A PHASE 2B, RANDOMIZED, DOUBLE BLIND, VEHICLE CONTROLLED, PARALLEL GROUP, DOSE RANGING STUDY TO ASSESS THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-06700841 CREAM APPLIED ONCE OR TWICE DAILY FOR 6 WEEKS IN PARTICIPANTS WITH MILD OR MODERATE ATOPIC DERMATITIS

Investigational Product Number:	PF-06700841
Investigational Product Name:	Not applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2018-003050-24
Protocol Number:	B7931022
Phase:	2b

Short Title: A Phase 2b, multicenter, randomized, double-blind, vehicle controlled, parallel group dose ranging study to assess efficacy, safety, tolerability and pharmacokinetics of PF-06700841 cream in participants with mild or moderate atopic dermatitis

[redacted]

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	31 October 2018	Not applicable (N/A)

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title:

A Phase 2b, multicenter, randomized, double-blind, vehicle controlled, parallel group dose ranging study to assess efficacy, safety, tolerability, and pharmacokinetics (PK) of PF-06700841 cream in participants with mild or moderate atopic dermatitis.

Rationale:

This multicenter, randomized, double-blind, vehicle controlled, parallel group, dose ranging study is being conducted to provide data on efficacy, safety, tolerability and PK of multiple topical formulation concentrations of PF-06700841 topical cream in the treatment of mild-to-moderate atopic dermatitis (AD). This is the first study where a PF-06700841 cream formulation is being applied topically to participants with AD. Additionally, the study is intended to enable selection of the dose and dosing regimen (once daily [QD] vs twice daily [BID] application) for the future clinical development of topical PF-06700841.

Objectives, Endpoints and Estimands:[a]

Objectives	Endpoints	Estimands[b]
Primary Objective	**Primary Endpoint(s)**	**Primary Estimands**
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle applied QD or BID, on percent change from baseline in Eczema Area and Severity Index (EASI) in participants with mild or moderate atopic dermatitis (AD).	Percent change from baseline in EASI total score at Week 6.	Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the investigational product (IP) on a continuous endpoint; without the benefit of additional prohibited medications during treatment and regardless of participant compliance with the IP dosing.
Secondary Objective(s):	**Secondary Endpoints**	**Secondary Estimands**
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, using Investigator's Global Assessment (IGA) score assessment as endpoint in participants with mild or moderate AD.	**Key Secondary Endpoint:** Proportion of participants achieving IGA score of clear (0) or almost clear (1) (on a 5 point scale) and a reduction from baseline of ≥2 points at Week 6.	Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant compliance with the IP dosing.

To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, on change from baseline in EASI in participants with mild or moderate AD.	Change from baseline in EASI total score at Week 6.	All continuous secondary endpoints will be analyzed descriptively and using estimand E1 described above, when appropriate. All categorical secondary endpoints will be analyzed descriptively and using estimand E2 described above, when appropriate.
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, using measures of patient reported outcomes (PRO), in participants with mild or moderate AD.	Proportion of participants having ≥2 grades of reduction in weekly averages of Peak Pruritus Numerical Rating Scale (PP-NRS) at all site visit time points specified in the SoA.	
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, using measures of disease affected area, in participants with mild or moderate AD.	Percent change from baseline in affected Body Surface Area (BSA) at Week 6 and at other time points specified in the SoA.	
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, using measures of disease severity and symptoms as endpoints in participants with mild or moderate AD.	Proportion of participants achieving EASI-75 (75% improvement from baseline).	
To characterize the safety and tolerablility of multiple doses of PF-06700841 cream versus vehicle applied QD or BID in participants with mild or moderate atopic dermatitis.	a. Incidence of treatment-emergent adverse events (AEs and SAEs), significant changes in vital signs, clinical laboratory abnormalities, and electrocardiogram (ECG). b. Incidence of severity grades in skin tolerability at times indicated in SoA.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
a. See Section 3 for Tertiary/Exploratory Objectives and Endpoints. b. See Section 3 for detailed Estimand description.		

Overall Design:

This multicenter, Phase 2b, randomized, double-blind, vehicle-controlled, parallel-group, dose-ranging study will assess efficacy, safety, tolerability, and PK of the topical cream formulation of PF-06700841 in the treatment of mild-to-moderate atopic dermatitis. Participants will be screened within 6 weeks prior to the Day 1 application of investigational

product (IP) to confirm they meet the selection criteria for the study. The treatment period will be 6 weeks, followed by follow-up period of 4 weeks.

Number of Participants:

The study will explore QD and BID dosing regimen and will enroll approximately 280 participants (approximately 35 participants per treatment arm) to allow for 224 completers (28 participants/arm).

Intervention Groups and Duration:

There will be 8 dosing arms:

- 4 arms with increasing doses of active IP in QD dosing regimen ie PF-06700841 cream in 0.1% (1 mg/g), 0.3% (3 mg/g), 1% (10 mg/g), and 3% (30 mg/g) strengths;
- 2 arms with increasing doses of active IP in BID dosing regimen ie PF-06700841 cream in 0.3% (3 mg/g) and 1% (10 mg/g) strengths;
- 1 vehicle cream arm in QD dosing regimen;
- 1 vehicle cream arm in BID dosing regimen.

Participants will be randomized into one of the doses in the QD dosing regimen or BID dosing regimen of PF-06700841 or its matching vehicle in equal ratio.

A study design schematic is presented in Section 1.2.

Data Monitoring Committee: Yes

Statistical Methods

The primary estimand will be estimated population-based average treatment effect on percent change from baseline in Eczema and Severity Index (EASI) score relative to vehicle at 6 weeks for all randomized participants in the absence of prohibited medication without regard to compliance.

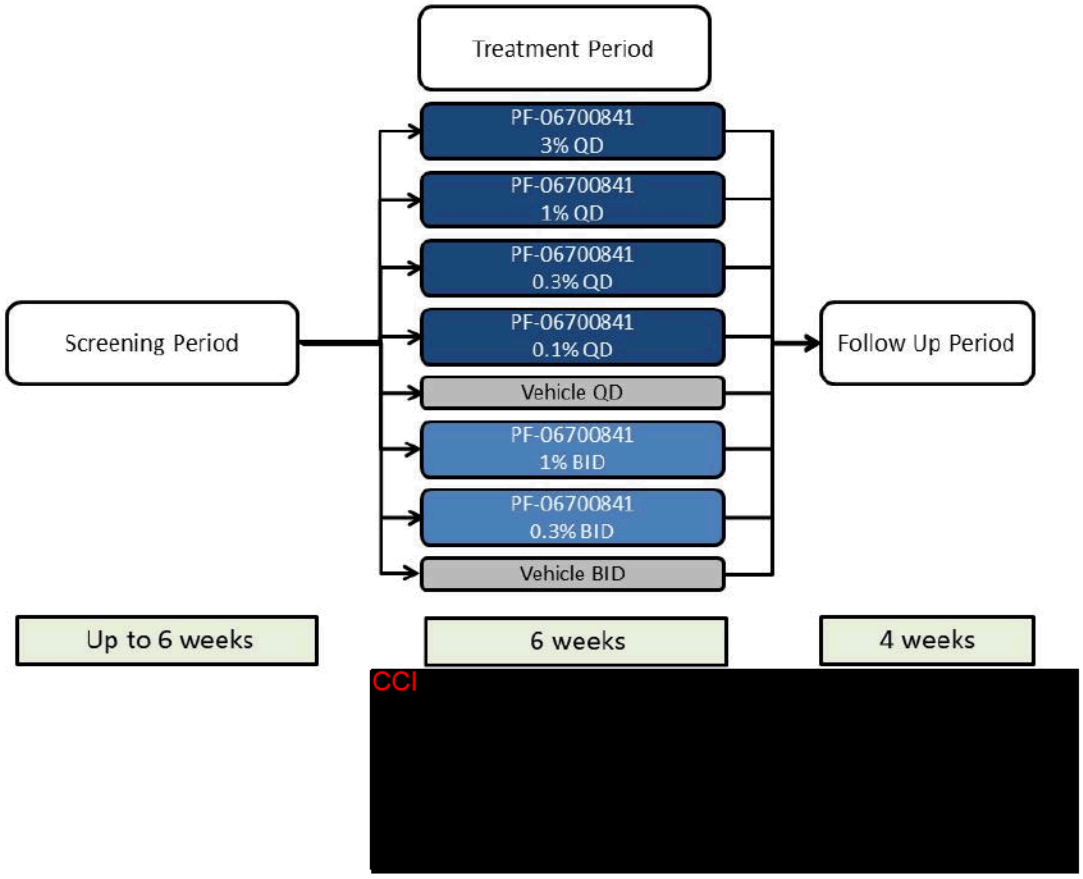
The secondary estimand will be the estimated population-based average treatment effect on the rates of Investigator's Global Assessment (IGA) response (percentage of participants with a score of 0 or 1 and a 2 point or greater decrease from baseline) at Week 6 relative to vehicle (with the same dosing schedule, QD or BID) without regard to compliance with IP in the absence of prohibited medication.

All other secondary continuous clinical endpoints will be analyzed using the primary estimand, while all other secondary categorical clinical endpoints will be analyzed using the secondary estimand described above.

Other estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of the results and to compare to available literature as needed. Details of these analyses will be presented in the statistical analysis plan (SAP).

1.2. Schema

Figure 1. Study Design Schema



1.3. Schedule of Activities (SoA)

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

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

Table 1. Schedule of Activities

Visit Identifier[a]	Screening & Washout	Day 1 (Baseline)	Day 8 Week 1	Day 15 Week 2	Day 22 Week 3	Day 29 Week 4	Day 43 Week 6 (EOT)	Follow-up (EOS)	Early Termination (ET)
Visit Window	**-42 to -1**	**N/A**	**8±1**	**15±2**	**22±2**	**29±2**	**43±2**	**28–35 Days post-last Dose**	
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Enrollment Procedures									
Informed Consent	X								
Eligibility Assessment	X	X							
Demography	X								
Medical and Atopic Dermatitis History[b]	X								
Medication History	X								
Randomization		X							
Clinical Assessments									
Complete Physical Exam[c]	X	X					X		
Targeted Physical Exam[c]			X	X		X		X	X
Vital Signs[d]	X	X		X			X		
Weight	X	X							
Height	X								
ECG[e]	X	X		X			X		
Chest Radiograph[f]	X								
C-SSRS[g]	X	X		X			X		X
Fitzpatrick Skin Type Assessment	X								
Laboratory Assessments									
Hematology, Blood Chemistry, and Urinalysis	X	X[h]	X	X		X	X	X	X
Lipid Panel (Fasting)[i]		X					X		
Tuberculosis Test[j]	X								

Visit Identifier[a]	Screening & Washout	Day 1 (Baseline)	Day 8 Week 1	Day 15 Week 2	Day 22 Week 3	Day 29 Week 4	Day 43 Week 6 (EOT)	Follow-up (EOS)	Early Termination (ET)
Visit Window	**-42 to -1**	**N/A**	**8±1**	**15±2**	**22±2**	**29±2**	**43±2**	**28–35 Days post-last Dose**	
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Follicle Stimulating Hormone (FSH) Test[k]	X								
Blood Pregnancy test[l]	X	X							X
Urine Pregnancy test[l]		X	X	X	X	X	X	X	X
Hepatitis Testing[m,n]	X						X		
HIV Testing	X								
VZV IgG Ab (adolescents only, if applicable)[o]	X								
Pharmacokinetics (PK)									
PK sampling (pre-dose)		X	X	X	X	X	X		
CCI [redacted]									
[redacted]									
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[redacted]									
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CCI [redacted]									
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Investigational Product Related Processes									
Dispense dosing diary/PROs and instruct on usage	X								
Assess BSA & calculate IP need	X	X	X	X		X			
Body Site Checklist		X	X	X	X	X	X		
Weigh and dispense IP		X	X	X		X			
IP application and observation (at site)		X	X	X		X	X		
Record dose and time of IP application in eDiary		X	→	→	→	→	X		
Collect and weigh returned IP tubes for compliance check			X	X		X	X		X
Review of dosing Diary/PROs		X	X	X		X	X	X	X
Collect dosing Diary/PROs		X[q]						X	X

Visit Identifier[a]	Screening & Washout	Day 1 (Baseline)	Day 8 Week 1	Day 15 Week 2	Day 22 Week 3	Day 29 Week 4	Day 43 Week 6 (EOT)	Follow-up (EOS)	Early Termination (ET)
Visit Window	**-42 to -1**	**N/A**	**8±1**	**15±2**	**22±2**	**29±2**	**43±2**	**28–35 Days post-last Dose**	
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	
AD-Related Clinical Assessments									
EASI	X	X	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X
Safety Monitoring									
Contraception check[r]	X	X	X	X	X	X	X	X	
Review Concomitant Treatment	X	X	X	X	X	X	X	X	X
Local Tolerability Assessments[s]		X	→	→	→	→	X	X	X
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	X	X
Patient Reported Outcomes (PRO) Assessments[t]									
in-clinic completion									
POEM		X	X	X			X	X	X
DLQI/CDLQI		X	X	X			X	X	X
CCI									
CCI									
at-home completion									
PP-NRS	At least 7 days prior to Day 1	X	→	→	→	→	X	X	X
CCI									
CCI									
CCI									

Abbreviations: →= ongoing/continuous event; BSA = Body Surface Area; CCI; C-SSRS = Columbia Suicide Severity Rating Scale; DLQI/CDLQI = Dermatology Life Quality Index/Children's DLQI; EASI = Eczema Assessment Severity Index; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early termination; βhCG = β-Human Chorionic Gonadotropin; HDL = High Density Lipoprotein; CCI; IGA = Investigator's Global Assessment; IP = Investigational Product; CCI; LDL = Low Density Lipoprotein; CCI; PCP = Primary Care Physician; PE: Physical Examination; CCI; CCI; POEM = Patient oriented eczema measure; PP-NRS = Peak Pruritis Numerical rating Scale; CCI; CCI; TB = Tuberculosis; VZV = Varcilla Zoster Virus.

