TITLE PAGE

Protocol Title: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY INVESTIGATING THE EFFICACY AND SAFETY OF PF-04965842 CO-ADMINISTERED WITH BACKGROUND MEDICATED TOPICAL THERAPY IN ADOLESCENT PARTICIPANTS 12 TO <18 YEARS OF AGE WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Protocol Number: B7451036

Amendment Number: 4

Compound Number: PF-04965842

Study Phase: Phase 3

Short Title: Study evaluating PF-04965842 in adolescents with moderate-to-severe atopic dermatitis on background medicated topical therapy

Acronym: JADE TEEN

Sponsor Name: Pfizer, Inc.

Legal Registered Address: 235 East 42nd Street, New York, NY 10017-5755, USA

Regulatory Agency Identifier Number(s)

Registry	**ID**
IND	CCI [redacted]
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Approval Date: 26 August 2019

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 04	26-Aug-2019
Amendment 03	03-May-2019
Amendment 02	15-Apr-2019
Amendment 01	05-Dec-2018
Original Protocol	13-Sep-2018

Amendment 04 (26-Aug-2019)

Overall Rationale for the Amendment:

Section # and Name	Description of Change		Brief Rationale
Multiple Sections (See Overall Rationale for Amendments 01, 02, 03, as noted below)	Protocol updates based on Country Specific Amendments 01, 02 and 03		Regulatory authorities and Ethic Committees in certain countries have requirements which are not applicable globally.
Schedule of Activities	A note has been added to clarify that the Dermatitis Family Impact Questionnaire (DFI) is required only when a parent or caregiver is present during the visit.		A subject may provide their own transportation to a clinic visit; whereas, a parent/caregiver does not accompany them.
Section 2.2.4 Population of Pharmacokinetics Section 5.1 Inclusion Criteria Inclusion Criterion #6 Section 9.5.1 Data Monitoring Committee (DMC)	Body weight criterion updated to ≥25 kg.		Pharmacokinetic (PK) simulations were performed to evaluate if the current inclusion criterion of body weight of ≥40 kg could be lowered. The efficacy- and safety-related pharmacological effects of JAK1 inhibitors are considered to be driven by AUC. Therefore, AUC values were simulated for patients of various body weights (to as low as 25 kg) based on available PK data from Phase 1, Phase 2 and the completed Phase 3 study B7451012, which included adolescent patients. The results showed that the exposures in adolescent patients were similar to those in adult patients. In addition, for both 100 mg and 200 mg QD doses, the increases in simulated AUC and Cmax with a decrease in body weight from 70 kg to 25 kg were predicted to be

			approximately 52% and 85%, respectively, which are not considered clinically significant.
Section 5.1 Inclusion Criteria Inclusion Criterion #2, first bullet	The duration for diagnosis of chronic moderate to severe AD has been deleted.		The duration of AD diagnosis has not been associated with the magnitude of treatment effect of other AD therapies. Given other current inclusion criteria, such as the requirement for recent inadequate response to topical therapies and/or treatment with (or consideration for) systemic therapies, deletion of this inclusion criterion is not anticipated to affect the study results.
Section 5.1 Inclusion Criteria Inclusion Criterion #2, second bullet	Study participants who are candidates for systemic therapy have been added to this inclusion criterion.		Patients with moderate-to-severe AD who are considered by their treating physicians to be candidates for systemic AD therapy based on the patients' unique circumstances, such as treatment history and likelihood of adverse reactions, but have not actually received systemic AD therapies may also be suitable candidates for this study.
Section 5.1 Inclusion Criteria Inclusion Criterion #2, last bullet	Moderate-to-severe AD (must fulfil all of the following criteria: affected BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$16, and Peak Pruritus NRS $\geq$ 4 at the baseline visit).		This revision clarifies that these criteria must all be met at the baseline visit for the subject to be considered to have moderate-to-severe AD.
Section 5.2 Exclusion Criterion #14 Section 5.3.3.1 Participant Specific Recommendations Section 8.2.Varicella Zoster Virus (VZV) IgG Antibody (Ab) Testing Section 10.2, Table 6, footnote #6 Protocol Required Safety Laboratory Assessments	Subjects with documented prior varicella zoster (VZV) infection (chickenpox) will not require additional serology testing for VZV IgG antibody.		Subjects who previously experienced primary varicella zoster infection (chickenpox) will be immunized to VZV; therefore, serological testing for VZV IgG antibody will not be required.

Section 5.2 Exclusion Criterion #6	Criterion restricting helminth infection have been removed		The criterion on helminth infection was copied by mistake from another Phase 3 protocol B7451029, which involves dupilumab as a randomized treatment arm. This exclusion criterion was included in the B7451029 protocol because the dupilumab product label has a warning stating that whether dupilumab will influence the immune response against helminth infections is unknown. This warning is not applicable to PF-04965842, and is absent in other PF-04965842 protocols that do not include dupilumab administration. Consistent with the other PF-04965842 protocols and the risk profile of PF-04965842 as described in the investigator brochure, this exclusion criterion is not applicable to study B7451036 will be deleted from the B7451036 protocol.
Section 5.2 Exclusion Criterion #18	Removed criteria pertinent to the European Voluntary Harmonisation Procedure (VHP)		This study is not submitting to the VHP for clinical trial applications in Europe.
Section 5.2 Exclusion Criterion #19	Exclusion criteria regarding QT/QTc prolongation have been removed.		In the completed thorough QTc study, PF-04965842 was not associated with a clinically relevant effect on QTc interval. Since QTc prolongation is no longer considered a potential risk for PF-04965842, the current exclusion criteria for QTcF interval and concomitant medications that prolong the QT/QTcF interval are unnecessary.
Section 10.5 Appendix 5 Monitoring and Discontinuation Criteria	'Confirmed Pregnancy' has been added to the list of Discontinuation Criteria, based on the notation for withdrawal in Section 8.2.10.		Discontinuation Criteria in Section 10.5 was updated to be consistent with requirement for withdrawal from study intervention noted in Section 8.2.10 *Pregnancy Testing*.
Multiple Sections	Protocol updates based on Protocol Administrative Clarification Letters issued: 01-Nov-2018, 29-Nov-2018, 13-Mar-2019 and 11-Jun-2019		When a protocol requires substantial changes, such is this case, the administrative changes described in the clarification letters must be incorporated into the amended protocol.

Amendment 03 (03-May-2019) Germany-specific

Overall Rationale for the Amendment:

Section # and Name	Description of Change		Brief Rationale
Section 1.3 Schedule of Activities; Section 8.2.2 Vital Signs 10.8. Appendix 8: Country-specific Requirements	For Germany only: Temperature monitoring has been added as part of the vital signs measurements		In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) required body temperature monitoring as part of vital sign measurements for surveillance of potential infection, since infection is a potential risk for PF-04965842.
Section 5.1 Inclusion Criteria Inclusion Criterion #2	Moderate-to-severe AD (must fulfil all of the following criteria: affected BSA ≥ 10%, IGA ≥ 3, EASI ≥16, and Peak Pruritus NRS ≥ 4 at the baseline visit).		In accordance with the request from BfArM, this revision clarifies that these criteria must all be met at the baseline visit for the subject to be considered to have moderate-to-severe AD.
Section 1.3 Schedule of Activities; Section 5.2 Exclusion Criterion 10; Section 8.2.3 Chest Imaging; Section 8.2.4 Tuberculosis Testing 10.8. Appendix 8: Country-specific Requirements	For Germany only: The recommendation to perform chest X-ray (or computed tomography) for screening in adolescents has been removed. In addition to the use of the QFT-G test, if the use of chest imagining is considered medically necessary to exclude active TB, chest MRI may be performed at the discretion of the Principal Investigator.		German medical guideline indicates that chest X-ray is not a suitable primary screening method for TB in adolescents due to the sensitivity of adolescents to radiation. Chest X-ray should only be used selectively to clarify immunodiagnostic test results. Subjects who have pulmonary symptoms or a positive QFT-G test should be excluded in the screening process. If chest imaging is needed to exclude pulmonary TB, MRI, which does not involve ionizing radiation, can be used instead of chest X-ray.

Amendment 02 (15-Apr-2019) UK-specific

Overall Rationale for the Amendment:

Section # and Name	Description of Change		Brief Rationale
Section 1.3 Schedule of Activities; Section 8.2.2 Vital Signs 10.8. Appendix 8: Country-specific Requirements	For United Kingdom (UK) only: Temperature Monitoring has been added as part of the Vital Signs measurements		The Medicines and Healthcare Products Regulatory Agency (MHRA) requires body temperature monitoring as part of routine vital sign measurements for surveillance of potential infection, since infection is potential risk for PF-04965842.

Section 10.5 Appendix 5 Monitoring and Discontinuation Criteria	'Confirmed Pregnancy' has been added to the list of Discontinuation Criteria, based on the notation for withdrawal in Section 8.2.10.		MHRA requested that 'Pregnancy' be listed as part of the Discontinuation Criteria in Section 10.5 based on the requirement for withdrawal from study intervention noted in Section 8.2.10 *Pregnancy Testing*.

Amendment 01 (05-Dec-2018) Japan/Taiwan-specific

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities; Section 5.2 Exclusion Criteria; Section 8.2.8.1 Hepatitis Testing; Appendix 2 Clinical Laboratory Tests 10.8. Appendix 8: Country-specific Requirements	For Japan and Taiwan only: Based upon hepatitis B serology at screening per Section 8.2.8.1, reflex testing for hepatitis B DNA will be performed. Participants with results negative for DNA or below LLQ may be randomized but will have HBV DNA repeated at Week 12 (End of Treatment/Early Termination).	Similar to China, other countries in Asia, such as Japan and Taiwan, have a high prevalence of hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (HBcAb) positive, and hepatitis B surface antibody (HBsAb) positive serology. Therefore, Taiwan will adopt the same requirements and Japan will adopt similar requirements as those outlined for China to monitor the risk of hepatitis B reactivation
Section 1.3: Schedule of Activities; Section 5.2 Exclusion Criteria; Section 8.2.4 Tuberculosis Testing; Appendix 2 Clinical Laboratory Tests 10.8. Appendix 8: Country-specific Requirements	For Japan only: The option of T-SPOT®.*TB* test was added as an alternative assessment for tuberculosis at screening.	Based on local practices for tuberculosis testing, if performance of QuantiFERON®- TB Gold In-Tube (QTF-G) testing is not possible, T-SPOT®.*TB* test performed at a local laboratory is acceptable as the screening TB test.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY INVESTIGATING THE EFFICACY AND SAFETY OF PF-04965842 CO-ADMINISTERED WITH BACKGROUND MEDICATED TOPICAL THERAPY IN ADOLESCENT PARTICIPANTS 12 TO <18 YEARS OF AGE WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

Short Title: Study evaluating PF-04965842 in adolescents with moderate-to-severe atopic dermatitis on background medicated topical therapy

Rationale:
PF-04965842 is a JAK1 inhibitor and is being developed as an oral treatment for patients with moderate-to-severe atopic dermatitis (AD).

