_1}}{(1+e^{\lambda_1})^2}\right]^2 Var(\lambda_1) + \left[\frac{e^{\lambda_2}}{(1+e^{\lambda_2})^2}\right]^2 Var(\lambda_2) - 2\left[\frac{e^{\lambda_1}}{(1+e^{\lambda_1})^2}\right]\left[\frac{e^{\lambda_2}}{(1+e^{\lambda_2})^2}\right] Cov(\lambda_1,\lambda_2) \quad (2)$$

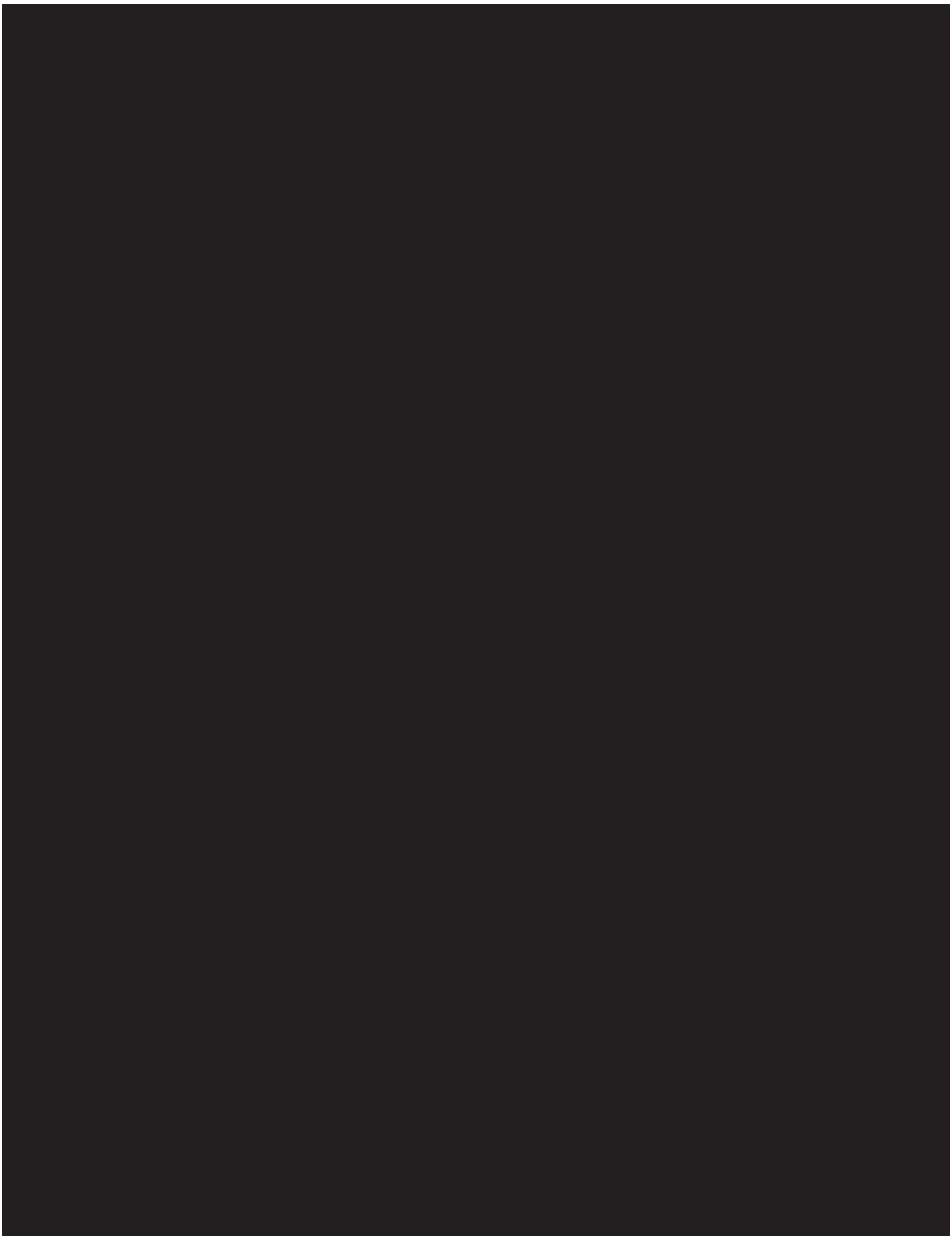
Now take $(\lambda_{10}, \lambda_{20}) = (\hat{\lambda}_1, \hat{\lambda}_2)$ where $(\hat{\lambda}_1, \hat{\lambda}_2)$ are the estimates of logits which are obtained by GLIMMIX procedure. Then by analogy with the above result, the corresponding estimated variance of the estimator is given by

$$\hat{Var}(f(\hat{\lambda}_1, \hat{\lambda}_2)) \approx \left[\frac{e^{\hat{\lambda}_1}}{(1+e^{\hat{\lambda}_1})^2}\right]^2 Var(\hat{\lambda}_1) + \left[\frac{e^{\hat{\lambda}_2}}{(1+e^{\hat{\lambda}_2})^2}\right]^2 Var(\hat{\lambda}_2)$$
$$- 2\left[\frac{e^{\hat{\lambda}_1}}{(1+e^{\hat{\lambda}_1})^2}\right]\left[\frac{e^{\hat{\lambda}_2}}{(1+e^{\hat{\lambda}_2})^2}\right] Cov(\hat{\lambda}_1, \hat{\lambda}_2) \quad (3)$$

In conclusion, using GLIMMIX the estimates of logit, variance of the estimate and the corresponding CI for π_1 - π_2 can be written as

$$\hat{\pi}_1 - \hat{\pi}_2 = \frac{e^{\hat{\lambda}_1}}{1+e^{\hat{\lambda}_1}} - \frac{e^{\hat{\lambda}_2}}{1+e^{\hat{\lambda}_2}};$$
$$\hat{Var}(\hat{\pi}_1 - \hat{\pi}_2) = \hat{Var}(f(\hat{\lambda}_1, \hat{\lambda}_2)); \quad (4)$$
$$(1-\alpha)\%\text{CI}: \hat{\pi}_1 - \hat{\pi}_2 \pm z_{1-\alpha/2}\sqrt{\hat{Var}(\hat{\pi}_1 - \hat{\pi}_2)}$$

Where $\hat{Var}(f(\hat{\lambda}_1, \hat{\lambda}_2))$ is given in (3).



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