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 taken during the 3 months/90 days prior to Screening/Washout with dose, duration of treatment, and reason for discontinuation. All other drugs (including sunscreen, over the counter medication, vitamins, and dietary supplements) taken within 28 days prior to the Screening/Washout visit should be recorded.

c. Full Physical Examination (PE): includes, but is not limited to the following organ or body systems-head, ears, eyes, nose, mouth, skin, heart and lung, lymph nodes, gastrointestinal, musculoskeletal, abdomen, cardiovascular, and neurological systems. In addition, an assessment will be made of the condition of all AD involved skin; Disease focused Physical Examination: includes all skin (treatable and non-treatable areas) and evaluation of any current or reported symptoms for clinically significant changes. Skin swabs may be obtained if herpetiform rash is noticed during the PE to rule out VZV infection.

d. Vital Signs: Temperature (Oral or tympanic temperature), pulse rate, and blood pressure will be taken in supine position, after the participant has been lying calmly for a minimum of 5 minutes. Assessment of vital signs should precede blood draw for clinical laboratory tests.

e. Local read, single ECG (in supine position) at all time points indicated. Triplicate ECG will be conducted as appropriate per Section 8.2.2.3.

f. Chest X-ray or other appropriate diagnostic image (ie, CAT or MRI) may be performed up to 12 weeks prior to Screening. Official reading must be located and available in the source documentation. See Section 8.2.1.3 for more details.

g. Site staff is to administer the Columbia Suicide Severity Scale (C-SSRS) to all participants at screening and score immediately. Participants who have recent or active suicidal ideation or behavior or clinically significant depression will be excluded from the study or discontinued from the study per Section 5.2. For participants meeting exclusionary results on the C-SSRS, it is recommended the participant's primary care physician (PCP) should be informed, and the participant referred to a mental health professional, either by the PCP or the investigator according to their usual practice. See Section 8.2.2.8 for more details.

h. Blood draw for hematology and serum chemistry on Day 1 will be performed before the in-clinic IP application. If the screening hematology and serum chemistry are performed within 7 days prior to Day 1, then Day 1 hematology and serum chemistry tests will be performed at the discretion of the investigator or his/her designee. Laboratory tests with abnormal results (per Section 7.1.5) may be repeated once during the screening period; the last value will be used to determine eligibility.

i. Participants must be fasting (water only) for 8 hours prior to visits when lipid panel is being taken. Includes total cholesterol, LDL, HDL and triglycerides.

j. A documented TB test performed within 12 weeks prior to Screening is acceptable. Participants with a history of tuberculosis may not require TB testing as per the protocol exclusion criteria in Section 5.2. In addition to protocol required TB testing, sites should follow their local standards for TB status determination, which may include chest X-ray, CAT or MRI (as per local regulation). See Section 8.2.1.2 for additional details. Official reading must be located in the source document.

k. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

l. Serum pregnancy testing at screening is required for women of childbearing potential (WOCBP). Pregnancy tests may also be repeated more frequently as per request of IRBs/ECs or if required by local regulations. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Two negative pregnancy tests are required before randomization (one negative serum pregnancy test at screening and one negative urine pregnancy test at Day 1 visit). Serum will also be collected at Day 1 to test pregnancy, the results of which may be received after Day 1. If urine pregnancy test is positive after IP application, serum pregnancy test will be conducted, IP application paused and sponsor clinician and sponsor medical monitor notified immediately.

m. Includes testing for Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb); Hepatitis B Surface Antibody (HBsAb) will be reflex tested if participants are positive for HBsAb. HBsAb will be tested for all participants if required by country-specific regulations, See country-specific details in Appendix 8. Hepatitis C Viral RNA (HCV RNA) will be reflex tested if participants are positive for HCVAb.

n. [if required by country-specific regulations] Hepatitis B virus (HBV) deoxyribonucleic acid (DNA) assessments will be reflex tested only if HBsAg and HBcAb are negative and HBsAb is positive without documentation of prior HBV vaccination at screening and for participants who had negative HBsAg, positive HBcAb and positive HBsAb with documentation of HBV vaccination at screening.

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

C [redacted]

q. Only for participants who do not meet randomization criteria.

r. The contraception check is an opportunity to confirm that contraception, if assigned, is used consistently and correctly. Also, it is the opportunity to assess changing potential to father/bear children and allows for altering contraception if new disease contraindicates a selected method of contraception or if non-childbearing status is achieved.

s. Local tolerability at the site of IP application will be assessed pre-dose and immediately after post-dose.

t. PP-NRS will be assessed daily during the screening period (at least 7 days immediately prior to Day 1) and from Day 1 to EOT visit (Week 6) and then, at follow-up; CCI [redacted]

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2. INTRODUCTION

PF-06700841 is a TYK2/JAK1 inhibitor that is currently being investigated for multiple therapeutic indications.

2.1. Study Rationale

The purpose of this study is to assess PF-06700841 efficacy, safety, tolerability and PK of multiple topical formulation concentrations of PF-06700841, in mild to moderate AD population. In addition, the study is intended to enable selection of a dose and dosing regimen (QD vs. BID) for the future clinical development of PF-06700841. Oral formulation of PF-06700841 has been studied in multiple indications, but this is the first study in topical formulation to be applied to participants with mild or moderate AD.

2.2. Background

Atopic dermatitis (AD), also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in quality of life. Atopic dermatitis can affect any age group.[1] Prevalence estimates suggest approximately 10% of adults and 10%-20% of children suffer from AD. AD usually begins in early childhood and continues to intermittently and unpredictably flare in adolescence and in adulthood. Up to 18% of those affected with AD suffer with severe disease. The burden of disease is substantial for children, adolescents, and adults, as well as their family members and caregivers.

Progress in the development of topical therapies for AD has not advanced as rapidly as other areas in dermatology. Patients with persistent AD often require long-term intermittent treatment, in addition to topical treatments, which can be self-administered at home, remain timely and are easily accessible option.

There are a limited number of treatments available for AD. Current treatments for AD include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. Crisaborole was approved as a topical treatment in December 2016 by the US Federal Drug Administration (FDA) for use in patients with mild to moderate AD. Additional treatments generally reserved for severe AD include phototherapy (eg, ultraviolet A light [UVA] with or without psoralen, ultraviolet B light [UVB] narrowband or broadband) and systemic agents (eg, corticosteroids, cyclosporine, recombinant IFN-γ, mycophenolate mofetil, methotrexate [MTX], azathioprine [AZA], intravenous immunoglobulin).[2] None of the currently available therapies offer a cure; therefore, the main aims of existing treatments are to reduce the occurrence of acute flares, increase the time between relapses, reduce pruritus and reduce the resulting sleep disturbances.[3,4]

For AD patients not responding to topical therapies and phototherapy, off-label use of systemic agents, which includes 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.

Other systemic agents used to treat AD are under clinical development or recently approved. Dupilumab, an injectable human monoclonal antibody targeting interleukin (IL)-4 and -13, was approved by the FDA in March 2017 and received marketing authorisation in Europe in September 2017. This offers a novel mechanism of action for the treatment of moderate to severe AD. However, the approved dosing for dupilumab as an initial dose of 2 x 300 mg subcutaneous injections followed by 300 mg every other week injections may limit the desirability of this treatment.

Therefore, the prominent unmet medical need in the topical treatment of AD is for an effective, safe topical agent without restrictions on long-term or continuous use, and without local or systemic side effects, and to be approved for use on all body regions, and will be approved for use in adolescents.

Mechanism of Action

The pathophysiology of AD is the product of a complex interaction between various susceptibility genes, host environmental factors, infectious agents, defects in skin barrier function, and immunologic responses. The predominant symptom of AD (ie 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 atopic dermatitis lesions. Acute atopic dermatitis lesions have been associated with a Th2 phenotype, showing dominance of interleukin (IL)-4, IL-5, IL-13, and IL-31 secretion. While IL-4 producing Th2 cells may drive the development of atopic skin lesions, chronic lesions show either the coexistence of both IL-4 producing Th2 and IFN-γ producing Th1 cells or Th1 dominance. This coexistence of Th2 and Th1 responses or Th1 dominance is more likely to be the underlying immunopathology in adult participants who have had atopic dermatitis chronically or intermittently since childhood. Recent evidence[5] supports IL-31 having an important role in pruritus and inflammation in AD.[6,7]

In the skin, cytokines induced by Janus Kinase (JAK) signaling impact several cellular inflammatory functions such as apoptosis of inflammatory T cell infiltrates and promoting T helper (Th) cell differentiation. C-X-C motif chemokine ligand 10 (CXCL10), C-C motif chemokine ligand 26 (CCL26) and matrix metalloprotease 12 (MMP12) have been reported to be induced by cytokines acting via the JAK class of kinases[8-11] and are implicated in inflammatory and autoimmune conditions of the skin.[12-17] In addition, impairment of the skin barrier protein filaggrin has also been implicated in inflammatory and autoimmune diseases of the skin,[18] and its expression has been reported to increase upon inhibition of JAK

enzymes.[9] Following topical application of the clinical formulation to freshly excised human skin, PF-06700841 caused a dose-dependent inhibition of gene expression of pro-inflammatory molecules CXCL10, CCL26 and MMP12 (measured by changes in messenger ribonucleic acid [mRNA] in the presence and absence of PF-06700841) and a dose-dependent stimulation of the skin barrier protein, filaggrin. Thus PF-06700841 showed pharmacology in human skin by the topical application, consistent with the known activity of PF-06700841 on JAK class of kinases.

The Tyrosing Kinase 2 (TYK2) activity of PF-06700841 will block IL-23 signaling which is important for Th17 and Th22 cell differentiation, bringing about the potential for activity in certain subtypes of AD that appear to have greater dependence on Th17 and Th22 pathways, including early-onset pediatric AD, intrinsic (non-allergic AD), and AD in Asian and African-American participants.[19-22]

PF-06700841 is a dual TYK2/JAK1 inhibitor with good selectivity profile over other human kinases. Based on its cytokine inhibition profile, PF-06700841 is expected to provide therapeutic benefit in the treatment of Atopic Dermatitis by targeting the signaling of cytokines in Th1, Th2 and Th17 lymphocytes.

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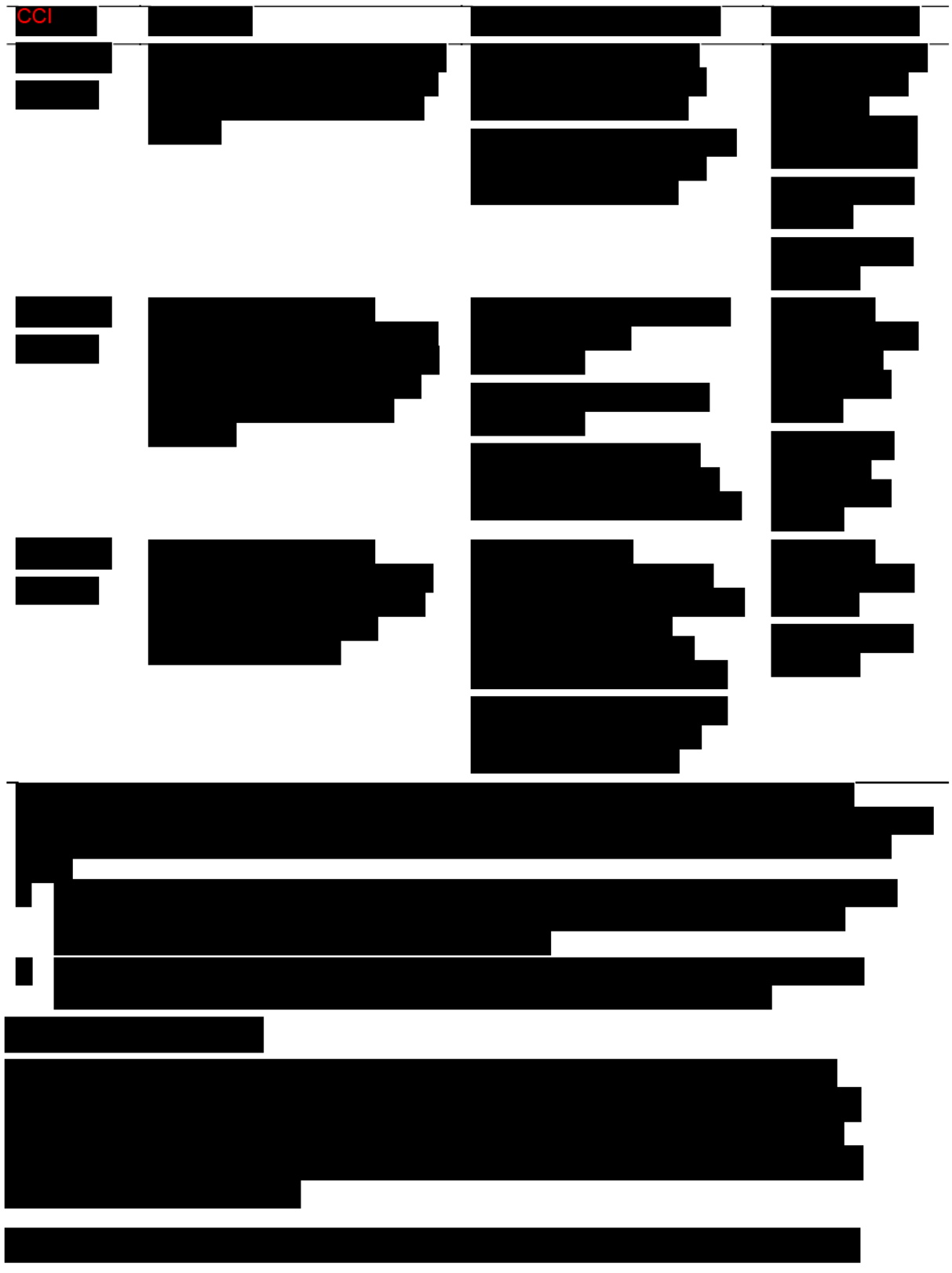

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2.3. Benefit/Risk Assessment

This is the first study where a PF-06700841 cream formulation is being applied topically to participants with atopic dermatitis. This is also the first study where PF-06700841 cream formulation will be applied to participants from 12-18 years of age with AD.

JAK kinase inhibitors have shown efficacious in AD studies. In addition, systemic exposures following topical application of PF-06700841 is expected to be lower than that observed following oral administration in alopecia areata (B7931005) and psoriasis (B7931004) studies therefore, no change is anticipated in benefit/risk profile.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-06700841 may be found in the IB, which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints	Estimands
Primary Objective:	**Primary Endpoint(s):**	**Primary Estimands:**
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, on percent change from baseline in Eczema Area and	Percent change from baseline in EASI total score at Week 6.	Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a continuous endpoint; without the benefit of additional prohibited medications

Severity Index (EASI) in participants with mild or moderate atopic dermatitis (AD).		during treatment and regardless of participant compliance with the IP dosing. Population: Participants with mild or moderate AD as defined by the inclusion and exclusion criteria; without the benefit of receiving prohibited medications during treatment and regardless of compliance. Inter-current Events: a. Prohibited medication – all scores in participants who receive prohibited medication post randomization will be omitted from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the IP treatment. b. Withdrawal and all other events leading to missing data will be treated similarly assuming participants have efficacy values similar to control participants. c. Inadequate compliance – participants data will be used as recorded. Population level summary: The percent change from baseline mean difference between treated and vehicle in EASI score.