Objectives, Estimands and Endpoints

Primary Objectives	Primary Endpoints
• To assess the efficacy of PF-04965842 compared with placebo when co-administered with background medicated topical therapy in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	Co-primary endpoints • Response based on the Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5 point scale) and a reduction from baseline of ≥2 points at Week 12; • Response based on the Eczema Area and Severity Index ≥75% improvement from baseline (EASI-75) response at Week 12.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of PF-04965842 co-administered with background medicated topical therapy on additional efficacy endpoints and patient reported outcomes over time in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	Key Secondary Endpoints • Response based on at least 4 points improvement in the Peak Pruritus NRS from baseline at Weeks 2, 4, and 12; • Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at Week 12. Secondary Efficacy Endpoints • Response based on at least 4 points improvement in the Peak Pruritus NRS from baseline at all scheduled

	time points other than Weeks 2, 4 and 12; • Time to achieve at least 4 points improvement in the Peak Pruritus NRS from baseline by Day 15; • Response based on the EASI-75 at all scheduled time points except Week 12; • Response based on the IGA of clear (0) or almost clear (1) and 2 point reduction from baseline at all scheduled time points except Week 12.
Immunogenicity Sub-Study Objective: • To evaluate the effect of PF-04965842 on the immunogenicity to Tdap vaccine in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	Immunogenicity sub-study endpoint • Mean fold increase from baseline at 4 weeks post-vaccination in concentrations of IgG against: • Tetanus toxoid; • Diphtheria toxoid; • Pertussis toxoid; • Pertactin (PRN); • Filamentous hemagglutinin (FHA); • Fimbriae types 2 and 3 (FIM).
Safety Objective	Safety Endpoints
• To evaluate the safety and tolerability of PF-04965842 co-administered with background medicated topical therapy in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	• Incidence of treatment emergent adverse events; • Incidence of SAEs; • Incidence of AEs leading to discontinuation; • The incidence of clinical abnormalities and change from baseline in clinical laboratory values, ECG measurements, and vital signs.
PK Objective	PK Endpoint
• To evaluate the PK of PF-04965842 in adolescent participants 12 to <18 years of age with moderate-	• Plasma concentrations of PF-04965842 in adolescent participants 12 to <18 years of age

to-severe AD.	with moderate-to-severe AD.

The primary estimand of the main study is a composite estimand (accounting for both treatment adherence and response), defined according to the primary objective and is in alignment with the primary endpoint. The secondary estimand of this study is the hypothetical estimand, which estimates the effect as if all patients maintain their randomized treatment.

No specific estimands are defined for the immunogenicity analyses (see Appendix 11).

Overall Design:
This is a randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study to evaluate the efficacy and safety of PF-04965842 in adolescent participants 12 to <18 years of age with moderate-to-severe AD. Participants will be screened within 28 days prior to the first dose of study intervention to confirm study eligibility. Approximately 225 participants will be randomized in a 1:1:1 ratio to receive once daily PF-04965842 at 200 mg, 100 mg, or placebo for 12 weeks.

This study includes an immunogenicity sub-study integrated into the last 4 weeks of the main study treatment period. At Week 8, up to approximately 90 participants (up to approximately 30 in each treatment arm) who have completed 8 weeks of treatment with study intervention will receive a tetanus, diphtheria and acellular pertussis combination vaccine (Tdap), and collection of blood samples for the evaluation of immunogenicity at Weeks 8 and 12. Participants of this sub-study will complete all other protocol-specified procedures in the main study.

At the end of the 12-week study treatment, qualified participants completing the study will have the option to enter the long-term extension (LTE) study B7451015. Participants discontinuing early from the study will undergo a 4 week follow-up period.

Disclosure Statement:
This is a Parallel Treatment study with 3 Arms that is Investigator, Sponsor and Participant blinded.

Number of Participants:
Approximately 225 participants will be randomized in the study; of those up to approximately 90 participants will participate in the immunogenicity sub-study between Week 8 and Week 12.

Intervention Groups and Duration:
Eligible participants will be randomized into 3 intervention groups in the main study:

Group 1 (N=75): 200 mg PF-04965842 once daily (QD) for 12 weeks (Sub-study: N=up to 30, Tdap vaccination at Week 8)

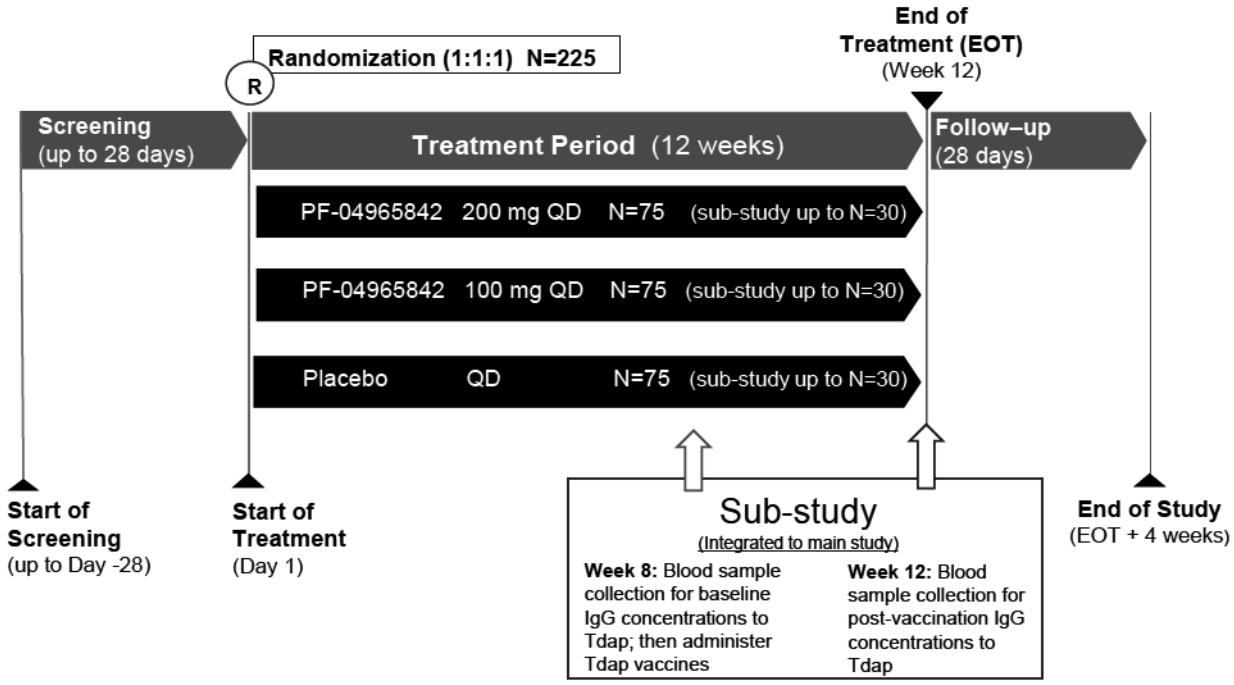
Group 2 (N=75): 100 mg PF-04965842 QD for 12 weeks (Sub-study: N=up to 30, Tdap vaccination at Week 8)

Group 3 (N=75): placebo QD for 12 weeks (Sub-study: N=up to 30, Tdap vaccination at Week 8)

The total duration of participation in the study, including the integrated sub-study, is up to 20 weeks, including up to 4 weeks for screening, 12 weeks study intervention and a follow-up period of 4 weeks after study intervention (for those participants that do not enter the LTE study).

Data Monitoring Committee: Yes

1.2. Schema



Note: The sample size for the immunogenicity sub-study is up to approximately 30 participants in each arm.

1.3. Schedule of Activities (SoA)

	Screening	Intervention Period							Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1** **Week 0** **Baseline**	**Day 8** **Week 1** **(by Phone)**	**Day 15** **Week 2**	**Day 29** **Week 4**	**Day 43** **Week 6** **(by Phone)**	**Day 57** **Week 8**	**Day 85** **Week 12** **(EOT/ET)**	**Day 113** **Week 16** **(EOS)**	Visit 9 is 4 weeks after last dose in case of early study termination
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	
Visit Window (days)	**None**	**None**	**±1**	**±1**	**±2**	**±3**	**±3**	**±3**	**±3**	
Enrollment Procedures										
Informed consent/assent	X									
Register subject using IRT	X									
Inclusion and exclusion criteria	X	X								
Demographics, Medical History, Tobacco and Alcohol History, AD Disease History and prior AD treatments	X									
Review Prior/Concomitant Medications & Treatments	X	X	X	X	X	X	X	X	X	
Dispense eDiary and instruct participants on use	X									

	Screening	Intervention Period							Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1** **Week 0** **Baseline**	**Day 8** **Week 1** **(by Phone)**	**Day 15** **Week 2**	**Day 29** **Week 4**	**Day 43** **Week 6** **(by Phone)**	**Day 57** **Week 8**	**Day 85** **Week 12** **(EOT/ET)**	**Day 113** **Week 16** **(EOS)**	Visit 9 is 4 weeks after last dose in case of early study termination
Instruct participants on washout of pre-baseline medications (if applicable)	X									See inclusion criteria #3 (Section 5.1) and exclusion criteria #16 (Section 5.2)
Train participants on use of background topical therapy for AD and daily recording in eDiary	X	X	X	X	X	X	X	X		See Section 6.5.1
Provide Patient Emergency Contact Card	X									
Medical Procedures										
Complete physical examination	X	X						X		See Section 8.2.1
Targeted Physical Exam				X	X		X		X	
Vital Signs (pulse rate, blood pressure, temperature)	X	X		X	X		X	X	X	See Section 8.2.2 Temperature collection applies to Germany and UK only. Temperature data will be recorded in source documents only.
Weight	X	X						X		See Section 8.2.1
Height	X							X		See Section 8.2.1

	Screening	Intervention Period							Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1** **Week 0** **Baseline**	**Day 8** **Week 1** **(by Phone)**	**Day 15** **Week 2**	**Day 29** **Week 4**	**Day 43** **Week 6** **(by Phone)**	**Day 57** **Week 8**	**Day 85** **Week 12** **(EOT/ET)**	**Day 113** **Week 16** **(EOS)**	Visit 9 is 4 weeks after last dose in case of early study termination
Chest Imaging / X-Ray	X									Recommended but not mandatory For Germany only: If chest imaging is considered medically necessary, MRI may be performed.
ECG (12-lead)	X	X		X	X		X	X	X	Central reading
Laboratory Procedures										
Serum chemistry and hematology (including coagulation panel)	X	X		X	X		X	X	X	See Appendix 2 See Section 8.2.8 for guidance on abnormal lab results
Lipid Panel		X			X			X	X	After 8-hour fast, when possible
CCI [redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]		[redacted]		[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Urinalysis	X	X		X	X		X	X	X	See Appendix 2

	Screening	Intervention Period							Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Baseline**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 43 Week 6 (by Phone)**	**Day 57 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 9 is 4 weeks after last dose in case of early study termination
Serum pregnancy test	X									Required for all WOCBP
Urine Pregnancy Test (conducted at study site)		X		X	X		X	X	X	
Blood Samples Collection for Viral Studies		X			X			X		Only analyzed on suspected viral infection/reactivation.
HIV Testing	X									
Hepatitis B (HBsAg, HBsAb and HBcAb) and Hepatitis C (HCV Ab, HCV RNA)	X									See Section 8.2.8.1
HBV DNA	X							X		Only for China, Taiwan, Japan and countries where HBV DNA testing is required (see Section 8.2.8.1 for country-specific guidance for assessment)
Varicella Zoster Virus IgG Ab	X									See Section 8.2.8.2
Tuberculosis Test	X									See Section 5.2 and Section 8.2.4