Secondary Objective(s):	Secondary Endpoints:	Secondary Estimands:
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, using Investigator's Global Assessment (IGA) score assessment as endpoint in participants with mild or moderate AD.	**Key Secondary Endpoint:** Proportion of participants achieving IGA score of clear (0) or almost clear (1) (on a 5 point scale) and a reduction from baseline of ≥2 points at Week 6.	Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant compliance with the IP dosing. Population: Participants with mild or moderate AD as defined by the inclusion and exclusion criteria; without the benefit of receiving prohibited medications during treatment and regardless of compliance. Inter-current Events: a. Prohibited medication – response will be considered negative for participants who receive prohibited medication post-randomization. b. Withdrawal and all other events leading to missing data will be treated similarly assuming that participants no longer receive benefit from the IP and hence will be treated as failure for endpoint above. c. Inadequate compliance – participants data will be used as recorded. Population level summary: The difference in proportions between IP treated and vehicle response rates.
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, on change from baseline in EASI in participants with mild or moderate AD.	Change from baseline in EASI total score at Week 6.	All continuous secondary endpoints will be analyzed descriptively and using estimand E1 described above, when appropriate. All categorical secondary endpoints will be analyzed descriptively and using estimand

To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, using measures of patient reported outcomes (PRO), in participants with mild or moderate AD.	Proportion of participants having ≥2 grades of reduction in weekly averages of Peak Pruritus Numerical Rating Scale (PP-NRS) at all site visit time points specified in the SoA.	E2 described above, when appropriate.
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle, applied QD or BID, using measures of disease affected area, in participants with mild or moderate AD.	Percent change from baseline in affected Body Surface Area (BSA) at Week 6 and at other time points specified in the SoA.	
To compare the efficacy of multiple dose levels of PF-06700841 topical cream versus vehicle cream, applied QD or BID, using measures of disease severity and symptoms as endpoints in participants with mild or moderate AD.	Proportion of participants achieving EASI-75 (75% improvement from baseline).	
To compare safety and tolerability of multiple doses of PF-06700841 cream versus vehicle, applied QD or BID, in participants with mild or moderate AD.	a. Incidence of treatment-emergent adverse events (AEs and SAEs), significant changes in vital signs, clinical laboratory abnormalities and ECG. b. Change from baseline in clinical laboratory values (chemistry and hematology, lipids). c. Change from baseline in ECG parameters (heart rate, QT, QTc, PR and QRS intervals). d. Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements). e. Incidence of severity grades in skin tolerability at times indicated in SoA.	There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.
CCI [redacted]	[redacted]	[redacted]
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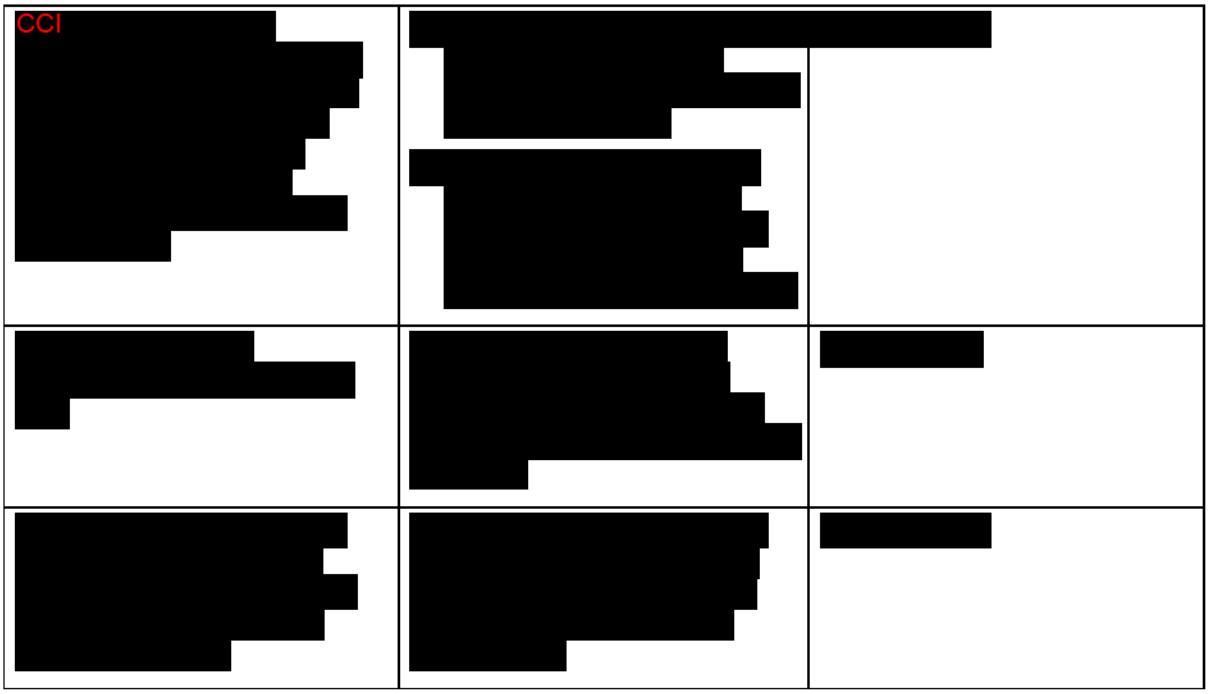


4. STUDY DESIGN

4.1. Overall Design

This Phase 2b, multi-center, randomized, double-blind, vehicle-controlled, parallel group, dose-ranging study will assess efficacy, safety, tolerability and PK of a topical formulation of PF-06700841, when applied once or twice daily, in participants with mild or moderate atopic dermatitis. This is the first study where a PF-06700841 cream formulation is being applied to participants with atopic dermatitis.

Participants will be screened within 6 weeks prior to the Day 1 dose of IP to confirm they meet the selection criteria for the study. The treatment will be 6 weeks, followed by a 4 week follow-up. The total study duration is approximately 16 weeks.

At the start of the study, adult participants ≥18-75 years of age (or minimum age based on country-specific criteria) with mild or moderate atopic dermatitis will be enrolled. Once approximately 20% of participants have completed at least 2 weeks (Week 2 visit) of treatment, assessment of safety and tolerability data will be conducted by an independent Internal Review Committee (IRC). After confirming acceptable safety and tolerability, the minimum age of male participants to be enrolled in this study with mild or moderate atopic dermatitis will be lowered to 12 years.

Assuming 20% dropout rate, a total of approximately 280 participants (approximately 35 participants per treatment arm) will be randomized to ensure completion of approximately 224 participants (28 participants/arm).

Multiple safety, efficacy, PK and pharmacodynamics (PD) related assessments will be performed during the treatment and follow-up period.

CCI [redacted]

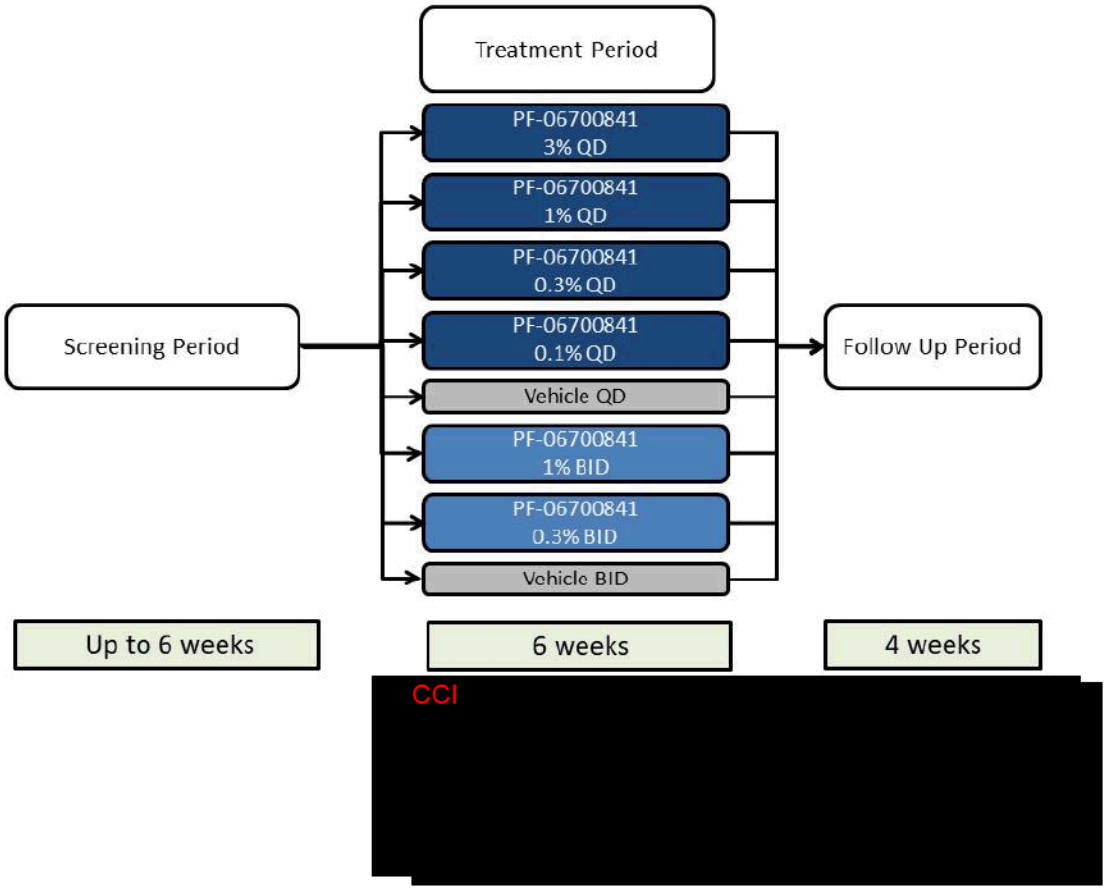
Participants will be randomized to 1 of 8 treatment arms in the ratio of 1:1:1:1:1:1:1:1. Investigators, participants, and the sponsor study team will be blinded as to investigational product (PF-06700841 cream vs vehicle cream).

Table 3. Treatment Arms

Treatment Arm	Target Number of Participants Randomized	Approximate Number of Completers	Investigational Product
A	35	28	Vehicle cream QD
B	35	28	PF-06700841 0.1% cream QD
C	35	28	PF-06700841 0.3% cream QD
D	35	28	PF-06700841 1.0% cream QD
E	35	28	PF-06700841 3.0% cream QD
F	35	28	Vehicle cream BID*
G	35	28	PF-06700841 0.3% cream BID*
H	35	28	PF-06700841 1.0% cream BID*

A study design schematic is in Figure 2 below.

Figure 2. Study Design Schema



4.2. Scientific Rationale for Study Design

This 6-week study is first time a topical PF-06700841 cream formulation is being evaluated in a mild-to-moderate AD population with an affected body surface area (BSA) of 2-20%. Multiple formulation concentrations are being tested in two dosing regimens (QD vs BID) to assess efficacy, safety, tolerability and PK. The duration of the study is appropriate to assess the efficacy, safety and tolerability profile of topical PF-06700841. The current nonclinical toxicology package supports the study durations of up to 12 weeks.

Primary and key secondary registration endpoints of this study are: percent change from baseline in Eczema Area and Severity Index (EASI), a continuous endpoint and Investigator's Global Assessment (IGA), a binary endpoint respectively.

Male Adolescents

Prevalence estimates suggest approximately 10%-20% children suffer from AD. AD usually begins in early childhood and continues to intermittently and unpredictably flare in adolescence and in adulthood. Therefore, inclusion of adolescent population will provide an estimate of the efficacy of PF-06700841 in this population and will assist in future registration and Phase 3 planning. PF-06700841 has been associated with fetotoxicity in animals. Since the systemic PF-06700841 exposure following topical treatment is unknown, only male adolescent participants will be enrolled at this time to avoid any risk of pregnancy in adolescent females in an unlikely event of failure to strictly follow contraception requirements.

PK Assessments

Since this is a first topical application study of PF-06700841, PK samples will be collected at each visit to characterize systemic PK. Understanding of systemic exposures will inform the potential contribution of systemic exposure to the overall pharmacology in this study.

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Patient-Reported Outcome Measures

Patient reported outcomes will evaluate changes in AD symptoms and health related quality of life. The CCI
Peak-Pruritis Numerical Rating Scale (PP-NRS) are assessments of the symptoms associated with AD, predominantly itching, redness, scaling, burning, stinging, cracking, flaking and pain. CCI
The Patient Oriented Eczema Measure (POEM) is an assessment of the frequency of the most common symptoms of AD, which has been assessed for labeling in other AD treatments. The Dermatology Life Quality Index (DLQI) assesses dermatology specific impact on quality of life, which has also been used for labeling of AD treatments. CCI

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[redacted]

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4.4. End of Study Definition

A participant is considered to have completed the study if they have completed all phases of the study including the follow-up visit (Visit 7), approximately 28-35 days post-last dose application.

The end of the study is defined as the date of the last visit (Visit 7) by last participant, across all sites.

5. STUDY POPULATION

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

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age and Sex:

1. Female participants between the ages of 18 and 75 years, inclusive, at the time of informed consent at Screening or male participants between the ages of 12 and 75 years, inclusive, at the time of informed consent at Screening.

   - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

   Note: Female participants who are of child-bearing potential must not be intending to become pregnant, currently pregnant, or lactating.

   Note: Male participants between the ages of 12 and <18 years (or the minimum country-specific age of consent) are eligible to enroll only after safety/tolerability is reviewed and deemed acceptable by an IRC review of the data from approximately 20% of enrolled participants.

Type of Participant and Disease Characteristics:

2. The following atopic dermatitis criteria must be met:

   a. Have a clinical diagnosis of atopic dermatitis (also known as atopic eczema) for at least 3 months (Appendix 9); the clinical diagnosis of atopic dermatitis will be confirmed according to the criteria of Hanifin and Rajka[26] at the Screening Visit.

   b. Have an Investigator's Global Assessment (IGA) score of 2 (mild), or 3 (moderate) at screening and at Day 1 (prior to first dose of the IP).

   c. Have atopic dermatitis on the head (including face, but excluding hair-bearing scalp), neck, trunk (excluding groin and genitals), or limbs, including palms and soles, covering at least 2% of total BSA and up to and including 20% of total BSA at Screening and at Day 1 (Visit 1). At least 2% of the total BSA will need to be on the head (including face, but excluding hair bearing scalp), neck, trunk (excluding groin and genitals), or limbs (excluding palms and soles).

      Note: Refer to Section 8.1.4 for methods of calculating %BSA.

   d. Have an EASI total score of ≥3 to ≤21 at Screening and at Day 1.

      Note: Refer to Section 8.1.3 for method of calculating EASI scores.

   e. Have Peak Pruritis - Numerical Rating Scale (PP-NRS) of Grade ≥2, at Day 1.

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

   Note: Refer to Section 5.3 for Lifestyle considerations.

Weight:

4. Body weight ≥40 kg and Body Mass Index (BMI) ≥17.5 kg/m^2 up to 35 kg/m^2 (inclusive) at Screening and at Day 1.

Informed Consent:

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Active forms of dermatitides/eczematous conditions (eg, contact dermatitis, seborrhhoeic, discoid, gravitational, asteatotic and dishydrotic eczema) or other inflammatory skin diseases, ie, not AD or evidence of skin conditions (eg, psoriasis, viral infection, fungal infection, bacterial infection) that would interfere with evaluation of atopic dermatitis or response to treatment.

2. Any psychiatric condition including recent or active suicidal ideation or behavior that meets any of the following criteria at Screening or Day 1:

   a. Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS) (Appendix 13);

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

   c. Any lifetime history of serious or recurrent suicidal behavior;

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

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

3. Fitzpatrick skin type score >5.

4. Current or recent history (approximately, within 3 months) of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurological disease.

5. A history of any lymphoproliferative disorder (such as Epstein Barr Virus [EBV] – related lymphoproliferative disorder), history of lymphoma, leukemia, malignancies or signs and symptoms suggestive of current lymphatic disease.

   Note: Adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma *in situ* are allowed.

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

7. A history of systemic (within approximately 3 months), chronic or acute skin infection (within approximately 2 weeks) requiring hospitalization, parenteral antimicrobial, antivirals, antiparasitics, antiprotozoals, or antifungals therapy, or as otherwise judged clinically significant by the investigator.

8. A known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.

9. Undergone significant trauma or major surgery within 1 month prior to screening.

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

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

Prior/Concomitant Therapy:

12. Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of IP, or is expected to be vaccinated or to have household exposure to these vaccines during treatment or up until follow-up visit.

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

Prior/Concurrent Clinical Study Experience:

13. Previous administration with an investigational drug within 4 weeks (or as determined by the local requirement) or 5 half-lives prior to Screening (whichever is longer).

    Note: local regulations or other factors may require more than 4 weeks.

    Note: Any investigational or experimental therapy taken or procedure performed for AD, psoriasis, psoriatic arthritis or rheumatoid arthritis in the previous 1 year should be discussed with the Pfizer Medical Monitor (or designee). Participants cannot participate in studies of other investigational or experimental therapies or procedures at any time during their participation in this study.

14. Participants who have received prior treatment with any TYK2 and/or JAK inhibitors within 3 months or 5 half-lives preceding Screening (whichever is longer).

Diagnostic Assessments:

15. A Screening 12-lead ECG that demonstrates clinically significant abnormalities requiring treatment (eg, acute myocardial infarction, serious tachy- or brady-arrhythmias) or that are indicative of serious underlying heart disease (eg, cardiomyopathy, major congenital heart disease, low voltage in all leads, Wolff-Parkinson-White syndrome) or criteria associated with Q wave interval (QT)/Fridericia-corrected Q wave interval (QTcF) abnormalities including.

16. A marked prolongation of QTcF interval (>450 milliseconds [msec]) on the screening ECG:

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

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

    c. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participant.

17. Participants with 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:

    a. Hemoglobin <11 g/dL (<100 g/L) or hematocrit <30%;

    b. White blood cell count $<3.0 \times 10^9$/L (<3000 mm^3);

c. Absolute neutrophil count <1.5 x 10^9/L (<1500 mm^3);

d. Absolute lymphocyte count of <1.0 x 10^9/L (<1000/mm^3);

e. Platelet count <100 x 10^9/L (<100,000/mm^3);

f. Estimated glomerular filteration rate (eGFR) <60 mL/min/1.73 m^2 using creatinine or cystatin C based calculations (Section 7.1.4);

g. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values ≥2 times the ULN;

h. Total bilirubin ≥1.5 times the ULN; participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN;

i. Creatinine kinase (CK) >3 times the ULN.

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

19. Infected with Mycobacterium tuberculosis (TB) as defined by the following:

    a. A positive Interferon Gamma Release Assay (IGRA) test or positive Mantoux/Purified Protein Derivative (PPD) tuberculin skin test;

    b. Any chest imaging (chest x-ray, computed tomography (CAT Scan) or Magnetic Resonance Imaging (MRI)) taken at screening (or performed and documented within 12 weeks prior to Screening) with changes suggestive of active TB infection will be excluded;

    c. A participant who has been treated or is currently being treated for active or latent TB infection;

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

20. Infected with human immunodeficiency virus (HIV), hepatitis B or hepatitis C viruses. (Also see country-specific exclusion criteria in Appendix 8).

    Note: For Hepatitis B, all participants will undergo testing for Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (HBcAb) during Screening. Participants who are HBsAg positive are not eligible for the study. Participants 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 participant is not eligible for the study.

Note: For Hepatitis C, all participants will undergo testing for Hepatitis C antibody (HCV Ab) during Screening. Participants who are hepatitis C antibody (HCV Ab) positive require further testing with HCV RNA polymerase chain reaction (PCR) and are allowed to enroll if HCV RNA PCR negative.

Other Exclusions:

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

22. A history of alcohol or substance abuse within 6 months prior to Screening that in the opinion of the investigator will preclude participation in the study.

23. In the opinion of the investigator or Sponsor Clinician or Sponsor Medical Monitor, the participant is inappropriate for entry into this study.

5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 and Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. Medications/Treatments Discontinuation, Non-Medicated Emollients and Bathing

Participants are required to discontinue and avoid using certain medications and treatments as described in participant selection criteria. Participants should be instructed at each visit to contact the study site investigator promptly if there are any intended changes or additions to concomitant medications.

All medications and treatments that could affect atopic dermatitis must be discontinued for the duration of the study. The only exception is that shampoo containing tar, salicylic acid or low or least potent corticosteroid products (Class 6 or 7 corticosteroids, namely hydrocortisone ≤1% and hydrocortisone acetate ≤1%) is allowed for atopic dermatitis on hair-bearing scalp throughout the study. Due to the potential to affect atopic dermatitis with ultraviolet light exposure, participants 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.

The non-medicated emollient and sunscreen are the only topical products permitted to be used on atopic dermatitis skin during the Washout/Screening period (only exception is the use of permitted topical products for atopic dermatitis on hair-bearing scalp). Participants will stop applying non-medicated emollient and sunscreen on atopic dermatitis skin on the day before Day 1 (Visit 1). During the study period, use of non-medicated emollient and sunscreen are allowed only on skin that was considered normal or non-lesional at Day 1 (Visit 1) (ie, never treated with IP). Any non-medicated emollient used by the participant during the study should be documented in study records and the Case Report Form (CRF).

Through and including Week 6 visit, participants are to continue to treat all treatment-eligible atopic dermatitis areas identified at Day 1 (Visit 1) once or twice daily in accordance with the original dosing regimen assigned, regardless of clearing or improvement of atopic dermatitis. Any new atopic dermatitis areas occurring following Day 1 (Visit 1) should also be treated with the IP.

The treatment areas should not be bathed or showered for at least 4 hours after applying the IP. Bathing or showering is permitted pre-dose and the application areas must be dry prior to cream application.

5.3.3. Dietary Supplements

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. Herbals eg, St. John's Wort that are known to have an effect on drug metabolism must be discontinued at least 4 weeks or 5 half-lives (whichever is longer) before Day 1.

Participants should not consume grapefruit or grapefruit juice or citrus fruits eg, Seville oranges, pomelos within 7 days prior to Day 1 and until collection of the final PK blood sample.

5.3.4. Vaccine and Exposure to Infection Guidelines

5.3.4.1. Participant Specific Recommendations

It is recommended that all participants should be up-to-date with respect to standard of care vaccinations (as defined by their country health ministry) or AD guidelines. Vaccination of participants with live components is prohibited within the 6 weeks prior to first dose of investigational product. Adolescent participants without documented evidence of having received at least one dose of the varicella vaccine or those who are without evidence of previous varicella zoster exposure as confirmed by VZV IgG Ab serological testing are excluded.

5.3.4.2. Guidance Regarding Household Contact Vaccine-Related Exposure

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

1. Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination.
2. Oral polio vaccination for 6 weeks following vaccination.
3. Attenuated rotavirus vaccine for 10 days following vaccination.
4. FluMist® (inhaled flu vaccine) for 1 week following vaccination.

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

5.3.5. Other Requirements

1. Agree to avoid strenuous exercise during the study, especially within one week prior to the scheduled study visits and maintain adequate hydration, if possible.
2. On study visit days, do not smoke or ingest caffeine (eg, tea, coffee, some soft drinks/colas/energy drinks and power bars) during the 30 minutes prior to blood pressure and pulse (heart) rate measurements.
3. On study visit days, showering or bathing is permitted prior to attending the study visit, but do not moisturize.
4. On study visit days, take prescribed permitted concomitant medication, as needed, prior to the study visit, if it can be administered with water only.
5. Must agree to avoid prolonged exposure to the sun and avoid use of tanning booths or other ultraviolet light sources during the study.
6. Contact the study site investigator if there are any changes or additions to concomitant medications.
7. Avoid having major elective surgery.
8. The participant should continue all non-pharmacological therapies, such as physical therapy, as indicated. However, the participant should avoid changing the type or intensity of therapy or initiating new therapy until after Week 6 visit.

9. When applying the IP, the participant will not be required to wear gloves. However, participants should be instructed to wash their hands with mild soap and water before and after each application.

10. If study participants needs someone else to assist with applying investigational product on hard to reach areas (eg back), this person must wear gloves to avoid accidental exposure to the IP. In order to limit the potential risk associated with accidental exposure, this individual should not be a pregnant or breastfeeding female.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions, unless the reason for the screen failure is the disease severity inclusion criteria.

All screening assessments must be repeated during re-screening, with the exception of chest radiograph, HIV, Hepatitis and TB testing. These assessments do not have to be repeated if re-screening is done within 3 months of the initial screening visit and these assessments were performed during the initial screening visit.

6. STUDY INTERVENTION

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

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

Study intervention cream will be packaged in tubes containing 54 or 57 grams of either vehicle or PF-06700841 for topical application. Treatment assignment will be blinded. The tubes will be provided in cartons and both will be labelled in a blinded fashion according to local regulatory requirements.

6.1. Study Intervention Administered

For this study, investigational products are the following:

- PF-06700841 cream, in 0.1%, 0.3%, 1%, and 3% strengths; may also be referred to as 1 mg/g, 3 mg/g, 10 mg/g, and 30 mg/g, respectively.

- Vehicle cream; may also be referred to as vehicle and/or placebo.

PF-06700841 creams will be supplied in four different strengths: 0.1%, 0.3%, 1% and 3% (w/w), light mineral oil, white petrolatum, oleyl alcohol, emulsifying wax, diethylene glycol monoethyl ether, polyethylene glycol 400, 2-phenoxyethanol, and purified water.

Vehicle cream (no active drug in the formulation) contains light mineral oil, white petrolatum, oleyl alcohol, emulsifying wax, diethylene glycol monoethyl ether, polyethylene glycol 400, 2-phenoxyethanol, and purified water.

All active and vehicle creams will be packaged in laminate tubes containing 54 grams or 57 grams of either vehicle cream or PF-06700841 cream for topical application. All tubes will be provided in cartons and labelled in a blinded fashion according to local regulatory requirements.

6.1.1. Administration

6.1.1.1. Treated Atopic Dermatitis Areas

Atopic Dermatitis treatment areas will be all areas affected by AD, except hair-bearing scalp

Before the Day 1 initial IP application is performed, the designated areas for treatment will be identified at the Day 1 Visit and documented in the participant's source document study records (body-site check list). The participant and/or caregiver will be provided with documentation of the designated treatment areas. Treated AD area identified on Day 1 should be continued to be treated even if substantial improvement or clearing of AD occurs. If new AD areas emerge during the study, IP should be applied to these new areas after consultation with the Investigator.

6.1.1.2. General Instructions

On study Day 1 until the final dose at Week 6 visit, the IP should be applied once or twice daily (around same time of the day), to all treatable AD involved areas (excluding the scalp) identified at Day 1.

All participants will be supplied with instructions on application and dose frequency commensurate to assigned treatment arm. Those participants having difficulty reaching treatment-eligible atopic dermatitis areas (eg, back) may be assisted by another person who will need to apply the IP to the participant according to the investigational product application instructions. The person assisting with the application must wear gloves to avoid any exposure to the IP. If a participant misses applying a dose, the participant should apply

this dose provided this dose should have been applied within the last 6 hours. For longer intervals, the dose should be skipped. The missed dose should be recorded in the dosing diary. The next dose should be applied according to the regular dosing regimen.

Day 1 (Baseline Visit)

Participants and/or caregivers will be encouraged to observe and participate in the initial IP application on Day 1. All subsequent doses, including the second dose on Day 1 (if applicable), will be applied at home. The participant and/or caregiver will be instructed to complete the Dosing Diary starting with the first dose applied in the clinic on Day 1 through Week 6 (each time IP is applied) for all IP doses applied.

A thin layer of IP cream will be applied at a target application rate of approximately 2 mg/cm^2.

In order for participant or caregiver to keep track of the treatable BSA cleared, a paper version of the body check list may be provided on Day 1.

Post Day 1 Visits

Post Day 1 (Baseline/Visit 1), any new atopic dermatitis on treatment-eligible areas identified by the participant or caregiver(s) should also be treated with the IP. Decision to apply the IP to new eligible areas should be made following assessment by the Investigator or his/her designee. Body site check-list will be updated and IP need will be re-assessed at every site visit during the treatment period. If the total, treatable BSA exceeds 20% (inclusion criteria requirement) during the six-week treatment period, the participant will still remain eligible for the study, given, that the total, treatable BSA does not exceed 22%. If the total, treatable BSA reaches ≥22%, the Sponsor may decide to discontinue the participant.

The reason for maintaining IP treatment areas the same as identified at Day 1 (Baseline/Visit 1) is to understand the efficacy, systemic safety, and local tolerability of PF-06700841 cream when applied to BSA of 2-20% for 6 weeks in participants with mild or moderate atopic dermatitis.

Participants and/or caregivers will be instructed not to wipe investigational product off the skin, avoid applying an occlusive dressing to the treated areas, and refrain from swimming or bathing/washing the treated areas within **4** hours after application.

Use of any topical product (eg, sunscreens, moisturizers or non-medicated emollients) is prohibited on AD skin from Day 1 (Baseline/Visit 1) to the end of treatment period (Week 6), except for permitted products on scalp.

Under no circumstances will the investigational drug application regimen be modified (eg, frequency of application increased or reduced, not stopped, or the application rate [target 2 mg/cm^2] increased or reduced) during the study. Temporary discontinuation of investigational drug may be appropriate under some circumstances (eg, surgery, non-serious

infections) and should be discussed with the Medical Monitor (or designee) preferably prior to temporary discontinuation of investigational drug.

6.2. Preparation/Handling/Storage/Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product manual (IP manual).

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

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

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

8. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation.

Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

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

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the IP ready for application or dispensing to the participant/caregiver by qualified staff. Dispensing is defined as the provision of IP, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

The IP will be dispensed in a blinded fashion using an interactive response technology (IRT) system at Day 1/Baseline, Week 1 (Visit 2), Week 2 (Visit 3), and Week 4 (Visit 5) visits. A qualified staff member will dispense the IP via unique container numbers on the cartons provided, in quantities appropriate for the study visit schedule and the treatable % BSA.

For doses to be applied at home, the participant or caregiver should be instructed to maintain the product in its original package provided throughout the course of dosing and return the product and its original package (including empty, partial used and unused tubes) to the site at the next study visit. All previously dispensed IP tubes will be retained by the site. For each participant, IP tubes with caps will be weighed individually or collectively by the study site before dispensing and after return and the weights will be recorded. The sponsor will use the recorded weights to estimate usage (eg, mg/cm^2/application) for each participant. Note that the weight recorded on the IP label is a nominal weight and not an exact weight of the IP and tube.

Investigational product will be assigned to participants at the Day 1 (Baseline/Visit 1) visit once the participant is successfully randomized through the IRT system. The investigator, appropriate delegate or site personnel will access the IRT system at screening and all subsequent **IP dispensing** visits to enter information including, but not limited to, the participants height, weight and % affected BSA to receive correct tube numbers to be dispensed to the participant. Alternatively, the tool to standardize the IP need calculation across participants and study sites may be provided by the sponsor.