	Screening	Intervention Period							Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Baseline**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 43 Week 6 (by Phone)**	**Day 57 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 9 is 4 weeks after last dose in case of early study termination
Pharmacokinetic										
Pharmacokinetic Blood Sampling (Pre-dose)							X			22 hours after last dose (±30 min)
Pharmacokinetic Blood Sampling (Post-dose)								X		2 hours post-dose (±30 min)
Study Treatment										
Randomization		X								
Drug dispensing		X			X		X			
Drug accountability				X	X		X	X		
Study intervention treatment		X----------						----------X		
Review eDiary to assess treatment compliance			X	X	X	X	X	X		
Assess eligibility for B7451015								X		
Application of non-medicated topical therapy at home	X----------								----------X	At least 7 days before Day 1 (see Section 6.5.1)

	Screening	Intervention Period							Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Baseline**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 43 Week 6 (by Phone)**	**Day 57 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 9 is 4 weeks after last dose in case of early study termination
Application of medicated topical therapy at home		X----------X								See Section 6.5.1
Clinical Assessments										
Fitzpatrick Skin Type Assessment		X								
Investigator's Global Assessment (IGA)	X	X		X	X		X	X	X	
Eczema Area and Severity Index (EASI)	X	X		X	X		X	X	X	
SCORing Atopic Dermatitis (SCORAD)	X	X		X	X		X	X	X	
C-SSRS, SBQ-R, PHQ-8	X									
Patient-reported Outcomes (PRO)										
Peak Pruritus Numerical Rating Scale (NRS)	X------X	X----------X			X		X	X	X	
Frequency of Pruritus NRS	X------X	X----------X			X		X	X	X	
CCI [redacted]	[redacted]	[redacted]			[redacted]		[redacted]	[redacted]	[redacted]	

	Screening	Intervention Period							Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1 Week 0 Baseline**	**Day 8 Week 1 (by Phone)**	**Day 15 Week 2**	**Day 29 Week 4**	**Day 43 Week 6 (by Phone)**	**Day 57 Week 8**	**Day 85 Week 12 (EOT/ET)**	**Day 113 Week 16 (EOS)**	Visit 9 is 4 weeks after last dose in case of early study termination
Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)	X------X	X----------X								
Patient Global Assessment (PtGA)		X		X	X		X	X	X	
Children's Dermatology Life Quality Index (CDLQI)		X		X	X		X	X	X	
Patient-Oriented Eczema Measure (POEM)		X		X	X		X	X	X	
Dermatitis Family Impact Questionnaire (DFI)		X		X	X		X	X	X	Required when a parent or caregiver is present during the visit
Hospital Anxiety and Depression Scale (HADS)		X		X	X		X	X	X	
EQ-5D-Y		X		X	X		X	X	X	
Peds-FACIT-F		X						X	X	
Safety										
Serious and non-serious adverse event monitoring	X	X	X	X	X	X	X	X	X	
Contraception Check	X	X	X	X	X	X	X	X	X	Required for all females

	Screening	Intervention Period							Follow-up	Notes
Visit Identifier	**Day -28**	**Day 1** **Week 0** **Baseline**	**Day 8** **Week 1** **(by Phone)**	**Day 15** **Week 2**	**Day 29** **Week 4**	**Day 43** **Week 6** **(by Phone)**	**Day 57** **Week 8**	**Day 85** **Week 12** **(EOT/ET)**	**Day 113** **Week 16** **(EOS)**	Visit 9 is 4 weeks after last dose in case of early study termination
Sub-study										
Sub-study eligibility							X			
Administration of Tdap vaccine							X			
Blood sampling for tetanus, diphtheria and pertussis-specific IgG concentrations							X	X		Day 57 (pre-vaccination) blood sample must be collected before administration of Tdap.

Abbreviations: AD = atopic dermatitis; CDLQI = Children's Dermatology Life Quality Index; C-SSRS = Columbia Suicide Severity Rating Scale; EASI = Eczema Area and Severity Index, DFI = Dermatitis Family Impact Questionnaire, ECG = electrocardiogram; EOS = End of Study, EOT = End of Treatment; ET= early termination; EQ-5D-Y = EuroQol Quality of Life 5-Dimension, Youth Scale; HADS = Hospital Anxiety and Depression Scale, HBsAg = hepatitis B surface antigen; HBsAb = hepatitis B surface antibody; HBcAb = hepatitis B core antibody; HBV DNA = hepatitis B viral deoxyribonucleic acid, HCV Ab = hepatitis C antibody; HCV RNA = hepatitis C viral ribonucleic acid; HIV = human immunodeficiency virus; CCI [redacted] IGA = Investigator's Global Assessment; IRT = Interactive Response System; NRS = Numerical Rating System, Peds-FACIT-F = Pediatric Functional Assessment of Chronic Illness Therapy Fatigue Scale; PHQ-8 = Patient Health Questionnaire 8 items; POEM = Patient-Oriented Eczema Measure, PSAAD = Pruritus and Symptoms Assessment for Atopic Dermatitis, PtGA = Patient Global Assessment, RNA = Ribonucleic acid; SBQ-R = Suicide Behaviors Questionnaire-Revised; SCORAD = SCORing Atopic Dermatitis, Tdap = tetanus, diphtheria and pertussis combination vaccine, VZV = varicella zoster virus; VZV IgG Ab = varicella zoster virus immunoglobulin G antibody.

2. INTRODUCTION

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

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

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

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

PF-04965842 is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the ATP binding site. PF-04965842 has a high degree of selectivity in vitro against other kinases: 28-fold selectivity over JAK2, >340-fold over JAK3 and 43-fold over TYK2, as well as a good selectivity profile over the broader range of human kinases. The selective inhibition of JAK1 will lead to modulation of multiple cytokine pathways involved in the pathophysiology of AD, including IL-4, IL-5, IL-13, IL-31 and IFN-γ. Data from a Phase 2b proof of concept (POC) study (B7451006) that evaluated participants with moderate-to-severe AD showed positive efficacy, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

2.1. Study Rationale

PF-04965842 is being developed as an oral treatment for patients with moderate-to-severe AD based on its mechanism of action, and the clinical results obtained in Phase 1 and Phase 2 studies. Other Phase 3 studies are ongoing or planned to evaluate PF-04965842 as monotherapy in adults and adolescents with AD, and when co-administered with background

medicated topical therapy in adults with AD. This study is designed to specifically evaluate PF-04965842 co-administered with background medicated topical therapy in adolescents with AD.

Additional information for this Phase 1 and Phase 2 study results may be found in the Investigator's Brochure (IB).

The administration of the tetanus, diphtheria and pertussis combination vaccine (Tdap) as a booster in adolescents is consistently recommended in vaccination guidelines worldwide. Findings of the sub-study will inform whether Tdap vaccination during PF-04965842 treatment will impair the immunogenicity to Tdap. It is expected the findings on immunogenicity to Tdap can be extrapolated to co-administration of PF-04965842 with other vaccines due to the broad array of T-dependent antigens contained in Tdap. These findings will be useful for evaluating the overall benefit-risk of PF-04965842 in adolescents, and to provide support for developing PF-049658042 in children < 12 years of age. Further details of the immunogenicity sub-study are provided in Appendix 11.

2.2. Background

Atopic dermatitis, also known as eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in the quality of life. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the United States (US).[2,3] AD is one of the most common, chronic, relapsing childhood dermatoses, impacting 15-30% of all children in the US and many have disease that persists into adulthood Earlier reports indicated that, in up to 70% of cases, the disease greatly improved or resolved by late childhood, however more recent findings suggest that disease activity remains manifest for a prolonged period of time. Based on a total of 7157 patients enrolled in the Pediatric Eczema Elective Registry (PEER) study, comprising a total of 22,550 person-years, it was concluded that symptoms associated with AD seem to persist well into the second decade of life and likely longer.[4] The majority of studies conducted across multiple age groups suggest a continued decrease in prevalence with older age.[5] Adult-onset AD does also occur, though it is less common. The prevalence of AD in adults is estimated to be 10%.[6]

Although much progress has been made in understanding the causes of AD, the complex pathophysiology of AD is still not completely understood. It has been established that the pathophysiology of AD includes a defective skin barrier function, allergic responses, defective antimicrobial immune defense, and a genetic predisposition. The predominant symptom of AD, pruritus and the resulting scratching, typically sets off an amplification cycle of atopic skin inflammation. Activation of T lymphocytes, dendritic cells, macrophages, keratinocytes, mast cells, and eosinophils results in a release of numerous pro-inflammatory cytokines and chemokines. This amplification cycle sustains the inflammatory responses characteristic of the AD lesions.[7]

Non-medicated topical therapies include emollients. Medicated topical therapies for moderate-to-severe AD include topical corticosteroids (TCS) (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (TCI) (eg, pimecrolimus, tacrolimus), and coal tar preparations. TCI have a limited role as a second line treatment, due to their limitations

in terms of the duration of treatment and the body region of treatment, inhibition of tumor surveillance in the skin, and safety concerns with malignancies. Crisaborole was approved as a medicated topical therapy in December 2016 by the Food and Drug Administration (FDA) for use in patients with mild to moderate AD. Additional treatments generally reserved for severe AD include phototherapy (eg, ultraviolet A light [UVA] with or without psoralen, ultraviolet B light [UVB] narrowband or broadband) and systemic agents (eg, corticosteroids, cyclosporine, recombinant IFN-γ, mycophenolate mofetil, methotrexate [MTX], azathioprine, intravenous immunoglobulin and dupilumab).[8] Of the currently available therapies, none offers a cure; therefore, the main aims of existing treatments are to reduce the occurrence of acute flares, to increase the time between relapses, reduce pruritus and the resulting sleep disturbance.[9,10]

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

PF-04965842 is an orally active JAK1 inhibitor. As mentioned above, a variety of pro-inflammatory cytokines such as IL-4, IL-5, IL-13, IL-31 and IFN-γ, have been suggested to have a role in the pathogenesis of AD. Many of these pathogenic cytokines use JAK1 for signaling. Therefore, JAK1 is an attractive therapeutic target for AD.

2.2.1. Non-Clinical and Phase 1 Data

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

2.2.2. Phase 2b in AD (B7451006)

B7451006 was a Phase 2b proof-of-concept trial in 269 adults (ages 18-75) with moderate-to-severe AD investigating doses of 10, 30, 100, and 200 mg PF-04965842 or placebo taken once daily for up to 12 weeks. The primary endpoint was the proportion of participants achieving an Investigator's Global Assessment (IGA) score of clear (0), or almost clear (1), and a ≥2-point improvement from baseline at Week 12. The baseline was defined as the IGA score on Day 1 pre-dose.