The calculation of % BSA is described in Section 8.1.4.

All tubes of investigational product dispensed or returned will be recorded and documented.

6.2.2. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP supplies. All investigational products will be accounted for using a drug accountability form/record. All tubes of the IP must be returned to the investigator by the participant at every visit and at the end of the trial.

The participant will be asked to bring all dispensed IP (including empty, partially used and unused tubes) at every 'compliance check' visit; participants will be asked to bring dosing diary to the clinic at every clinic visit. Detailed drug accountability records, including tube weights measured in the clinic, will be maintained by study staff for each participant.

The original IP accountability log, or equivalent document, must be accurately completed, signed by the Investigator, and retained at the study site (with a copy supplied to the Sponsor) when the study is complete.

6.2.3. Destruction of Investigational Product Supplies

For all IP returned to the investigator by the participant, the investigator will maintain the returned supply until destruction is authorized.

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

Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Allocation to treatment will occur via an Interactive Response Technology (IRT) system. The system will be programmed with blind-breaking instructions. Refer to Section 6.3.2 for further details.

6.3.1. Allocation to Investigational Product

For this study, the IP is PF-06700841 (or its matching vehicle) topical cream. Participants will be randomized into one of the doses in QD dosing regimen or BID dosing regimen of PF-06700841 cream or its matching vehicle cream.

At the Day 1 (Baseline/Visit 1) visit, provided all inclusion/exclusion criteria have been met, the participant will be randomized to trial medication. The investigative site will contact an interactive response technology (IRT) system (or interactive Web-based response [IWR]). Allocation of participants to treatment arms will proceed through IRT. The site personnel (study coordinator or specified designee) will be required to enter or select information

including but not limited to the user's identification (ID) and password, the protocol number, the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Investigational product will be dispensed at the study visits summarized in the SoA.

Returned IP must not be re-dispensed to the participants.

6.3.2. Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for blind breaking. The method will be an electronic process and will use IRT system. The IRT will be programmed with blind-breaking instructions. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. In case of an emergency, the investigator has the sole responsibility for determining if un-blinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that un-blinding is warranted, the investigator should make every effort to contact the sponsor prior to un-blinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF).

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

Participants whose code is broken will be discontinued from treatment and the entire procedures equivalent to end of treatment will be performed where possible.

The participant's data will be included in any full analyses. Any broken blinds will be documented in the study report.

6.4. Study Intervention Compliance

The participant and/or a caregiver will apply IP at home and during in-clinic visits as specified in Schedule of Activities (SoA). The participant and/or caregiver will be instructed to complete the Dosing Diary starting with the first dose applied in the clinic on Day 1 through Week 6 (each time IP is applied) for the IP doses applied at home. In addition, participants will be instructed to bring to the clinic all used, partially used and empty IP tubes in their original containers for weighing, at each visit.

Participant compliance with IP will be assessed on visits identified in Schedule of Activities (SoA). Compliance will be assessed by review of the participant/caregiver completed Dosing Diary and by weighing of the returned IP tubes. The difference in weight(s) of the returned IP tubes will be used to estimate the doses applied. Source documents will be placed in the participant's study file. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

From Day 1 (Visit 1) through and including Week 6 visit (Visit 6), non-compliance is defined as less than 80% or more than 120% of IP applications. If non-compliance is identified, or even if a few dose applications are missed or over-applied, then, participants will be re-trained on the importance and the process of proper IP application. If non-compliance persists, the investigator, in consultation with the Sponsor, may withdraw any participant from the study for reasons of non-compliance with the dosing regimen. Investigators should indicate on the appropriate CRF page noncompliance with study intervention and provide an explanation.

Inventory control of all IPs must be rigorously maintained throughout the duration of the study until all medication has been accounted for and/or returned to the sponsor. Any discrepancies noted between drug dispensing records and the drug inventory must be reported to Pfizer.

6.5. Concomitant Therapy

Medications that are taken in the Screening period (after informed consent is obtained and before the first dose of IP) will be documented as prior medications. Medications taken after the first dose of IP 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 application. Participants will be queried about concomitant medication (including topical medications and treatments, over-the-counter and prescription medications and treatments, and vaccinations) at each study visit. Any new concomitant medications or dose changes to current concomitant medications should be evaluated for potential new or worsening adverse events.

See Appendix 10 on prohibited medications and procedures.

In addition, the following concomitant medications are allowed, unless excluded in Prohibited Medications list (Appendix 10):

1. Antihistamines.

2. Acetaminophen/paracetamol and Ibuprofen.

3. Medications for regulation of thyroid function.

4. Selective leukotriene receptor antagonists (eg, montelukast sodium, zafirlukast), mast cell stabilizers (eg, cromolyn sodium or nedocromil sodium).

5. Corticosteroid inhalers and intranasal sprays provided participants are on stable dose for at least 1 week before Day 1 and/or during treatment period.

6. Ophthalmic corticosteroids, provided participants are on stable dose for at least 1 week before Day 1 and/or during treatment period.

7. Hormone replacement therapy (HRT) and hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are women of childbearing potential (WOCBP) (see Appendix 4).

8. Medications for chronic stable medical conditions (eg, hypertension) provided these are not expected to affect the study assessments and participant is on a stable dosage. If prescribed, change in medication for hypertension is allowed.

9. Topical treatments applied to areas not treated with IP unless prohibited in Appendix 10.

10. Sunscreen and regular moisturizers applied to areas not treated with IP. Site staff must verify that these are not emollients.

Any other concomitant medication will be considered on a case by case basis by the investigator in consultation with the Sponsor Medical Monitor.

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the adverse events (AEs) observed with PF-06700841; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Not applicable.

6.7. Intervention after the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue IP. Per the study estimands, if IP is permanently discontinued, the participant will proceed to early termination and follow-up visit per Schedule of Activities (SoA). The site will inform Sponsor Medical Monitor or Sponsor clinician if the below criteria for permanent discontinuation of the IP are triggered.

Note that discontinuation of investigational product does not represent withdrawal from the study.

7.1.1. ECG Changes

A participant who meets either of the bulleted criteria based on the average of triplicate ECG readings (also see Section 8.2.2.3) will be withdrawn from the study.

- QTcF >500 msec.
- Change from baseline: QTc >60 msec.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.2. Local Tolerability

All participant-reported and observed application site adverse events (AEs) should be recorded along with the body region location, severity, duration and outcome as indicated on the CRF.

- If a participant experiences severity Grade 3 (severe) or 4 (very severe) on the local tolerability assessment (Section 8.2.2.9), study treatment will be discontinued permanently and participant will proceed to early termination (ET) visit and follow-up as described in Schedule of Activities (SoA).
- If a participant experiences application site reaction of Grade 2 (moderate) on the local tolerability assessment, investigator may temporarily discontinue application of IP for up to 48 hours without consulting the Sponsor. If in the clinical judgment of the investigator IP interruption beyond 48 hours is advisable, the investigator must obtain agreement from the Pfizer medical monitor to continue withholding IP. If temporary IP interruption for more than 5 consecutive days is needed, then the participant should be permanently withdrawn from treatment and should follow-up with the site until complete or near complete resolution of the AE. This dosing gap may occur only once for the same participant.

7.1.3. Adverse Events

All treated infections occurring during the study, including, but not limited to, respiratory infections, cutaneous infections, urinary tract infections and episodes of suspicious or febrile diarrhea, should be cultured and any identified organisms noted in the Case Report Form. Infections should be classified as either serious infections or treated infections, as defined below.

7.1.3.1. Serious Infections

A serious infection is any infection that requires hospitalization for treatment or requires parenteral antimicrobial therapy or meets other criteria that require it to be classified as a serious adverse event. A participant who experiences a serious infection should be discontinued from the study and the serious adverse event should be listed as the reason for discontinuation in the Case Report Form. Appropriate laboratory investigations, including but not limited to cultures should be performed to establish the etiology of any serious infection. All adverse events, including serious adverse events, should be reported as described in Appendix 3 on Adverse Event Reporting.

7.1.3.2. Treated Infections

A treated infection is any infection that requires antimicrobial therapy by any route of administration or any surgical intervention (eg, incision and drainage). Participants who experience infections that require treatment can have their blinded IP temporarily discontinued during antimicrobial therapy in consultation with the sponsor. This information should be noted in the Case Report Form.

7.1.4. Potential Cases of Decreased eGFR

All participants will have serum creatinine based and serum cystatin-C based eGFR calculated at all time points.

Abnormal values in serum creatinine concurrent with absence of increase in blood urea nitrogen (BUN) that meet the below criteria, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

If an individual participant demonstrates CONCOMITANT serum creatinine-based AND serum Cystatin C-based eGFR decline of ≥30% (See Section 8.2.2.6) compared to the participant's baseline eGFR (pre-dose, Day 1), then the participant should not be further dosed and adequate, immediate, supportive measures including immediate evaluation by a nephrologist (preferably within 24 hours) with appropriate management and treatment as clinically indicated. Results should be repeated as indicated by the nephrologist or weekly at a minimum until the eGFR returns to baseline ±15%, or the renal parameters are deemed to be stable by the nephrologist and/or Principal Investigator (PI).

If the participant cannot be seen by a nephrologist within 24 hours (as described above), then the participant should be sent to a local emergency room for evaluation and treatment as clinically indicated.

Participants should return to the investigational site and be evaluated as soon as possible, **preferably within 24-48 hours** from awareness of the abnormal eGFR result (CONCOMITANT serum creatinine based AND serum cystatin C based eGFR decline of ≥30% compared to the participant's baseline eGFR) for a safety follow-up visit. Follow-up evaluations should include laboratory tests, detailed history, and physical assessment. In addition to repeating serum creatinine and serum cystatin C, laboratory tests should also

include: serum BUN, serum CK, serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, calcium), in addition to urine dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified should be considered as potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal serum creatinine.

All relevant test results will be forwarded to Pfizer for review immediately upon receipt by the PI.

7.1.5. Laboratory Abnormalities

All the following laboratory abnormalities require discontinuation if they are confirmed. Confirmation through re-testing should occur within 2-5 days:

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/mm3; <0.5x10^9/L
Chemistry	
AST[a]	>2.5x ULN
ALT	>2.5x ULN
Total bilirubin[b]	>1.5x ULN

a. Additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption should be done; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the Pfizer Medical Monitor or designee.

b. Participants with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible to remain in the provided the direct bilirubin is ≤ ULN.

7.1.6. Pregnancy

Pregnancy confirmed by serum beta-human beta-human chorionic gonadotropin (β-hCG) testing. Sponsor Clinician or Medical Monitor should be notified immediately.

7.1.7. Suicidal Ideation and Behavior

Participants triggering criteria for suicidal ideation and behavior as described in Section 8.2.2.8.

7.1.8. Temporary Discontinuation

Temporary discontinuations of IP

- will occur in cases of positive urine pregnancy test which if confirmed by serum pregnancy test will lead to permanent discontinuation (Section 7.1.6).
- may apply in some cases application site reaction during local tolerability assessments (Section 8.2.2.9).
- additional instances of temporary discontinuation may be appropriate (eg, surgery, infection, etc).

All temporary discontinuations should be discussed with Sponsor Clinician or Sponsor Medical Monitor to determine if participant may continue in the study. If possible, site will consult sponsor prior to temporary discontinuation.

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

Any participant meeting discontinuation criteria must enter into the Follow up Period with their first follow up visit occurring 1 week after their last dose whenever possible (instead of two weeks described in Schedule of Activities (SoA) and continue visits per Investigator's discretion until the event has returned to normal or baseline levels or is deemed clinically stable. The procedures scheduled for Week 6 (end of treatment) visit will be performed on the last day the participant takes the investigational product or as soon as possible thereafter. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. 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.

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

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

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

If the participant withdraws from the study and also withdraws consent (see below) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

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

Withdrawal of Consent:

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

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

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

The total blood sampling volume for individual participants during treatment period is approximately 195 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

All efficacy assessments will be based on areas treated with IP, but excluding scalp, palms and soles.

8.1.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Rater Assessment Manual provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.1.2. Investigator's Global Assessment (IGA)

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

The assessment will be a static evaluation without regard to the score at a previous visit.

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

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

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

8.1.3. Eczema Area and Severity Index (EASI)

The EASI quantifies the severity of a participant's atopic dermatitis based on both severity of lesion by 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.

8.1.3.1. 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 below.

Table 6. 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.

8.1.3.2. Percent BSA with Atopic Dermatitis (for efficacy)

Percent BSA affected by AD should be calculated in each of the four body regions ie head and neck (h), upper extremities (u), trunk (t), and lower extremities (l). The area within each body region with the key signs of the disease is estimated using handprint as a measure, where the full palmar hand of the participant (ie, the participant's fully extended palm, fingers and thumb together) represents approximately 1% of the total BSA.

Each region is typically assigned proportionate body surface areas of 10 (h), 20 (u), 30 (t), and 40 (l) handprints respectively. Refer to Table 7 to identify the surface area equivalent of 1 handprint in each respective body region.

Table 7. Determination of Body Region Surface Area

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)	30	3.33%
Lower Limbs (including buttocks)	40	2.5%

Area Score

The extent (%) to which each of the four body regions is involved with AD (by using Table 7 above) is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 8).

Table 8. 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 9).

Table 9. Body Region Weighting

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

8.1.3.3. Calculation of EASI Score

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.

Equation: $EASI = 0.1Ah(E_h+I_h+Ex_h+L_h) + 0.2Au(E_u+I_u+Ex_u+L_u) + 0.3At(E_t+I_t+Ex_t+L_t) + 0.4Al(E_l+I_l+Ex_l+L_l)$

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. Since the scalp, palms and soles (even if hairless scalp, palms and soles are being treated with the IP) will be excluded from the EASI assessment in this study, the maximum possible score will be less than 72.0.

Calculation will be done centrally by Sponsor programmers.

8.1.4. Body Surface Area

The BSA affected (%) is calculated by adding the %BSA affected in each body region area. The extent to which each of the four areas of the body is affected (% BSA) is obtained by multiplying the % obtained from Table 7 with a weighting factor as shown in Table 9. The % BSA is captured on the CRF (to 2 decimal places, as necessary).

The sum of the weighted percent involvement obtained for each of the four body areas is the grand total BSA with AD, as described in the following equation:

$$\text{BSA (\%)} = \frac{0.1S_h + 0.2S_u + 0.3S_t + 0.4S_l}{}$$

where S = body region surface area with AD; h = head; u = upper limbs; t = trunk; l = lower limbs.

Symptoms (eg, pruritus), along with secondary signs (eg, xerosis, scaling) are excluded from the area assessments.

8.1.4.1. Body Surface Area for IP need

Evaluation of BSA for IP need is the total BSA across all body locations being treated with the IP. BSA for IP need evaluation method will be the same as the BSA Efficacy evaluation (Section 8.1.4), except that the BSA for IP need will include AD on all IP treated body locations, some of which may be excluded from the BSA Efficacy evaluation. If a participant has atopic dermatitis on palms, and/or soles, these body locations will be included in the BSA for IP need estimation.