At Week 12, IGA response rates of the PF-04965842 200 mg and 100 mg dose groups were significantly greater than the placebo group, 44.5%, 27.8% and 6.3%, respectively. As a result, the estimated differences from placebo in the 200 mg and 100 mg groups were 38.2% (P=0.0032) and 21.5% (P=0.0184), respectively. The percent change from baseline in Eczema Area and Severity Index (EASI) scores at Week 12 were significantly higher for both the 200 mg and 100 mg groups compared to placebo, 63.7%, 41.6%, and 15.6% respectively. At Week 12, the proportion of participants achieving EASI-75 response was

15.6% in the placebo group, 63.7% in the 200 mg group and 41.6% in the 100 mg group. As a result, the difference from placebo was 41.8% (P<0.0001) for the 200 mg group and 26.0% (P=0.0043) in the 100 mg group. Response rates at Week 12 for the 10 mg and 30 mg groups were not significantly different from placebo.

At Day 15, the proportion of response based on achieving Peak Pruritus numerical rating scale 4 points improvement from baseline (NRS4) of PF-04965842 100 mg and 200 mg dose groups was greater than placebo. The estimated proportion of Peak Pruritus NRS4 responses at Day 15 were 69.8%, 41.1% and 15.7% for 200 mg, 100 mg and placebo groups, respectively.

PF-04965842 demonstrated a rapid onset of action. In the 200 mg group, IGA and EASI scores improved until Week 4 and Week 6, respectively, and maintained their effect through 12 weeks of treatment. A key differentiating feature for the JAK1 inhibitor is rapid resolution of itch associated with AD. Significant separation from placebo was achieved for the Peak Pruritus numerical rating scale (NRS) score as early as 2 days after initiation of treatment for the 200 mg dose group.

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

PF-04965842 appeared generally safe and well tolerated in this study. Overall, adverse events (AE)s and Serious Adverse Events (SAE)s were numerically higher in participants receiving PF-04965842 compared to placebo, but did not appear to increase with dose. The most common AEs were in the Infections and infestations, skin and subcutaneous tissue disorders and Gastrointestinal disorders system organ class (SOC), and the majority of the AEs were mild. There were 2 cases of herpes zoster, one in the 10 mg group (not treatment related), and one in the 30 mg group (treatment related). There were dose-dependent decreases in platelet counts observed in the study, which plateaued at Week 4. Further details of the clinical Phase 2 development program can be found in the IB.

2.2.3. Summary of PF-04965842 Clinical Pharmacokinetics

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

Following QD administration over the dose range 30 mg to 400 mg and 100 mg and 200 mg twice a day (BID) for 10 days, median T_{max} ranged between 0.50 to 0.77 hours

(B7451001). After attainment of C_{max}, the disposition of PF-04965842 was consistent with that observed following single-dose administration, showing a biphasic decline following all but the lowest dose and an arithmetic mean terminal phase $t_{½}$ between 2.8 to 5.0 hours. The observed accumulation ratio (R_{ac}) for area under the curve over dosing interval tau (AUC_{tau}) and C_{max} following QD dosing was minimal (between 1.1 and 1.5), consistent with the prediction from $t_{½}$. Urinary recovery of PF-04965842 was low, with <5% of the dose recovered unchanged in urine across all doses and regimens in all cohorts.

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

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

2.2.4. Population Pharmacokinetics

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

In order to ensure similarity of systemic exposure, only adolescent patients with body weight ≥40 kg were initially included in the study. This was based on the lowest body weight of 44.5 kg evaluated in the prior population PK analysis in adult patients where no effect of body weight on oral clearance was found. Therefore, no adjustment of the adult dose is needed for adolescent participants planned for enrolment in this study.

Pharmacokinetic simulations were subsequently conducted to evaluate if the inclusion criterion of body weight ≥ 40 kg could be relaxed by comparing the predicted steady-state Cmax and AUC values for study populations using body weight cut off values of ≥ 35, 30 and 25 kg. Simulations were performed based on available PK data from Phase 1, Phase 2 as well as the completed Phase 3 study B7451012 that included adolescent patients (minimum weight of 40.8 kg). For both 100 and 200 mg QD doses, the exposures in adolescent patients were similar to those in adult patients. The simulated PF-04965842 AUC and Cmax values are approximately 52% and 85% higher, respectively, in adolescent patients with body weight of 25 kg when compared with adults with body weight of 70 kg. The efficacy and safety pharmacological effects of JAK1 inhibitors are considered to be driven by AUC, and the approximately 50% increase in simulated AUC is not considered clinically relevant. The absolute exposures predicted for a ≥25 kg body weight inclusion criterion do not exceed any pre-specified safety threshold values. Specifically, the population typical Cmax simulated for 25 kg individuals and 70 kg individuals receiving PF-04965842 200 mg once daily were 1888 and 1018 ng/mL, respectively, both of which are markedly below the threshold PF-04965842 concentration expected to achieve >10 msec QTc prolongation. Overall, these differences are not considered clinically significant. Therefore, based on these PK simulations, the body weight inclusion criterion will be amended from ≥40 kg to ≥25 kg.

2.3. Benefit/Risk Assessment

There was clinically meaningful benefit demonstrated for PF-04965842 200 mg QD and 100 mg QD in the Phase 2b POC study in adult patients with moderate-to-severe AD. It is expected that similar therapeutic benefit will be observed in adolescents with AD. The potential risks of treatment include those that were noted in Phase 2b and/ or those based on the pharmacology of JAK inhibitors and include viral reactivation, serious and opportunistic infections, hematopoietic effects (including reduced platelet count), malignancy and immunoproliferative disorders.

There is a high medical need for new treatment options in adolescent subjects with AD.[11,12] While other studies in the ongoing PF-04965842 Phase 3 AD program enroll both adolescents (12 to <18 years of age) and adults (≥18 years of age) to support product approval in both age groups, this study will only enroll adolescent subjects to further strengthen clinical data in this age group. This is in alignment with the International Conference on Harmonisation (ICH) guidance on timing of initiation of studies in paediatric subjects[13], and the recent draft guidance from the United States Food and Drug Administration recommending early inclusion of pediatric subjects in the development of drugs for atopic dermatitis[14]. In addition, while other studies in the Phase 3 AD program include adolescents in evaluating PF-04965842 monotherapy, and adults in evaluating PF-04965842 in combination with topical medications, this study is unique in evaluating PF-04965842 in blinded comparison to placebo when co-administered with topical medications in adolescents.

The inclusion of adolescents for short-term and long-term treatment in the PF-04965842 AD Phase 3 clinical studies is supported by rodent and non-rodent toxicity studies. Pfizer has completed nonclinical toxicity studies up to 9-months in duration in accordance with ICH

guideline M3. The completed toxicity studies support clinical trials in adolescents and adults (≥12 years old).

The potential benefits and potential risks for including adolescents in the PF-04965842 Phase 3 clinical program are as follows:

- Based on skin physiology and similar clinical phenotype of AD in adolescents and adults, the efficacy observed for PF-04965842 in adults with AD in the POC study B7451006 is expected for adolescents. The skin is anatomically mature at birth and continues functional development during the first year of age. By the time of adolescence and puberty, epidermal skin physiology and function and total body surface area (BSA) to body mass ratio are all similar to those of adults[15-17]. Adolescents and adults are similar in their clinical characteristics of AD.[18,19] Furthermore, available data suggest that children respond similarly to AD therapies that are effective in adults[12].

- Based on the mechanism of action of PF-04965842, and available data for similar agents, e.g., tofacitinib (a JAK1/3 inhibitor), unique safety risks for adolescents that are different from those for adults are not expected.

- Appropriate risk evaluation and mitigation strategies have been incorporated into this protocol.

- The efficacy and safety data obtained from this study would be useful for supporting future development of PF-04965842 in pediatric AD patients <12 years of age.

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

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-04965842 is provided in the IB, which is the single reference safety document (SRSD) for this study.

See Appendix 11 for benefit/risk of immunogenicity sub-study.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the efficacy of PF-04965842 compared with placebo when co-administered with background medicated topical therapy in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	Co-primary endpoints • Response based on the Investigator's Global Assessment (IGA) score of clear (0) or almost clear (1) (on a 5 point scale) and a reduction from baseline of ≥2 points at Week 12; • Response based on the Eczema Area and Severity Index ≥75% improvement from baseline (EASI-75) response at Week 12.
Secondary	
• To evaluate the effect of PF-04965842 co-administered with background medicated topical therapy on additional efficacy endpoints and patient reported outcomes over time in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	Key Secondary Endpoints • Response based on at least 4 points improvement in the Peak Pruritus NRS from baseline at Weeks 2, 4, and 12; • Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at Week 12. Secondary Efficacy Endpoints • Response based on at least 4 points improvement in the Peak Pruritus NRS from baseline at all scheduled time points other than Weeks 2, 4 and 12; • Time to achieve at least 4 points improvement in the Peak Pruritus NRS from baseline by Day 15; • Response based on the EASI-75 at all scheduled time points except Week 12; • Response based on the IGA of clear

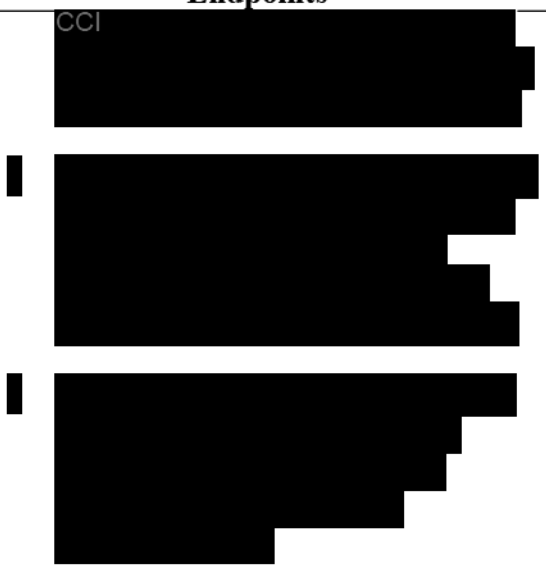
Objectives	Endpoints
	(0) or almost clear (1) and 2 point reduction from baseline at all scheduled time points except Week 12. Other Efficacy Endpoints • Response based on a ≥50%, ≥90% and 100% improvement in the EASI total score (EASI-50, EASI-90 and EASI-100) at all scheduled time points; • Change from baseline in the percentage Body Surface Area (BSA) affected at all scheduled time points; • Proportion of participants with affected BSA <5% at Week 12; • Response based on a ≥50% and ≥75% improvement in Scoring Atopic Dermatitis (SCORAD50, SCORAD75) from baseline at all scheduled time points; • Change from baseline at all scheduled time points in Scoring Atopic Dermatitis (SCORAD) subjective assessments of itch and sleep loss. Patient-Reported Outcomes • Change from baseline at Week 12 in Children's Dermatology Life Quality Index (CDLQI) and at all other scheduled time points; • Change from baseline at Week 12 in Hospital Anxiety and Depression Scale (HADS) and at all other scheduled time points; • Change from baseline at Week 12 in Patient Oriented Eczema Measure (POEM) and at all other scheduled time points;

Objectives	Endpoints
	• Change from baseline at Week 12 in Dermatitis Family Impact (DFI) questionnaire; • Change from baseline of Patient Global Assessment (PtGA) at Week 12 and at all other scheduled time points; • Change from baseline of EuroQol Quality of Life 5 Dimension Youth Scale (EQ-5D-Y) at Week 12 and at all other scheduled time points; • Change from baseline of Pediatric Functional Assessment of Chronic Illness Therapy Fatigue Scale (Peds FACIT-F) at Week 12 and at all other scheduled time points.