Participants with atopic dermatitis on the groin or genitals at Day 1 (Visit 1) are not eligible for the study. If new atopic dermatitis occurs on the groin and/or genitals following Day 1 (Visit 1), the groin and/or genitals may be treated with IP, but the groin and genitals will be excluded from the clinical evaluation of atopic dermatitis for efficacy. New atopic dermatitis occurring on the groin and/or genitals following Day 1 (Visit 1) will be included in the clinical evaluation of atopic dermatitis BSA for IP need to ensure the participant has an adequate supply of IP.

Investigational product should be applied to the BSA determined at Day 1 (Visit 1) throughout the treatment period regardless of clearing or improvement of atopic dermatitis. Any new atopic dermatitis on treatment-eligible locations occurring following Day 1 (Visit 1) should also be treated with the IP. Therefore, the BSA for IP need at subsequent visits should be equal to or greater than the value at Day 1.

A checklist of body site areas currently affected by AD will be completed at the Day 1 visit. Location of skin lesions will be selected from a prepopulated listing of body locations.

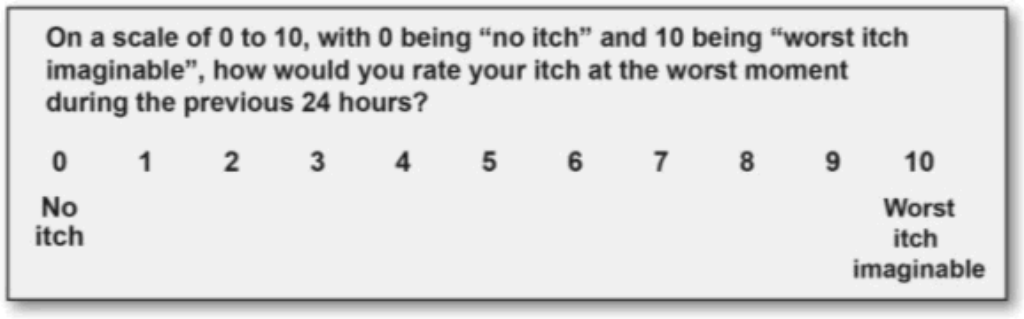
The body site checklist will be reviewed at every visit to the site to update for any new, treatable areas, if needed.

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

The intensity of pruritus will be assessed by a numerical rating scale (NRS), an 11-category numeric rating scale from 0 to 10, which is patient reported (see Appendix 12). The PP-NRS will be completed by participant. The PP-NRS will be completed once daily at least 7 days prior to Day 1, and completed once daily every day from Day 1 to Week 6 before IP morning dose is applied preferably at the same time of each day if applicable, as noted in the Schedule of Activities (SoA).

Pruritus will be evaluated by asking participants to assign a numerical score representing the worst imaginable itch over the last 24 hours on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The PP-NRS is presented in Figure 3. This item will be administered to all participants.

Figure 3. Peak Pruritus Numerical Rating Scale (PP-NRS)



8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (SoA). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Assessments at Screening Only

8.2.1.1. Medical History

Investigators should make all reasonable efforts to obtain an accurate and complete medical history and history of prior medication use when evaluating whether a participant is eligible for the study. The following will be collected at Screening: complete medical history, AD disease history (including disease duration and prior treatments) and alcohol and tobacco use history.

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 taken during the 3 months/90 days prior to Screening/Washout with dose, duration of treatment, and reason for discontinuation. All other drugs (including sunscreen, over the counter medication, vitamins, and dietary supplements) taken within 28 days prior to the Screening/Washout visit should be recorded.

Medical history in addition to AD history including disease duration will be collected at screening. Medical history also includes history of alcohol and tobacco use. Smoking status and average weekly alcohol consumption (units/week) will be collected, where a unit contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz/150 mL (a glass) of wine, 12 oz/360 mL of beer, or 1.5 oz/45 mL of 90 proof of spirits.

If the status of a participant's medical history is in doubt or information pertaining to a critical variable is conflicting, every reasonable step to secure proper documentation of correct medical status should be attempted. Documentation of the medical and medication histories over the protocol defined time periods should be available for sponsor review during the source data verification process. Questions about prior medications or eligibility should be directed to the Sponsor Clinician or Sponsor Medical Monitor.

8.2.1.2. Tuberculosis Testing

At the time of screening, all participants will undergo tuberculosis (TB) testing unless performed within 12 weeks of Screening (with available documentation) using one of the tests below.

8.2.1.2.1. Interferon Gamma Release Assay (IGRA) Tuberculin Test

Participants may be screened for TB using an IGRA per local guidelines. Interferon gamma release assay will be tested during screening or within 12 weeks prior to Day 1. The following are acceptable IGRA assays: QuantiFERON®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT® TB test. Site personnel should follow the processing and analyses steps based on the assay chosen. Ensure incubation steps are followed as appropriate.

An IGRA is preferred for participants with a prior bacille Calmette-Guerin (BCG) vaccination, but may be used for any participant. Documentation of IGRA product used and the test result must be in the participants' source documentation.

If the results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.

Participants with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, participant would be acceptable for immunosuppressant (eg, anti-tumor necrosis factor [TNF]) treatment without additional action).

Participants who test positive for IGRA test (including borderline T-SPOT result), but in the opinion of the PI are at low risk of TB infection may be referred to pulmonary or infectious disease specialist for consultation and potential IGRA test repeated once. Participants will be eligible if the repeat test is negative before the randomization.

Refer to lab manual for any additional processing information and shipping instructions.

8.2.1.2.2. Mantoux/Purified Protein Derivative (PPD) Tuberculin Skin Test

Participants 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. Participants 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.

8.2.1.3. Chest Radiograph

Participants must have chest radiograph (posterior-anterior and lateral views are recommended however local guidelines should be followed) or other appropriate diagnostic image of the chest/thorax (ie, computerized axial tomography [CAT] or magnetic resonance imaging [MRI]) taken at Screening and read by a qualified radiologist. Documentation of official reading must be available in source documentation. Chest imaging may be performed to aid in TB status determination for all adults, and recommended for adolescents according to local guidelines and standard of care and/or in countries with a high incidence rate of TB.

If chest radiograph had been taken within 12 weeks prior to Screening and read by a qualified radiologist as normal, the test does not have to be repeated at screening, provided documentation is available.

Participants with evidence of currently active TB, general infections, heart failure or malignancy will be excluded. Participants with changes suggestive of untreated latent or active TB infection may be enrolled after consultation with a pulmonary or infectious disease specialist who determines low risk of infection.

8.2.1.4. Skin Type Assessment

As part of screening, a skin type assessment will be done using the Fitzpatrick Skin Type assessment (Refer to Appendix 11). This is used to classify a person's skin type by their response to sun exposure (ie, burning or tanning).

8.2.2. Assessments during Study

8.2.2.1. Physical Examinations

Physical examinations, including height, and weight will be performed at times specified in the Schedules of Activities section of this protocol.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Full Physical Examination: includes, but is not limited to the following organ or body systems-head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, abdomen, cardiovascular, and neurological systems. In addition, an assessment will be made of the condition of all AD involved skin (skin assessments should be completed by PI or Sub-I).

A full physical examination will be performed at Screening, Day 1, and at Week 6 visit.

Disease focused Physical Examination: includes all AD involved skin (in treatable and non-treatable areas) and evaluation of any current or reported symptoms for clinically significant changes. A disease-focused physical examination will be performed at Week 1, Week 2, Week 4, follow-up and at early termination (ET) visits.

Any clinically significant changes from the most recent physical examination should be recorded as adverse events (AEs). Lack of efficacy is generally not considered an AE.

Any treatment-emergent finding of other forms of dermatitides/eczematous conditions, (eg, contact dermatitis, seborrhoeic, discoid, gravitational, asteatotic) should be recorded as an AE.

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

8.2.2.1.1. Weight and Height

It is recommended that weight be measured in kilograms (kg) to the nearest 0.1 kg and that height be measured in centimeters (cm) with shoes removed.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

8.2.2.2. Vital Signs

Vital signs will be measured with the participant in supine position after 5 minutes of rest as indicated in the Schedule of Activities (SoA) and will include temperature, systolic and diastolic blood pressure, and pulse rate (PR). On study day visits when clinical laboratory tests are performed, assessment of vital signs should precede blood draw.

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

Blood pressure (BP) will be measured using a standard calibrated blood pressure measuring device. A BP device that uses multiple cuff sizes based on the arm circumference is the required type of device. The following method should be used to record the blood pressure:

- Participants should be seated in a chair, back supported, and arms bared (free of restrictions such as rolled-up sleeves, etc.) and supported at heart level.
- Measurements should be taken on the same arm at each visit (preferably non-dominant) and in same position (sitting or supine) as their baseline visit.
- Participants should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements. Measurements should begin after at least 5 minutes of rest without distractions. 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.
- The appropriate cuff size for the participant must be used to ensure accurate measurement. The arm circumference at the midpoint of the length of the upper arm should be measured to determine the appropriate cuff size in accordance with the specifications of the BP measuring device. The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time.
- BP should be recorded to the nearest mmHg value.

Pulse rate should be measured at approximately the same time as BP for a minimum of 30 seconds.

8.2.2.3. Electrocardiograms

A single 12-Lead ECGs should be collected at times specified in the Schedule of Activities (SoA) section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Additional ECG may be performed upon request by the Sponsor Clinician or the Sponsor Medical Monitor.

All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in supine position. When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, BP, and pulse rate.

ECGs will be read and interpreted locally. To ensure safety of the participants, a qualified individual (eg, sub-investigator) at the investigator site will make comparisons to baseline measurements taken at Day 1. ECG parameters (PR, QT, QTc and QRS intervals) should be recorded on the CRF. A copy of the ECG should be available as source document for review.

During screening, if participants have initial screening value QTcF >450 milliseconds (ms), ECG should be repeated two more times and the average of the three QTcF should be used to determine the participant eligibility.

If at any subsequent time QTcF ≥500 msec or change from baseline QTc ≥60 msec, ECG should be repeated two more times and average of these values should be used to determine withdrawal from IP (see Section 7.1.1). If average is above these thresholds, participants should be monitored hourly with triple ECGs.

If a postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.2.4. Herpetiform Rash

For any occurrence of a suspected herpetiform rash (eg, herpes zoster and herpes simplex), specimens for viral deoxyribonucleic acid (DNA) analysis will be obtained: A swab of the affected area will be collected for confirmation; a blood sample for viral surveillance will be collected for the analysis of viral load. Details for these collections will be provided in the laboratory manual.

8.2.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency.

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

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

If the screening serum chemistry and hematology tests are performed within 7 days prior to Day 1, whether the Day 1 serum chemistry and hematology tests are to be performed will be at the discretion of the investigator or his/her designee.

At the discretion of the investigator or his/her designee, a lidocaine-based topical anesthetic (eg, lidocaine 4% cream) may be used prior to clinical laboratory sample collection to decrease potential discomfort to the participant provided the anesthetic does not contain propylene glycol (PG). However, the skin must be thoroughly cleansed prior to blood sample collection.

The Investigator will review all clinical laboratory test results for safety evaluation upon receipt. After reviewing the laboratory reports and evaluating the results for clinical significance, the investigator or his/her designee must sign and date the laboratory report. Clinically significant laboratory abnormalities are defined as abnormal values that have clinical manifestations or require medical intervention. Clinically significant laboratory abnormalities noted from the Screening Visit will be recorded in the medical history.

A clinically significant laboratory abnormality detected after the Screening Visit may reflect the development of an AE. Whenever possible, Investigators should report the clinical diagnosis suggested by the laboratory abnormality rather than listing individual abnormal test results as AEs. If no diagnosis has been found to explain the abnormal laboratory result, the clinically significant lab result should be recorded as an AE.

8.2.2.6. Creatinine, Cystatin C, and estimates of Glomerular Filtration Rate

Serum creatinine will be measured as part of serum chemistry at times specified in the Schedule of Activities (SoA) section of the protocol. Creatinine elevations above the upper limit of normal (ULN) will be followed until resolution or baseline. Serum creatinine based eGFR will be calculated. Serum cystatin C will be measured and cystatin C based eGFR will be calculated at corresponding times per Schedule of Activities (SoA).

The eGFR will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which utilize serum creatinine (SCr) and serum cystatin C (S Cystatin C) respectively (Appendix 14).

8.2.2.7. Samples for Lipid Analysis

Blood samples (3.5 mL) to provide approximately 1.2 mL serum for the analysis of lipids will be collected as per Schedule of Activities (SoA).

8.2.2.8. Suicidal Ideation and Behavior Risk Monitoring

Participants meeting exclusionary results as described in Section 5.2 on the C-SSRS should be excluded from participation; it is recommended the participant's primary care physician (PCP) should be informed, and the participant referred to a mental health professional, either by the PCP or the investigator according to their usual practice.

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

The Columbia Suicide Severity Rating Scale is a validated tool for investigative staff to use to evaluate suicidal ideation and behavior (Appendix 13). At the screening visit, if there are "yes" answers on items 4 or 5 in the past year or on any question in the suicidal behavior section of the C-SSRS in the past 5 years, the participant will not be included in the study. Trained site staff is to administer the C-SSRS to all participants at screening and assess the participant's eligibility based on the answers.

At any of the visits in Schedule of Activities (SoA) when C-SSRS will be administered, if there are "yes" answers on items 4, 5 or on any question in the suicidal behavior section of the C-SSRS, the participant will be discontinued from the IP and referred to a mental health professional for appropriate evaluation and treatment. If the participant cannot be seen by a mental health professional within 24 hours, then the participant should be sent to a local emergency room for psychiatric assessment.

8.2.2.9. Local Tolerability

The investigator or designee will assess tolerability at the site of IP application (pre-dose and immediately post-dose). This assessment will focus on the treated non-lesional skin using scale in Table 10.[27] See Section 7.1.2 for permanent and temporary discontinuation criteria based on local tolerability assessment.

Table 10. Skin Tolerability Grading System

Grade	Severity	Description
0	None	No evidence of local intolerance
1	Mild	Minimal erythema and/or oedema, slight glazed appearance
2	Moderate	Definite erythema and/or oedema with peeling and/or cracking but needs no adaptation of posology
3	Severe (to be reported as an AE)	Erythema, oedema glazing with fissures, few vesicles or papules: consider removing topical agent (if still in place)
4	Very severe (to be reported as an AE)	Strong reaction spreading beyond the treated area, bullous reaction, erosions: removal of topical agent (if still in place)

8.2.2.10. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving 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. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

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

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

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

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

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

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

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

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

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

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

8.3.5. Exposure during Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 28 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

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

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

8.3.6. Medication Errors

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

Exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant 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 study participant.

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of investigational product greater than BID dosing within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until investigational product can no longer be detected systemically (at least 7 days).

3. Obtain a blood sample for PK analysis within 1 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Blood samples of approximately 3 mL, to provide a minimum of 1.5 mL plasma will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) for measurement of plasma concentrations of PF-06700841 as specified in the Schedule of Activities (SoA). Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. The actual times may change, but the number of samples will remain the same.