Immunogenicity Sub-Study Objective
• To evaluate the effect of PF-04965842 on the immunogenicity to Tdap vaccine in adolescent participants 12 to <18 years of age with moderate-to-severe AD.
	Immunogenicity sub-study endpoint
	• Mean fold increase from baseline at 4 weeks post-vaccination in concentrations of IgG against:
	  • Tetanus toxoid;
	  • Diphtheria toxoid;
	  • Pertussis toxoid;
	  • Pertactin (PRN);
	  • Filamentous hemagglutinin (FHA);
	  • Fimbriae types 2 and 3 (FIM).

Safety Objective	Safety Endpoints
• To evaluate the safety and tolerability of PF-04965842 co-administered with background medicated topical therapy in adolescent participants 12 to <18 years of age with	• Incidence of treatment emergent adverse events; • Incidence of SAEs • Incidence of AEs leading to

Objectives	Endpoints
moderate-to-severe AD.	discontinuation; • The incidence of clinical abnormalities and change from baseline in clinical laboratory values, ECG measurements, and vital signs.
PK Objective	PK Endpoint
• To evaluate the PK of PF-04965842 in adolescent participants 12 to <18 years of age with moderate-to-severe AD.	• Plasma concentrations of PF-04965842 in adolescent participants 12 to <18 years of age with moderate-to-severe AD.
CCI	
[redacted]	[redacted]

Objectives	Endpoints
	CCI 

The primary estimand of the main study is a composite estimand (accounting for both treatment adherence and response), defined according to the primary objective and is in alignment with the primary endpoint. The secondary estimand of this study is the hypothetical estimand, which estimates the effect as if all patients maintain their randomized treatment.

No specific estimands are defined for the immunogenicity analyses (see Appendix 11).

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double blind, placebo controlled, parallel group, Phase 3 study to evaluate the efficacy and safety of PF-04965842 in adolescent participants 12 to <18 years of age with moderate-to-severe AD co-administered with background topical therapy. A total of approximately 225 participants will be enrolled from approximately 120 sites located globally (see Schema). The participants will be randomized 1:1:1 to receive once daily PF-04965842 at 200 mg, 100 mg, or placebo for 12 weeks. In a sub-study, up to approximately 90 participants (up to 30 in each respective study group) who have completed 8 weeks of treatment with study intervention will receive a tetanus, diphtheria and pertussis combination vaccine (Tdap) at Week 8, and will have blood samples collected for the evaluation of immunogenicity to the vaccine at Weeks 8 and 12 (see Appendix 11). The participants in the immunogenicity sub-study will complete all other protocol-specified procedures in the main study.

Qualified participants completing 12-week treatment with study intervention will have the option to enter the long-term extension (LTE) study B7451015. Participants discontinuing early from the study will undergo a 4-week follow-up.

Participants who have chronic moderate-to-severe AD as defined per the inclusion criteria will be enrolled in this study. Investigators, participants, and the sponsor study team will be blinded as to treatment group assignment. Prior to any study procedure the informed consent including any required assent will be obtained at the screening visit. Parent(s)/legal guardian will provide supplementary or sole written consent and minor children will provide assent, according to local regulations and rules regarding ability to give assent and consent.

Participants will be screened within 28 days prior to the first dose of study intervention to confirm study eligibility. During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Eligible participants must have a documented history, within 6 months of the screening visit, of inadequate response to treatment with medicated topical therapy, or must have required systemic therapies for control of their disease. Eligible participants must meet the eligibility criteria at both screening and baseline visits. All treatments for AD must have been washed out for at least 7 days prior to Day 1. In addition, participants are required to use non-medicated topical therapy (ie, emollients) at least twice daily for the last 7 days prior to Day 1, and must also be willing and able to use standardized background medicated topical therapy, as per protocol guidelines, throughout the duration of the study. Participants who continue to meet eligibility criteria at baseline will undergo Day 1/baseline assessments and be randomized in a 1:1:1 ratio to receive 200 mg PF-04965842 (N=75) or 100 mg PF-04965842 QD (N=75) or matching placebo (N=75) from Day 1. Randomization will be stratified by baseline disease severity (moderate [IGA = 3] vs. severe [IGA = 4] AD).

4.2. Scientific Rationale for Study Design

This study is part of the global Phase 3 clinical development program investigating the safety and efficacy of PF-04965842 200 mg and 100 mg QD regimens. Medicated topical therapy is commonly used to treat AD. This study is designed to specifically evaluate PF-04965842 co-administered with background medicated topical therapy in adolescents with AD.

Global guidelines of vaccination recommend administration of various vaccines in adolescents. The effect of PF-04965842 on immunogenicity after vaccination in adolescents has not been evaluated. A sub-study is therefore added to investigate the effect of PF-04965842 on the immunogenicity to the Tdap vaccine. Findings of the sub-study will inform whether administration of PF-04965842 and Tdap would impair the immunogenicity to Tdap. Tdap is chosen due to its widespread use globally, inclusion of multiple antigens in this combination vaccine, and durable immune response after vaccination. Available literature data do not suggest an effect of the Tdap vaccine on AD disease activity or disease course. It is therefore considered suitable to conduct the immunogenicity sub-study during the main study.

4.3. Justification for Dose

Dose selection for Phase 3 was based on efficacy and safety of PF-04965842 from a dose-ranging Phase 2b study, B7451006 that evaluated a 20-fold dose range (10 mg to 200 mg QD) in adults with moderate-to-severe AD. The 200 mg QD dose is expected to provide efficacy similar to that of currently approved systemic treatments in moderate-to-severe AD, and was therefore selected as the high dose for evaluation in Phase 3 studies. An additional dose of 100 mg QD was also selected for evaluation in Phase 3, since this dose is expected to provide clinically efficacy in IGA response, while differentiating from the higher dose in terms of expected efficacy and systemic exposure. This will inform the selection of the dose with the most optimal benefit-risk. Both 100 mg and 200 mg QD doses demonstrated acceptable safety and tolerability in the Phase 2 study. There was no evidence of dose-dependent changes in safety endpoints such as serious infections or adverse events. Dose-response was evident only for changes from baseline in platelet counts. Mean platelet count decreases from baseline were observed with a nadir at Week 4. At Week 4 the mean platelet count and the 90% confidence interval (CI) were within the normal reference range for the 100 mg dose and 200 mg dose. The mean platelet counts increased towards baseline after Week 4. One (1) PF-04965842 treated subject with an adverse event (AE) of thrombocytopenia, had a value less than 0.5 x lower limit of normal. There were no reported adverse clinical effects potentially associated with reduced platelet counts, such as bleeding events, observed in the Phase 2 study. Further details are available in the IB.

The emerging efficacy and safety data in this study will be monitored periodically by E-DMC to ensure acceptable benefit-risk for this patient population.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including follow-up assessments after the End of Treatment (EOT). Details of early termination are provided in. Section 7.

The end of the study is defined as the date of the last study visit shown in the Schedule of Activities for the last participant in the study globally.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Additional eligibility criteria for the sub-study are provided in Appendix 11.

5.1. Inclusion Criteria

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

Age

1. Participant must be 12 to < 18 years of age, inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who meet the following AD criteria:
    - Confirmed diagnosis of AD at the screening and baseline visits according to Hanafin and Rajka criteria for AD[20] (see Appendix 10).
    - Documentation of any of the following:
        - Inadequate response to treatment with medicated topical therapy for AD for at least 4 consecutive weeks, within 6 months before the screening visit; or
        - Treatment with systemic therapy for AD within 6 months before the screening visit; or
        - Participant is a candidate for systemic therapy for AD.

      NOTE: Medicated topical therapy is defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over-the-counter [OTC] or prescribed product).
    - Moderate-to-severe AD (must fulfil all of the following criteria: affected BSA ≥ 10%, IGA ≥ 3, EASI ≥ 16, and Peak Pruritus NRS ≥ 4 at the baseline visit).
3. During the last 7 days prior to Day 1, for the treatment of AD, the subject must have used only non-medicated topical therapy (ie, emollient) at least twice daily, without other active ingredients indicated to treat AD, or other additives which could affect AD (eg, hyaluronic acid, urea, ceramide or filaggrin degradation products), with response to treatment remaining inadequate at baseline. The participant must also be willing and able to comply with standardized background topical therapy, as per protocol guidelines (Section 6.5.1), throughout the remainder of the study.
4. Must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.
5. If receiving concomitant medications for any reason other than AD, must be on a stable regimen, which is defined as not starting a new drug or changing dosage within

7 days or 5 half-lives (whichever is longer) prior to Day 1 and through the duration of the study.

Weight

6. Body weight ≥ 25 kg.

Sex

7. Male or Female

Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:

No contraceptive measures required.

b. Female participants:

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

- Is not a woman of childbearing potential (WOCBP) (see definition in Appendix 4)

  OR

- Is a WOCBP (all female participants, regardless of whether or not they have experienced/reported menarche, are considered WOCBP unless they are permanently sterile or confirmed infertile). A WOCBP who is sexually active must use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the intervention period and for at least 28 days after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive (Appendix 2) serum pregnancy test at the screening visit. A urine pregnancy test with a sensitivity of at least 25 mIU/mL, will be performed before the first dose of study intervention and at every site visit including the EOT and follow-up visits to confirm the subject has not become pregnant. 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 from participation if the serum pregnancy result is positive.
- 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.

Informed Consent

8. Capable of giving signed informed consent/assent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
9. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

5.2. Exclusion Criteria

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

Medical Conditions

1. Other acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or study intervention 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.
2. Any psychiatric condition including recent or active suicidal ideation or behavior that meets any of the following criteria:
   - Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS) (Section 8.2.9.1);
   - Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS;
   - Any lifetime history of recurrent suicidal behavior;
   - Suicidal behaviors questionnaire – revised (SBQ-R) total score ≥8 (Section 8.2.9.2);
   - Clinically significant depression: patient health questionnaire-8 items (PHQ-8) total score ≥15 (Section 8.2.9.3);
   - The presence of any significant impairment from a psychiatric disorder and/or one that is not explicitly permitted in the inclusion/exclusion criteria;
   - In the opinion of the investigator or Pfizer (or designee) exclusion is required.
3. A current or past medical history of conditions associated with thrombocytopenia, coagulopathy or platelet dysfunction.

4. Currently have active forms of other inflammatory skin diseases, ie, not AD or have evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, lupus) at the time of Day 1 that would interfere with evaluation of AD or response to treatment.
5. Have a history of any lymphoproliferative disorder such as Epstein Barr virus (EBV)-related lymphoproliferative disorder, history of lymphoma, leukemia, or signs or symptoms suggestive of current lymphatic or lymphoid disease.
6. Infection History:

    - Have a history of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1;

    - Have active chronic or acute skin infection requiring treatment with systemic antimicrobials within 2 weeks prior to Day 1, or superficial skin infections within 1 week prior to Day 1

    - A participant known to be infected with Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C (Section 8.2.8.1).

        - For China, Taiwan and countries where hepatitis B viral deoxyribonucleic acid (HBV DNA) testing is required (except for Japan): Participants who are hepatitis B surface antigen negative (HBsAg-), hepatitis B core antibody positive (HBcAb+), and hepatitis B surface antibody positive (HBsAb+) will have reflex testing for HBV DNA. Participants who have HBV DNA at or above lower limit of quantification (LLQ) will be excluded. Participants who are HBV DNA negative or below LLQ may be randomized.

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

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

7. Have a history of alcohol or substance abuse within 6 months prior to Day 1 that in the opinion of the investigator will preclude participation in the study.
8. Have a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.
9. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.
10. Have evidence of active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB) as evidenced by any of the following:

    - A positive QuantiFERON®-TB Gold In-Tube test (QFT-G) or positive Mantoux/Purified Protein Derivative (PPD)/ tuberculin skin test (if appropriate per Section 8.2.4) performed at or within the 12 weeks prior to Day 1 is exclusionary; a negative test is required for eligibility. QFT-G is the preferred testing method. If the QFT-G test cannot be performed, or if the results cannot be determined by the reference laboratory to be either positive or negative, then participants may be screened using the PPD test with approval of the Pfizer clinician.

        - For Japan only: While QFT-G is the preferred testing method, the T-SPOT®.TB test is also permitted. Borderline results from the T-SPOT®.TB test should be considered exclusionary. If the test results are indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, then participants may be screened using Mantoux/PPD skin testing following consultation and agreement with the Pfizer Medical Monitor. See Section 8.2.4.

        - It is recommended that participants with a history of Bacille Calmette Guérin (BCG) vaccination be tested with the QFT-G test since the Mantoux/PPD/tuberculin skin test may be positive due to vaccination. A QFT-G or PPD skin test is not required if the subject has previously received a documented adequate course of therapy for either latent or active TB infection.

        - A negative QFT-G, T-SPOT®.*TB* test (Japan only) or PPD skin test is required unless the subject has previously received a documented adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi-drug TB resistance are <5% or an acceptable alternative regimen) or active (acceptable multi-drug regimen) TB infection. If the current incidence rates of multi-drug resistant TB infection in the locale are unavailable, an adequate treatment regimen should be defined as the regimen recommended by the health ministry or expert panel in the locale;

    - Chest X-ray (or chest computed tomography scan, or magnetic resonance imaging [MRI]) taken at screening with changes suggestive of active TB

infection as determined by a qualified radiologist. Chest X-ray or other appropriate imaging is recommended for adolescents per local standard/guidelines, unless previously performed and documented within 12 weeks prior to Study Day 1.

- For Germany only: Chest Imaging using magnetic resonance imaging [MRI] performed at screening with changes suggestive of active TB infection as determined by a qualified radiologist. MRI is not required for screening in this study. If the use of chest imaging is considered medically necessary to exclude active TB, chest MRI may be performed at the discretion of the Principal Investigator for screening, unless previously performed and documented within 12 weeks prior to Study Day 1.

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

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

Prior/Concomitant Therapy

11. Require treatment with prohibited concomitant medication(s) (Section 6.5.2 and Appendix 7) or have received a prohibited concomitant medication within the specified time frame prior to the first dose of study medication.
12. Receiving anti-coagulants or medications known to cause thrombocytopenia, (unless considered safe to stop and washout for the duration of the study).
13. Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of study intervention, or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of study intervention.
14. Participants without documentation confirming prior varicella-zoster infection (chickenpox) or 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.
15. Participants who have received prior treatment with systemic JAK inhibitors.
16. Have received any of the following treatment regimens specified in the timeframes outlined below:

<u>Within 1 year of first dose of study intervention:</u>

- Prior treatment with non B cell-specific lymphocyte depleting agents/therapies (eg, alemtuzumab [CAMPATH®], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc.). Participants who have received rituximab or other selective B lymphocyte depleting agents (including

experimental agents) are eligible if they have not received such therapy for at least 1 year prior to study baseline and have normal cluster of differentiation (CD) 19/20+ counts by fluorescence-activated cell sorting (FACS) analysis.

Within 12 weeks of first dose of study intervention:

- Biologics other than dupilumab: within 12 weeks of first dose of study intervention or 5 half-lives (if known), whichever is longer.

Within 6 weeks of first dose of study intervention:

- Use of dupilumab.

Within 4 weeks of first dose of study intervention:

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

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

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

- Use of CYP2C9 and CYP2C19 inducers within 5 half-lives of the inducer plus 14 days of first dose of study intervention. For example, the average half-life of carbamazepine after repeat dosing is 15 hours. The washout period is calculated as the sum of 5 half-lives (approximately 3 days) and an additional 14 days for a total of 17 days prior to the first dose of study intervention.

- Phototherapy narrowband UVB (NB-UVB) or broad band phototherapy;

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

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

Within 1 week of first dose of study intervention:

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

NOTE: Non-medicated topical therapy (ie, emollients), as detailed in Section 6.5.1 are permitted.

- Use of CYP2C9 and CYP2C19 inhibitors within 1 week of first dose of study intervention or within 5 half-lives (if known) of the inhibitor, whichever is longer.

- Anti-platelet drugs.

Prior/Concurrent Clinical Study Experience

17. Participation in other studies involving investigational drug(s) within 8 weeks or within 5 half-lives (if known) whichever is longer, prior to study entry and/or during study participation.
    Note: Any investigational or experimental therapy taken or procedure performed for AD, psoriasis, psoriatic arthritis or rheumatoid arthritis in the previous 1 year should be discussed with the Pfizer clinician (or designee). Participants cannot participate in studies of other investigational or experimental therapies or procedures at any time during their participation in this study.

Diagnostic assessments

18. **ANY** of the following abnormalities in the clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:
    - Absolute neutrophil count of $<1.2 \times 10^9$/L ($<1200/mm^3$);
    - Hemoglobin <10.0 g/dL or hematocrit <30%;
    - Platelet count of $<150 \times 10^9$/L ($<150,000/mm^3$);
    - Absolute lymphocyte count of $<0.50 \times 10^9$ /L ($<500/mm^3$);
    - Estimated creatinine clearance <40 mL/min based on the age appropriate calculation, or serum creatinine >1.5 times the upper limit of normal (ULN);
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values >2 times the ULN;
    - Total bilirubin ≥ 1.5 times the ULN; 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.

19. A Screening 12-lead electrocardiogram (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 that may represent risk factors for Torsade de Pointes (TdP) (eg, Fridericia corrected Q wave interval (QTcF) >500 milliseconds [ms]) on the screening ECG.

Other Exclusions

20. In the opinion of the investigator or sponsor, have any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the subject's participation in the study.
21. Have undergone significant trauma or major surgery within 1 month of the first dose of study intervention.
22. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.
    See Appendix 11 for additional exclusion criteria for the vaccine sub-study.

5.3. Lifestyle Considerations

1. On study visit days, participants must not take the dose of study intervention until instructed to do so by the investigator or designated study site staff.

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

3. On study visit days, topical therapy (ie, non-medicated topical therapy and medicated topical therapy, per protocol guidelines as described in Section 6.5.1) are not permitted to be applied prior to attending the study visit. Topical therapies are required to be applied after the visit (per protocol guidelines as described in Section 6.5.1). An exception can be made for afternoon/evening visits, when topical therapy can be applied $\geq$ 8 hours before the scheduled visit.

4. WOCBP participants who are sexually active must agree to use one highly effective method of contraception (as specified in Appendix 4), as applicable.

5.3.1. Meals and Dietary Restrictions

On study visit days (Day 1, Weeks 4, 12, and End of study [EOS]), participants should comply with fasting requirements for at least 8 hours prior to the visit, when possible. Water and permitted non-study medications are allowed (Section 8.2.8).

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will abstain from using tobacco products or ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for at least 30 minutes before pulse rate and blood pressure measurements.

5.3.3. Vaccine and Exposure to Infections Guidelines

5.3.3.1. 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 study

intervention. Participants without documentation confirming prior VZV infection (chickenpox) or 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 antibody serological testing will be excluded.

In order to enroll in the immunogenicity sub-study, the participants must not have received tetanus, diphtheria or pertussis vaccination within 5 years prior to Week 8 of the main study. See Appendix 11 for more information on the sub-study.

5.3.3.2. Guidance Regarding Household Contact Vaccine-Related Exposure

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

a. Varicella or attenuated typhoid fever vaccination for 4 weeks following vaccination.

b. Oral polio vaccination for 6 weeks following vaccination.

c. Attenuated rotavirus vaccine for 10 days following vaccination.

d. FluMist® (inhaled flu vaccine) for 1 week following vaccination.

e. Measles, Mumps and Rubella vaccine for 4 weeks following vaccination.

f. Yellow fever vaccine for 4 weeks following vaccination.

The list of live vaccines in this section is not exhaustive. For questions on household contacts who have received other live vaccines, such as dengue vaccine, please contact Pfizer clinician.

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

5.3.4. Surgery

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

The Pfizer clinician or designee should be notified if a participant requires surgery (including dental surgery) during the study to determine whether the participant should discontinue from the study and/or discontinue study intervention prior to the surgical procedure. In general, planned surgical procedures should not be performed unless the study intervention has been

discontinued for at least 28 days (unless otherwise advised by the Pfizer clinician or designee). The Pfizer clinician or designee should be notified as soon as possible if a participant undergoes a surgical procedure without first informing the study staff.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered 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 rescreened once after discussion with Pfizer if they fail the screening evaluation for reasons related to incidental transitory conditions. Individuals for whom screen failure is related to failing the disease severity (including extent of disease) inclusion criterion and who subsequently experience worsening AD, which in the investigator's judgement would make them eligible for participation, may be considered for re-screening. Such cases should be discussed with the Pfizer Medical Monitor (or designee) to determine if re-screening is appropriate.

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 main study, the interventions are PF-04965842 and placebo (see Appendix 11 for study interventions in the sub-study). PF-04965842 will be administered orally at doses of 100 mg or 200 mg given QD for 12 weeks based on treatment assignment. In addition, one treatment group will be assigned to receive PF-04965842-matching placebo.

6.1. Study Intervention(s) Administered

PF-04965842 100 mg tablets and matching placebo will be provided by the sponsor. The Tdap vaccines will be sourced locally (see Appendix 11 for further details).

ARM Name	PF-04965842 200 mg QD	PF-04965842 100 mg QD	Placebo
Intervention Name	PF-04965842	PF-04965842	Placebo
Type	Small molecule	Small molecule	Placebo
Dosage Form	Tablet	Tablet	Tablet
Dose Strength	100 mg	100 mg	
Dosage	100 mg – 2 tablets	100 mg – 1 tablet Placebo – 1 tablet	Placebo – 2 tablets
Route of Administration	Oral	Oral	Oral
Sourcing	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.
Packaging and Labeling	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.

QD = once daily,

6.2. Preparation/Handling/Storage/Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study

intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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).

4. Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Product (IP) Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinded study using central randomization via IRT system.	Participants will be randomized into the study provided they or their parent(s)/legal guardian, if applicable, have signed an informed consent document to participate in the study, have undergone all screening procedures, and have met all inclusion and none of the exclusion criteria for participation in the study at screening and Day 1. A computer-generated randomization schedule will be used to assign participants to the treatment groups using an Interactive Response Technology (IRT). In the sub-study, Tdap administration will not be blinded. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, protocol number, the participant number and the year of birth of the subject. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when PF-04965842 / placebo study intervention is being supplied via the IRT. The IRT system will provide a confirmation report containing the subject number and DU or container number assigned. The confirmation report must be stored in the site's files. There is a 24 hour-a-day, 365 days-a-year IRT help desk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT. Note: The IRT is the source of the subject number. The IRT system will provide the subject number at the end of the first IRT subject transaction.