All efforts will be made to obtain the samples at the exact nominal time relative to dosing. The exact time of the collection should be noted on the source document and data collection tool (eg, CRF).

Samples collected for analyses of PF-06700841 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-06700841 will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), 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.

Drug concentration information that may un-blind the study will not be reported to investigator sites or blinded personnel.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

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8.7. Genetics

8.7.1. Specified Genetics

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

CCI [redacted]

8.8. Biomarkers

Biospecimens collected for biomarker assessments may include peripheral blood and skin tissue and may be used to analyze DNA, RNA, proteins, or metabolic biomarkers, for achieving planned biomarker objectives. Refer to the Schedule of Activities (SoA) for sample collection time points and the laboratory manual for sample processing and shipping.

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[redacted]

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[redacted]

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.10. Patient Reported Outcomes

Every effort should be made for the participant to complete all patient reported outcome (PRO) questionnaires before any other evaluations. The amount of time required for participants to complete the PRO questionnaires is approximately 10-30 minutes (depending on the visit and associated PROs). The PROs should be checked for completeness by the study site staff at every in-clinic visit.

Once participants have met all inclusion/exclusion criteria, they will be provided a handheld device (provided by the Sponsor) for dosing diary and patient-reported-outcomes (ePROs) or paper versions of the above to be completed at home as per the time points defined in Schedule of Activities (SoA). The clinic sites may use paper versions of PROs.

The following PROs will be completed only on study visit days identified in Schedule of Activities (SoA), starting on Day 1: POEM, DLQI/Childrens DLQI (CDLQI), and CCI [redacted] Other protocol-specified PROs ie, PP-NRS, CCI [redacted] and CCI [redacted] will be used by participants for daily completion of PROs at home, starting from 7 days prior to the dosing/randomization day (Day 1) and as defined in the Schedule of Activities (SoA).

All participants will complete PROs at follow-up visit in clinic.

Delegated site staff will monitor completion of PROs for adherence and will review adherence with participants at each visit and counsel as appropriate. If a participant has repeated non adherence, the participant should be retrained on use of the device or filling out paper versions. If a participant is unable to complete ePROs due to documented technical issue or disability or other limitation, the participant will be permitted to enter or remain in the study providing that a valid alternate source of daily data entry is completed and reviewed by investigational site staff. No protocol deviations will be recorded in regard to PRO completion adherence. In the event of electronic malfunction of an ePRO or misplacement of paper versions of the PROs, a replacement device or paper PROs will be shipped to the site. Examples of the validated paper versions of Patient Reported Outcomes instruments are included in the Appendices of this protocol. The electronic version may differ slightly in format or wording compared with the paper version to facilitate electronic implementation.

8.10.1. Patient-Oriented Eczema Measure (POEM)

The POEM is a validated 7-item PRO measure used to assess the impact of AD recalled over the past week (Appendix 12). The POEM should be completed in clinic as per Schedule of Activities (SoA).

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

The DLQI is a validated general dermatology questionnaire that consists of 10 items to assess participant-reported health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment) (Appendix 12). It has been

extensively used in clinical trials for AD. The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to be responsive to change. The minimally important difference for the DLQI has been estimated as a 3 to 5 point change from baseline. A version of the instrument specifically developed and validated for use by adolescents from age 12 to 17 is called the CDLQI (Appendix 12).

The DLQI/CDLQI should be completed in clinic as per Schedule of Activities (SoA).

CCI [redacted]

CCI [redacted]

8.10.5. Peak Pruritis Numerical Rating Scale (PP-NRS)

See Section 8.1.5 for details.

CCI [redacted]

CCI

[redacted]

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[redacted]

CCI [redacted]

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

The primary estimand will be the population average treatment effect on percent change from baseline in EASI score relative to vehicle (with the same dosing schedule, QD or BID) at 6 weeks in the absence of prohibited medication without regard to compliance. All observations after the initiation of prohibited medication will be set to missing. Missing data from all causes, including post-prohibited medication use will be imputed in the PF-06700841 arms using a jump to control method using the distribution of the vehicle group with matching BID or QD regimen (ie missing data in 1% QD regimen will be imputed from the distribution of participants on QD vehicle). Participants with inadequate compliance will have their recorded EASI scores used as-is in the analysis. The population based treatment effect will be the differences in the mean change from baseline in each treatment arm compared to the corresponding vehicle.

The secondary estimand will be the estimated population average treatment effect on the rates of IGA response (participants with a score of 0 or 1 and a 2 point or greater decrease from baseline) at Week 6 relative to vehicle (with the same dosing schedule, QD or BID) without regard to compliance with IP in the absence of prohibited medication. This is a composite estimand where success is defined as achievement of an IGA response as defined above while remaining on study, providing data and not taking prohibited medication; lack of compliance or adverse events will not be counted as a failure. The population based treatment effect will be the differences in the proportions of success in each treatment arm

compared to the corresponding vehicle. EASI-75 and other EASI scores will be treated in a similar manner.

All other secondary continuous clinical endpoints will be analyzed using the primary estimand, while all other secondary categorical clinical endpoints will be analyzed using the secondary estimand described above. Tertiary and Exploratory analyses may or may not be analyzed using these estimands and may be analyzed in a descriptive manner without reference to an estimand. Other estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of the results and to compare to available literature as needed. Details of these analyses will be presented in the statistical analysis plan (SAP).

9.2. Sample Size Determination

The sample size calculation is based on the primary endpoint (percentage change from baseline in EASI score at Week 6) and the key secondary endpoint (IGA response rate of clear or almost clear and ≥2 points improvement at Week 6). A total of 280 randomized participants in 6 treatments groups and two vehicle groups (35/arm) will provide approximately 90% power to detect a difference of 50 in percentage change from baseline with a common standard deviation 48% between PF-06700841 and a vehicle arm, controlling the one-sided family wise error rate a 0.05 with a Bonferroni correction (alpha=0.008 after Bonferroni adjustment for 6 comparisons). These calculations allow for a 20% dropout rate leaving 224 evaluable participants (28/arm).

For the key secondary endpoint, IGA response rate of clear or almost clear and ≥2 points improvement at Week 6, assuming 20% rate for vehicle and 60% rate for the treatment, this sample size also ensures the 80% power.

9.3. Populations for Analysis

For purposes of analysis, the following populations are defined:

Population	Description
Safety Analysis Set	All participants randomly assigned to IP and who apply at least 1 dose of IP. Participants will be analyzed according to the product they actually received.

Defined Population for Analysis	Description
Modified Intention to Treat (mITT)	All participants randomly assigned to IP and who apply at least 1 dose of IP.
PK concentration set	All enrolled participants who applied at least one dose of PF-06700481 and in whom at least once concentration value is reported.

9.4. Statistical Analyses

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

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	A landmark analysis using analysis of covariance of percent change from baseline in EASI, adjusting for the baseline EASI score, to estimate the effect of the initially randomized treatment in the absence of prohibited medication regardless of treatment compliance. The analysis will use the mITT analysis set. Missing data due to any cause including censoring due to initiation of prohibited medication will be imputed using the corresponding vehicle arm, missing data in a vehicle arm will be imputed using data from the vehicle arm assuming data are missing at random (MAR). The analysis will combine the results from the multiple imputations using Rubin's rule's as implemented in SAS PROC MIANALYZE. The overall family wise Type I error rate will be controlled at the one-sided 0.05 level using the Hochberg step up procedure.
Secondary	A landmark analysis of the composite endpoint; achieving IGA without prohibited medication, while remaining on study and providing data. The analysis will use the mITT analysis set. Based on the definition of the composite endpoint all participants in the mITT set will have a response for all visits (ie, there is no missing data). The proportions responding and the corresponding risk difference comparing active treatment arm to vehicle group will be analyzed using the unconditional exact method; the risk differences and the corresponding 2-sided unconditional exact 90% confidence intervals will be computed using Chan and Zhang[28] (1999) method. No adjustments for multiplicity will be made.
CCI [redacted]	[redacted]

Other continuous secondary endpoints at time points specified in the Schedule of Activities (SoA) including change from baseline EASI, will be analyzed as described for the primary estimand along with descriptive statistics and possibly graphical displays. No adjustments for multiplicity will be made for these endpoints.

CCI [redacted] EASI-90[redacted], IGA of clear or almost clear will be analyzed as described for the secondary estimand along with descriptive statistics and possibly graphical displays. No adjustments for multiplicity will be made for these endpoints.

CCI [redacted]

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive IP (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include: □ Treatment-emergent AEs and SAEs; □ Withdrawals from active treatment due to AEs; □ Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials; □ Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and lipid profiles); □ Vital signs. Change from baseline on laboratory data and vital signs will be additionally summarized. Participant listings will also be produced for these safety endpoints.
CCI [redacted]	

9.4.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

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9.5. Interim Analyses

An interim analysis will be performed once approximately 20% of enrolled participants (≥18 years of age) complete at least Week 2 (Day 15) visit. The objective of this analysis is to evaluate the safety and tolerability of PF-06700841 cream, as compared to vehicle cream. If available, systemic exposure (PK) data will also be reviewed during this interim analysis. The interim analysis will provide safety/tolerability data to commence enrollment of male population of 12-18 years of age in the study.

Interim analysis results may also be used for internal business decisions regarding future study planning. In that case, before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an internal review committee (IRC) charter. The results will only be distributed to a select list of individuals involved in the internal decision-making process in order to protect the integrity of the study. This list of individuals will be provided in the interim analysis plan. The results of the interim analysis will not enable individuals directly involved in running the study (such as investigators) to identify treatment assignments for individual participants still in the study. There are no prospective plans to stop the study early for success as a result of the interim analyses.

Since the analysis approach will be identical between the primary analysis conducted on the data based on the snap shot of the database and specified final analysis approaches, there will be no separate statistical analysis plan (SAP).

9.5.1. Data Monitoring Committee

This study will use an internal review committee (IRC). The IRC will be responsible for ongoing monitoring of safety of participants in the study according to the charter. Members of the IRC will be qualified and experienced in reviewing and interpreting clinical study data. They will be external to and independent of the study team, and unblinded to treatment. The recommendations made by the IRC to alter the conduct of the study will be forwarded to Pfizer for final decision. This will not include the members of the study team. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. Pfizer may perform an interim analysis which may include safety and efficacy. If an interim analysis is performed, the same IRC will be used. Details of the IRC are described in the IRC charter.

CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative defined as parent or legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

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

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in study completion guidelines.

10.1.8. Study and Site Closure

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

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

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

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

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

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

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

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the Schedule of Activities (SoA) section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 11. Protocol-Required Laboratory Assessments

Hematology[a]	Chemistry[a]	Urinalysis[a]	Other
Hemoglobin Hematocrit RBC count and indices (MCH, MCHC, MCV, RBC Morphology) Reticulocyte count Platelet count WBC count with differential Total neutrophils (%, Abs) Eosinophils (%, Abs) Monocytes (%, Abs) Basophils (%, Abs) Lymphocytes (%, Abs)	BUN/urea & Creatinine Cystatin C Glucose (fasting) Calcium Sodium Potassium Chloride Total CO2 (bicarbonate) AST, ALT GGT Total, Indirect & Direct Bilirubin Alkaline phosphatase Lactate Dehydrogenase Uric acid Albumin Total protein Creatinine Kinase[f]	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[d]	At screening only: FSH[b] HIV HBsAg HBcAb HbsAb[c] HBV DNA test (reflex tested in countries where required by local regulations) HCV Ab HCV RNA[e] IGRA or PPD (if pplicable) VZV IgG Ab Coagulation Panel (as part of Hematology) -aPTT -PT/INR At visits in SoA: Pregnancy test (β-hCG)[g] Skin swabs for herpetiform rash[h] CCI [redacted] Lipid Panel[i] -Total Cholesterol -LDL -HDL -Triglycerides

Abbreviations: Ab = antibody; Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; Chemokine (C-C motif) ligand 17; CO2 = carbon dioxide; CCI [redacted] IgG = immunoglobulin G; FSH = follicle-stimulating hormone; GGT = Gamma Glutamyl Transferase; HBcAb = Hepatitis B Core Antibody; HBsAb = Hepatitis B Surface Antibody; HBsAg = Hepatitis B Surface Antigen; HCV Ab = Hepatitis C Virus Antibody; HCV RNA = Hepatitis C Virus Ribonucleic Acid; HDL = high density lipoprotein; HIV = Human Immunodeficiency Virus; CCI [redacted]; IGRA = Interferon Gamma Release Assay; INR = International Normalized Ratio; CCI [redacted] LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PPD = purified protein derivative; qual = qualitative; RBC = red blood cell; CCI [redacted]; VZV = Varcilla Zoster Virus; WBC = white blood cell.

a. Safety labs include hematology, chemistry and urinalysis.
b. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
c. Hepatitis B Surface Antibody (HBsAb) will be reflex tested if participants are positive for HBsAb. HBsAB will also be tested for all participants when required by country-specific local regulations. See country-specific details in Appendix 8.
d. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
e. Hepatitis C Viral RNA (HCV RNA) will be reflex tested if participants are positive for HCVAb.
f. Fractionation only if CK is elevated >3 x ULN.
g. Serum pregnancy testing at screening is required for women of childbearing potential (WOCBP). Serum will also be collected at Day 1 to test pregnancy, the results of which may be received after Day 1. Pregnancy tests may also be repeated more frequently as per request of IRBs/ECs or if required by local regulations women of child-bearing potential. Urine pregnancy tests will be used at Day 1 and at other visits.
h. In cases of suspected herpetiform rash (eg, suspected herpes zoster and herpes simplex).
i. Lipid Profile Panel requires at least an 8 hour fast.

Investigators must document their review of each laboratory safety report.

Laboratory results that could un-blind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

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

10.3.1. Definition of AE

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

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

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

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from

baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

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

Assessment of Intensity

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

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

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as

described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- 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. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

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

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

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate study intervention(s):

- Refrain from donating sperm.

  PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any study intervention(s). In addition, a second effective method of contraception, as described below, must be

used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

OR

- Is a WOCBP and is abstinent from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and be the preferred and usual lifestyle of the participant.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:

    - A postmenopausal state is defined as age 60 years or older or no menses for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).

- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device (IUD).

3. Intrauterine hormone-releasing system (IUS).

4. Bilateral tubal occlusion.

5. Vasectomized partner.

Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent (must be used in combination with another effective method; see below)

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - oral;

   - intravaginal;

   - transdermal;

   - injectable.

2. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - oral;

   - injectable.