Blind Break (IRT)	Investigators, participants and the sponsor study team will be blinded as to treatment group. The study will be participant (including caregiver) and investigator blinded. At all times, treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, or the sponsor's study team until following the conclusion of the study, with the exception described in this section. At the initiation of the study, the study site will be instructed on procedures for breaking the blind. Blinding codes should only be broken in emergency situations for reasons of subject safety. The method will be an electronic process. When the blind for a participant has been broken, the reason must be fully documented and entered on the Case Report Form (CRF). Whenever possible, the investigator should contact Pfizer before breaking the blind. If the blind is broken, the investigator should promptly inform the Pfizer Clinician. The participant for whom the blind has been broken will be discontinued from the study and undergo the early termination (ET) procedures.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

For self-administration of PF-04965842 / placebo at home, compliance will be recorded by the participant. Participants will be issued an electronic dosing diary (eDiary) and will be educated to record the time of their daily dosing, once they have taken the study intervention.

When study intervention is administered at the research facility, it will be administered under the supervision of study personnel.

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

Study intervention should be taken in the morning. Participants should be instructed that if a dose is inadvertently missed then it should be taken as soon as remembered, but not within 12 hours of the next scheduled dose.

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

- Participants interrupting study intervention for more than 4 consecutive days or for a total of more than 7 days between visits;

- Participants administering >8 tablets in one day or administering ≥4 tablets/day for 4 consecutive days;

- Participants who have an overall compliance of <80% or >120% between visits.

Any deviation from protocol specified dosing should be recorded as a protocol deviation and the investigator or designee is to counsel the participant and parent(s)/legal guardian (if applicable) and ensure steps are taken to improve compliance. In addition, if the compliance deviation reaches the thresholds defined above it should also be recorded as a medication error (see Section 8.3.6).

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Pfizer clinician should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking new prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit (see Appendix 7 for washout periods for CYP2C9 and CYP2C19 inhibitors and inducers), unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Participants will abstain from all prohibited concomitant medications as described in Section 6.5.2 and Appendix 7. Medications that are taken in the Screening/Washout period (after informed consent is obtained and before the first dose of study intervention) will be documented as prior medications. Medications taken after the first dose of study intervention has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in study records with indication (if AD), reference to any associated adverse event, dose, and start and stop dates of administration. 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.

6.5.1. Permitted Concomitant Treatments

Participants must comply with standardized background topical therapy guidance throughout the study. Background topical therapy will not be provided by the sponsor. Standardized

background topical therapy refers to the guidance below, in accordance with the local standard of care and according to the Investigator's usual practice:

Non-medicated Topical Therapy

- Non-medicated topical emollient without other active ingredients indicated to treat AD, or other additives which could affect AD (eg, hyaluronic acid, urea, ceramide or filaggrin degradation products): must be applied at least twice daily to all body areas affected with AD in the last 7 days prior to Day 1 and throughout the remainder of the study.

Medicated Topical Therapy

- TCS must be applied once daily to areas with active lesions, starting on Day 1 (Baseline) and throughout the study, according to the guidance below:
    - Medium potency TCS (eg, Triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment) must be applied to body areas with active lesions that are suitable for the use of medium potency TCS. Participants must be clinically monitored for toxicity to TCS and stepped down as needed.
        - After lesions are under control (clear or almost clear), treat once daily for a further 7 days, then stop;
        - If lesions return then resume treatment with medium potency TCS, but use the approach described above upon lesion resolution.
    - Low potency TCS (ie, hydrocortisone 1% cream) must be applied to body areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) with active lesions instead of medium potency TCS or to body areas where continued treatment with medium potency TCS is considered unsafe. Participants must be clinically monitored for toxicity to TCS and stepped down as needed.
        - After lesions are under control (clear or almost clear), treat once daily for a further 7 days, then stop;
        - If lesions return then resume treatment with low potency TCS, but use the approach described above upon lesion resolution.
- Topical calcineurin inhibitors (eg, tacrolimus, pimecrolimus) or a phosphodiesterase type 4 (PDE4) inhibitor (eg, crisaborole) may be used instead of corticosteroids in body areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) with active lesions or if continued treatment with TCS of any potency is considered unsafe, and according to locally approved label at the investigator's discretion and considering prior response or intolerance to these medications.

NOTE: Background topical therapy must not be applied prior to attending a study visit, on the day of the study visit. Background topical therapy should instead be applied after the visit, on study visit days.

Other Concomitant AD Therapies

The following other concomitant AD therapies are permitted during the study and will not be provided by the sponsor:

- Oral antihistamines.

The following concomitant medications are permitted during the study:

- Corticosteroid inhalers and intranasal sprays are permissible for participants receiving a stable dose;
- Ophthalmic corticosteroids are permissible for participants receiving a stable dose;
- Acetaminophen/paracetamol may be used intermittently, not to exceed 1 gram per day;
- Dietary supplements (defined as vitamins and minerals, and purified food substances) of standard potency are allowed in amounts not known to be associated with adverse effects (such as hyper-vitaminosis).

Unless prohibited by the protocol, participants may be administered any other medications necessary for the treatment of medical disorders as deemed necessary by the treating physician. The addition of concomitant medications or any change in the dosage should be limited to those considered medically essential.

The concomitant medication for any reason must be a locally-approved medication and dose. Participants are not allowed any other investigational drugs or treatments during the study.

Participants should report any changes to medications during the study to the investigator as soon as they occur. Medication changes must be documented in the participant's record and eCRF.

6.5.2. Prohibited Medications and Treatments

Participants are required to discontinue and avoid using certain medications and treatments (see Inclusion Criteria and Exclusion Criteria and Appendix 7). 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 AD must be discontinued except oral antihistamines. Medicated topical therapy for AD must be washed out one week prior to Day 1 (Baseline). Starting on Day 1, standardized background topical therapy will be used as per protocol guidance in Section 6.5.1.

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

Participants who received prior treatment with systemic JAK inhibitors are to be excluded from the study.

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

Restrictions on certain vaccinations are described in Section 5.3.3.

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

6.6. Dose Modification

Dose modification of the study intervention is not permitted in this study.

6.7. Intervention after the End of the Study

There is no intervention required by the protocol following the end of the study. Participant may enroll in the LTE study if eligible.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In certain instances, it may be necessary for a patient to permanently discontinue study intervention (ie, study treatment). If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for EOT assessments (per Schedule of activities).

Note that discontinuation of study treatment does not represent withdrawal from the study. Refer to Appendix 5 for discontinuation criteria.

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

7.1.1. Temporary Discontinuation

Temporary interruption to dosing is not allowed in this study, except when indicated for participant safety. Sponsor clinician must be informed when temporary interruption occurs and the duration of temporary interruption must not exceed 14 days.

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. This is expected to be uncommon.

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

- The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- 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, to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

- 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.

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 are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities. 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 Schedule of Activities, 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. Participants will be screened (Visit 1) within 28 days prior to administration of the study intervention to confirm that they meet the participant selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each participant, or parent(s)/legal guardian (and assent from the participant, as appropriate), in accordance with the procedures described in Section 10.1.3.
- Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results; the last value will be used to determine eligibility. If results return to normal within the 4-week screening period, the participant may enter the study.
- Due to possible need for PPD testing and chest radiograph, screening procedures may be performed over more than 1 visit in the 28 days prior to the Day 1 visit.
- Visit windows are based on Day 1 visit. To assure consistency and reduce variability, all study visits should occur in the morning whenever possible. On days of study visits, participants will receive their dose at the clinic during the visit.
- When possible, participants should fast for at least 8 hours prior to all visits that include lipid profile panel testing (Day 1, Week 4, Week 12, and EOS). During the fasting period, participants should refrain from all food and liquids (water and permitted non-study medications are allowed).
- ECGs will be interpreted by a central reader for all visits.
- Urine pregnancy test must be performed prior to dosing with the study intervention for WOCBP through the EOT visit.
- Prior to attending a study visit, participants are allowed to shower and bathe but should not moisturize or apply emollient.
- Participants will be instructed about the use of standardized background topical therapy (see Sections 6.5.1 and 8.1.5).
- See Appendix 11 for additional procedures required for the immunogenicity sub-study.

8.1. Efficacy Assessments

8.1.1. Rater Qualifications

Clinical evaluations of AD will be performed by an experienced and qualified dermatologist (board certified or equivalent). An experienced and qualified non-dermatologist physician or experienced medical professional with experience in the conduct of dermatology clinical trials may be permitted to perform the clinical evaluations of AD when designated by the primary site Investigator. The evaluator must receive and document protocol specific and applicable efficacy assessment scales training prior to performing these evaluations. **To assure consistency and reduce variability, the same evaluator must assess all dermatological clinical evaluations for any individual subject throughout the study whenever possible**; a back-up experienced and qualified, protocol-trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation.

8.1.2. Investigator's Global Assessment (IGA)

The Investigator's Global Assessment of AD is scored on a 5-point scale (0-4), reflecting a global consideration of the erythema, induration and scaling. The clinical evaluator of AD will perform an assessment of the overall severity of AD and assign an IGA score and category as described in Table 1 The assessment will be a static evaluation without regard to the score at a previous visit.

Table 1. 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.

Table 1. Investigator's Global Assessment (IGA) Score

Score	Category	Description*

* 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 subject's AD based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring by the AD clinical evaluator of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.

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

Table 2. 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

Table 2. Clinical Sign Severity Scoring Criteria for the Eczema Area and Severity Index (EASI)

Score		Description*
3	Severe	Severe linear or picked scratch marks or penetrating surface injury
Lichenification (L)		
0	Absent	None
1	Mild	Barely perceptible to slight, but definite thickened skin, fine skin markings, and lichenoid scale
2	Moderate	Moderate thickened skin, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale

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

Percent BSA with Atopic Dermatitis: The number of handprints of skin afflicted with AD in a body region can be used to determine the extent (%) to which a body region is involved with AD (Table 3). When measuring, the handprint unit refers to the size of each individual subject's hand with fingers in a closed position.

Table 3. Handprint Determination of Body Surface Area (BSA)

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

Handprint refers to the hand size of each individual subject.
* The number of handprints will be for the entire body region; these values will not be adjusted for exclusion of scalp, palms, and soles from the BSA assessment.

The extent (%) to which each of the four body regions is involved with AD is categorized to a numerical Area Score using a non-linear scaling method according to the following BSA scoring criteria (Table 4).

Table 4. Eczema Area and Severity Index (EASI) Area Score Criteria

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

Body Region Weighting: Each body region is weighted according to its approximate percentage of the whole body (Table 5).

Table 5. Eczema Area and Severity Index (EASI) Body Region Weighting

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

* No adjustment for body regions excluded for assessment

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

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

A = Area Score; E = erythema; I = induration/papulation; Ex = excoriation; L = lichenification; h = head and neck; u = upper limbs; t = trunk; l = lower limbs
The EASI score can vary in increments of 0.1 and range from 0.0 to 72.0, with higher scores representing greater severity of AD.