Effective Methods

1. Male or female condom with or without spermicide.

2. Cervical cap, diaphragm, or sponge with spermicide.

3. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

Collection of Pregnancy Information

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-06700841 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

[redacted]

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Re-challenge Guidelines

Potential Cases of Drug-Induced Liver Injury

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

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

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

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

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

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 msec.
- New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset left bundle branch block (QRS >120 msec).
- New-onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
    - In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
    - In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
    - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and

monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes). • Type II second-degree (Mobitz II) AV block. • Complete (third-degree) heart block.
ECG Findings That Qualify as Serious Adverse Events
• Change in pattern suggestive of new myocardial infarction. • Sustained ventricular tachyarrhythmias (>30 seconds' duration). • Second- or third-degree AV block requiring pacemaker placement. • Asystolic pauses requiring pacemaker placement. • Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion. • Ventricular fibrillation/flutter. • At the discretion of the investigator, any arrhythmia classified as an adverse experience.
The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Country-Specific Requirements

Exclusion Criteria #20

In countries where required, all participants may undergo testing for Hepatitis B Virus (HBV) surface antigen (HBsAg), HBV core antibody (HBcAb), and HBV surface antibody (HBsAb). The testing will be performed in Clinical Laboratory Improvement Amendments (CLIA) certified Laboratory or similar.

Participants who are negative for all three serology tests may be eligible.

Participants who are HBsAg positive will be excluded.

Participants who have negative HBsAg, positive HBcAb, and negative HBsAb will be excluded.

Participants who have negative HBsAg, negative HBcAb and positive HBsAb and provide a documentation of prior HBV vaccination, may be eligible for the study and will not require HBV DNA monitoring during the study.

Participants who have negative HBsAg, negative HBcAb and positive HBsAb without documentation of prior HBV vaccination, and participants who have negative HBsAg, positive HBcAb and positive HBsAb are required to undergo HBV DNA testing

- If detectable HBV DNA, participants will be excluded; and
- If not detectable HBV DNA, participants may be eligible. If enrolled, HBV DNA will be assessed at Week 6 also.

10.9. Appendix 9: Diagnosis Criteria for Atopic Dermatitis

Per Inclusion Criterion #2, a participant is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.[26]

Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

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

10.10. Appendix 10: Prohibited Concomitant Medications

The following medications & procedures are prohibited until the last Follow-up visit, unless stated otherwise. If a participant receives prohibited medication or procedure, the investigator should either 1) ask the participant to stop IP immediately and schedule ET visit as soon as possible with follow-up visits per Schedule of Activities or 2) contact Sponsor Clinician or Sponsor Medical monitor to determine if participant may stay in the study. This will be based on the Table below. Medications listed below are prohibited even if used for a different indication than noted below.

Drug Classes and/or Drugs and/or Procedures	Timeframe of Restriction Prior to Screening Visit	If taken, then	
		Stop IP, Proceed to ET and F/UP	Contact Sponsor
Light therapy Narrow-band Ultraviolet B light (UVB) Broadband phototherapy Ultraviolet A light (UVA) Excimer laser (308 nm)	1 month		X
Any cell-depleting agents, including but not limited to Rituximab Alemtuzumab [CamPath®] Alkylating agents [eg, cyclophosphamide or chlorambucil] Total lymphoid irradiation, etc	6 months or 5 half-lives, whichever is longer OR until lymphocyte count returns to normal, whichever is longer	X	
Anti-AD or psoriasis biologics Efalizumab (Raptiva®) Certolizumab pegol (Cimzia®) Alefacept (Amevive®) Duplimab Infliximab (Remicade®) and biosimilar Adalimumab (Humira®) and biosimilar	2 months	X	
Ustekinumab (Stelara®) Secukinumab (Cosentyx) Ixekizumab (Taltz) Brodalumab (Siliq®) Guselkumab (Tremfya®) Tildrakizumab Risankizumab	3 months	X	
Etanercept (Enbrel®) and biosimilar	1 month	X	
Systemic treatments other than biologics that could affect AD, including but not limited to: oral or injectable (eg, intraarticular, intramuscular, or intravenous) corticosteroids retinoids methotrexate cyclosporine fumaric acid derivatives sulfasalazine hydroxycarbamide (hydroxyurea)	2 weeks	X	

Drug Classes and/or Drugs and/or Procedures	Timeframe of Restriction Prior to Screening Visit	If taken, then	
		Stop IP, Proceed to ET and F/UP	Contact Sponsor
azathioprine intramuscular gold Otezla (Apremilast®) Any herbal medicine Other systemic treatments known to possibly worsen AD unless on a stable dose for >12 weeks (eg lithium, β-blockers, angiotensin-converting enzyme inhibitors, synthetic anti-malarials, anticonvulsants, antidepressants, cyclosporine, testosterone/estrogens, imiquimod, calcium channel blockers, etc)			
Tofacitinib Any other oral JAK inhibitors	1 month or 5 half–live whichever is longer	X	
Topical treatments applied on AD areas treated with IP and which could affect AD. If applied to other areas not treated with IP, this is allowed. Including but not limited to: Corticosteroids Tars Keratolytics Anthralin vitamin D analogues retinoids	2 weeks	X	
sunscreens, moisturizers or non-medicated emollients	2 weeks		X
Topical AD medication (eg Eucrisa®)	1 month or 5 half–live whichever is longer	X	
Any topical JAK inhibitors	1 month or 5 half–live whichever is longer		X
CYP3A4, 5, 7 Inhibitors HIV antivirals: delavirdine (Rescriptor®) indinavir (Crixivan®) nelfinavir (Viracept®) ritonavir (Kaletra®, Norvir®) saquinavir (Fortovase®) cimetidine (Tagamet®) ciprofloxacin (Cipro®) clarithromycin (Biaxin®, Prevpac®) diethyl-dithiocarbamate diltiazem (Cardizem®, Tiazac®) fluconazole (Diflucan®) fluvoxamine (Luvox®) gestodene (Femodene®, Melodene®, Minulette®,	1 month or 5 half-lives, whichever is longer	X	

Drug Classes and/or Drugs and/or Procedures	Timeframe of Restriction Prior to Screening Visit	If taken, then	
		Stop IP, Proceed to ET and F/UP	Contact Sponsor
Mirelle®, Triodene ED®) grapefruit juice and marmalade itraconazole (Sporanox®) ketoconazole (Nizoral®) Itraconazole Erythromycin protease inhibitors verapamil diltiazem			
Amiodarone	10 months	X	
CYP3A Inducers barbiturates 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®)	1 month or 5 half-lives, whichever is longer		X
Strong P-gp inhibitors Quinidine	1 month or 5 half-lives, whichever is longer	X	
Substrates of MDR1 Digoxin	1 month or 5 half-lives, whichever is longer	X	
Substrates of OCT2/MATE Dofetilide	1 month or 5 half-lives, whichever is longer	X	
Vaccination with live or attenuated live vaccine (See Section 5.3.4)	6 weeks	X	

10.11. Appendix 11: 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

10.12. Appendix 12: Patient Reported Outcomes

10.12.1. Peak Pruritis Numerical Severity Scale (PP-NRS)

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

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	1
N itch										Worst itch imaginable

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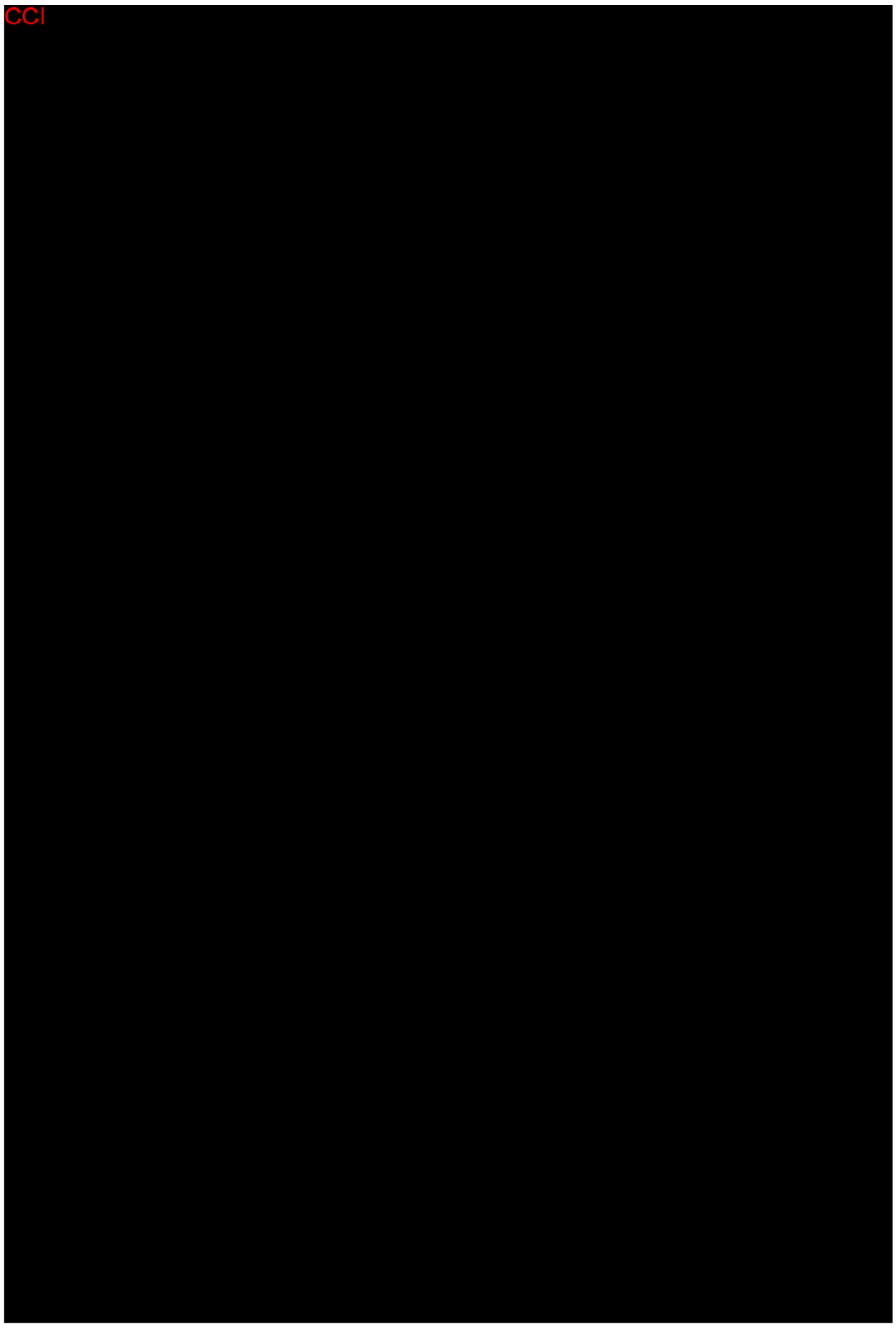
[redacted]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10.12.3. Patient-Oriented Eczema Measure (POEM)

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Total POEM Score (Maximum 28): _____

10.12.4. Dermatology Life Quality Index (DLQI)/Children's DLQI

DERMATOLOGY LIFE QUALITY INDEX

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

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

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

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

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

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

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[redacted]

10.13. Appendix 13: C-SSRS – Columbia Suicide Severity Rating Scale

C-SSRS for Screening and Baseline Visits:

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** ____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

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

C-SSRS for post-baseline visits

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.14. Appendix 14: eGFR Calculations

The estimated GFR (eGFR) will be calculated using the 2 sets of equations developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which utilize serum creatinine (SCr) and serum Cystatin C (S Cystatin C) respectively.

$CKD\text{-}EPI_{2009Scr}$

If female and SCr is ≤0.7 mg/dL:

- GFR (mL/min/1.73 m^2) = 144 x $(Scr/0.7)^{-0.329}$ x 0.993^{age} (x 1.159, if black).

If female and SCr is >0.7 mg/dL:

- GFR (mL/min/1.73 m^2) = 144 x $(Scr/0.7)^{-1.209}$ x 0.993^{age} (x 1.159, if black).

If male and SCr is ≤0.9 mg/dL:

- GFR (mL/min/1.73 m^2) = 141 x $(Scr/0.9)^{-0.411}$ x 0.993^{age} (x 1.159, if black).

If male and SCr is >0.9 mg/dL:

- GFR (mL/min/1.73 m^2) = 141 x $(Scr/0.9)^{-1.209}$ x 0.993^{age} (x 1.159, if black).

$CKD\text{-}EPI_{2012cys}$

If female and Scys is ≤0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-0.499}$ x 0.996^{age} x 0.932.

If female and Scys is >0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-1.328}$ x 0.996^{age} x 0.932.

If male and Scys is ≤0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-0.499}$ x 0.996^{age}.

If male and Scys is >0.8 mg/L:

- GFR (mL/min/1.73 m^2) = 133 x $(Scys/0.8)^{-1.328}$ x 0.996^{age}.

10.15. Appendix 15: Abbreviations

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

Abbreviation	Term
AA	alopecia areata
Ab	antibody
Abs	absolute
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours after dose
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{tau}	area under the concentration-time curve during any dosing interval at steady state
AZA	azathioprine
CCI	[redacted]
BCG	bacille Calmette-Guerin
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CAT	computerized axial tomography
C_{av}	average concentrations
CD	Crohn's disease
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed concentration
CMV	Cytomegalovirus
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia suicide severity rating scale
CT	clinical trial

Abbreviation	Term
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index
EBV	Epstein Barr virus
EC_{50}	Half-maximal effective concentration
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ePRO	electronic patient reported outcome
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
F	bioavailibility
FDA	Federal Drug Administration
FSH	follicle-stimulating hormone
Fu	fraction unbound
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B visrus
HCVAb	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
CCI [redacted]	[redacted]
IB	investigator's brochure
IC_{50}	half-maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IFN-α	Interferon alpha
IGA	Investigator's Global Assessment
CCI [redacted]	[redacted]

Abbreviation	Term
IgG	immunoglobulin G
IGRA	Interferon Gamma Release Assay
IL-	interleukin
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
CCI [redacted]	[redacted]
IP manual	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantification
JAK	Janus Kinase
LDL	low density lipoprotein
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
Mg	milligram
MMP12	Matrix metalloproteinase 12
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
Msec	millisecond
MTX	methotrexate
N/A	not applicable
NOAEL	no-observed-adverse-effect level
NRS	Numerical Rating Scale
CCI [redacted]	[redacted]
PASI	Psoriasis area and severity index
PCD	primary completion date
PCP	primary care physician
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PG	polypropyle glycol
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
PI	principal investigator
PK	pharmacokinetic(s)

Abbreviation	Term
POEM	Patient Oriented Eczema Measure
PPD	Purified Protein Derivative
PP-NRS	Peak Pruritus Numerical Rating Scale
PR	pulse rate
PRO	Patient reported outcomes
CCI [redacted]	[redacted]
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QFT-G	QuantiFERON-TB Gold Test
QFT-GIT	QuantiFERON-TB Gold In-tube Test
QT	Q wave interval
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
Qual	qualitative
QW	once a week
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
S Cystatin C	serum Cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SSID	subject study identification n
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
t1/2	half-life
CCI [redacted]	[redacted]
TB	tuberculosis
TBili	total bilirubin
TdP	Torsade de Pointes
TEAE	treatment emergent adverse events
Tmax	time taken to reach the maximum concentration
TNF	tumor necrosis factor
TYK2	Tyrosine Kinase 2
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
UVA	ultraviolet A light
Vss	volume of distribution

Abbreviation	Term
UVB	ultraviolet B light
VZV	varicella zoster virus
WBC	white blood cell
WOCBP	woman of childbearing potential

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