8.1.3.1. Body Surface Area – Efficacy (BSA Efficacy)

BSA Efficacy will be derived from the sum of the BSA in handprints across 4 body regions assessed as part of the EASI assessment (Table 3). Handprint refers to that of each individual subject for their own measurement. The BSA Efficacy ranges from 0 to 100%, with higher values representing greater severity of AD. Since the scalp, palms, and soles will be excluded from the BSA (Efficacy) assessment, the maximum possible value will be less than 100%.

8.1.4. Scoring Atopic Dermatitis (SCORAD)

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

Extent (A, maximum score of 100%)
To determine extent of AD, rule of 9 is used to calculate body surface area affected by AD as a percentage of the whole body surface area. Body surface area as percentage of total body surface area for each body region is as follows:

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

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

Severity (B, maximum score of 18)
A representative area of AD is selected. In this area, the severity of each of the following signs is assessed as none (0), mild (1), moderate (2) or severe (3).

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

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

Subjective Symptoms (C, maximum score of 20)
Subjective symptoms (ie, itch and sleep loss) are each scored by the subject using a visual analog scale (VAS) where “0” is no itch (or no sleep loss) and “10” is the worst imaginable itch (or sleep loss). The value for each should reflect the average on a 10 point scale for the last 3 days/nights. These scores are added to give 'C' (maximum score of 20).

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

8.1.5. Standardized Background Topical Therapy

Participants will be instructed to keep a daily record of use of standardized background topical therapy. At each visit, participant's understanding of background topical therapy requirements (see Section 6.5.1) and adherence to the use of background topical therapy will be checked. Participants will be re-educated as required. Standardized background topical therapy use and adherence with guidelines will be recorded daily in the participant eDiary during the screening period and through the EOS visit:

- Non-medicated topical therapy must be applied at least twice daily to all body areas affected with AD in the last 7 days prior to Day 1, and continued through the EOS visit;

- Medicated topical therapy that could affect AD (eg, corticosteroids, calcineurin inhibitors, tars, antibiotic creams, topical antihistamines) must be discontinued for at least 7 days prior to Day 1. See Section 6.5.1 for required background medicated topical therapy during treatment through the EOS visit.

8.1.6. Patient-reported Outcomes (PROs)

Participants will complete the PROs at the clinic prior to other clinical activities and study intervention administration. The PROs should be checked for completeness by the study site staff before proceeding with other steps of the clinical visit procedures. Compliance with scheduled PROs activities will be monitored. Delegated site staff will oversee the administration of PROs at site visits to ensure protocol compliance. Participants are given a handheld device to complete the Peak Pruritus NRS, frequency of pruritus NRS, Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) [redacted] Delegated site staff will review compliance at each visit and counsel as appropriate. If a subject has repeated non-compliance, the subject should be re-trained on the device. If a subject is unable to complete the PROs on the handheld device due to documented difficulty using the technological devices or other limitation, the subject will be permitted to enter or remain in the study. In the event of electronic malfunction, a replacement device will be shipped to the site.

Examples of the validated paper versions of Patient-Reported Outcomes instruments are included in the Appendices of this protocol. In instances where an electronic device is used to collect the PRO data, the electronic version may differ slightly in format or wording compared with the paper version to facilitate electronic implementation.

8.1.6.1. Peak Pruritus Numerical Rating Scale (NRS)

The severity of itch (pruritus) due to AD will be assessed using the Peak Pruritus NRS, a validated horizontal NRS (see Appendix 12).[21,22] Participants will be asked to assess their worst itching due to AD over the past 24 hours on an NRS anchored by the terms "no

itch" (0) and "worst itch imaginable" (10). This item will be administered to all participants. Participants will enter Peak Pruritus NRS assessment into an eDiary.

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

8.1.6.2. Frequency of Pruritus

The frequency of itch (pruritus) due to AD will be assessed using a horizontal NRS (see Appendix 13). Participants will be asked to assess frequency of itching due to AD over the past 24 hours on an NRS anchored by the terms "never/no itching" (0) and "always/constant itching" (10). This item will be administered to all participants. Participants will enter the frequency of pruritus NRS assessment into an eDiary.

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

CCI

[redacted]

8.1.6.4. Patient Global Assessment (PtGA)

The PtGA asks the subject to evaluate the overall cutaneous disease at that point in time on a single-item, 5-point scale (see Appendix 15). The same category labels used in the Investigator's Global Assessment will be used for the Patient Global Assessment, ie, "severe (4)", "moderate (3)", "mild (2)", "almost clear (1)", and "clear (0)". The PtGA should be completed as per Schedule of Activities. This single-item scale will be administered to all participants.

8.1.6.5. EuroQol Quality of Life 5-Dimension Youth Scale (EQ-5D-Y)

The EQ-5D is a validated, standardized, generic instrument that is the most widely used preference-based health-related quality of life questionnaire in cost-effectiveness and health technologies assessment (HTA) (See Appendix 16).[23-26] Recently, a version of the instrument specifically developed and validated for use by youths age 12 through 17 years is called the EQ-5D-Y.[27-29]

The EQ-5D-Y should be completed as per Schedule of Activities.

8.1.6.6. Children's Dermatology Life Quality Index (CDLQI)

The DLQI is a validated general dermatology questionnaire that consists of 10 items to assess subject-reported health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment) (see Appendix 17).[30] It has been extensively used in clinical trials for AD. The CDLQI 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.[31] A version of the instrument specifically developed and validated for use by adolescents from age 12 to 17 is called the CLDQI.[32] The CDLQI should be completed as per Schedule of Activities.

8.1.6.7. 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 (see Appendix 18). This instrument is appropriate for use by participants aged 12 and older.[33,34] The POEM should be completed as per Schedule of Activities.

8.1.6.8. Dermatitis Family Impact (DFI) Questionnaire

The DFI is a validated 10-item measure filled out by the parent/caregiver of the patient used to assess the impact of the patient's eczema on the family (see Appendix 25). The instrument has a recall period of 7 days, and should be completed as the Schedule of Activities.

8.1.6.9. Hospital Anxiety and Depression Scale (HADS)

The HADS is a validated 14-item PRO measure used to assess states of anxiety and depression over the past week[35] (see Appendix 19). The instrument has been validated for use by adolescents aged 12 and older.[35] The HADS should be completed as per Schedule of Activities.

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

The PSAAD is a daily patient reported symptom diary. The preliminary version (see Appendix 20) is a 15-item questionnaire that includes 11 items developed to measure symptoms of AD, capturing those identified by patients to be most important, based on a 24-hour recall. Analysis of the PSAAD will be based solely on these 11 items. Four additional items were added for CCI psychometric validation purposes (Sleep & Usual Activities Questions and Patient Global Impression of Severity [PGIS] & Patient Global Impression of Change Questions [PGIC]). The PSAAD is an electronic PRO that was developed through concept elicitation and cognitive debriefing in AD patients ages 12 to 67; CCI [redacted] All technical documents describing measurement properties of the PSAAD will be submitted as required to the Regulatory Agencies upon finalization. The PSAAD should be completed by participants as per Schedule of Activities on an eDiary.

8.1.6.11. Pediatric FACIT-F (Peds-FACIT-F)

The Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT–F) is a validated subject completed questionnaire consisting of 13 items that assess fatigue. Instrument scoring yields a range from 0 to 52, with higher scores representing better overall health status (less fatigue) (see Appendix 21).[36] The Pediatric FACIT-F, suitable or adolescents 12-17, should be complete as per the Schedule of Activities.[37]

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of activities.

8.2.1. Physical Examinations and Medical 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. 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. Additionally, a record of prior vaccinations will be obtained to determine if the subject has received tetanus, diphtheria and/or pertussis vaccines within the past 5 years.

- Complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose, except as noted below:

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

  - 1 year: Previous non-systemic drug treatments for AD including topical treatments;
  - Lifetime history of previous systemic treatment for AD and reason for stopping any systemic treatment for AD;
  - Lifetime history of intolerance/allergy to any drug, regardless of indication.

- A complete physical examination will include, at a minimum, assessments of the general appearance; skin; head, eyes, ears, nose and throat (HEENT); mouth, heart; lungs; breast (optional); abdomen; external genitalia (optional); extremities; neurologic function; and lymph nodes. Complete physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines. Height (inches or centimeters) and weight (lbs. or kg) will be measured and recorded in the source document at the screening visit. Height and

weight will be measured without the participant wearing shoes. Height and weight (lbs. or kg) will continue to be measured and recorded at various time points described in the SCHEDULE OF ACTIVITIES.

- A targeted physical examination will include, at a minimum, assessments of the skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the participant. Targeted physical examinations must be performed by the investigator, sub-investigator or a qualified health professional per local guidelines.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Pulse rate and blood pressure will be assessed pre-dose. The same method should be used consistently throughout the study.
- For Germany and UK only: Temperature will be assessed pre-dose. The same method/location should be used consistently for a given subject throughout the study, based on standard local practice (e.g. oral, tympanic, rectal, axillary, skin, temporal artery). Temperatures are being collected for investigator use in assessing potential infection and will be maintained in the source documents only.
- Pulse rate and blood pressure measurements will be assessed in a seated position, 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) with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Pulse rate and blood pressure measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Participants should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurements.

8.2.3. Chest Imaging

Chest X-ray (posterior-anterior and lateral views) or other appropriate diagnostic image (ie, chest computed tomography or MRI) is recommended but not mandatory for adolescents (as per local guidelines and standard of care) at screening or within 12 weeks prior to Study Day 1. Such imaging must be read by a qualified radiologist and show no evidence of current, active TB. Documentation of the official reading must be located and available in the source documentation.

For Germany only: Chest imaging is not required for screening in this study. In addition to the use of the QFT-G testing, if the use of chest imaging is considered medically necessary to exclude active TB, chest MRI may be performed at the discretion of the Principal Investigator for screening, unless previously performed and documented within 12 weeks

prior to Study Day 1. If performed, the MRI must be read by a qualified radiologist and show no evidence of current, active TB. Documentation of the official reading must be located and available in the source documentation.

8.2.4. Tuberculosis Testing

At the time of screening, all participants will undergo tuberculosis (TB) testing unless performed within 12 weeks of Day 1. QFT-G is the preferred testing method. If the QFT-G test cannot be performed, or if the results cannot be determined by the reference laboratory to be either positive or negative, then participants may be screened using the PPD test with approval of the Pfizer clinician.

For Japan only: While QuantiFERON® is the preferred testing method, the T-SPOT®.*TB* test is also permitted. Like QuantiFERON®, the T-SPOT®.*TB* test is an in vitro diagnostic test for *M. tuberculosis* infection; however, it differs in that it uses a peptide cocktail simulating ESAT-6 and CFP-10 proteins to stimulate peripheral blood mononuclear cells. T-SPOT®.*TB* testing will be performed at the site's local laboratory. Borderline results from the T-SPOT®.*TB* test should be considered exclusionary. If the T-SPOT®.*TB* test results are indeterminate, the test should be repeated. If the result of the repeat test is indeterminate, then participants may be screened using Mantoux/PPD skin testing following consultation and agreement with the Pfizer Medical Monitor.

In addition to TB testing as specified in this clinical protocol, a chest X-ray (or other appropriate diagnostic image (see Section 8.2.3) is recommended for adolescents.

For Germany only: In addition to TB testing as specified in this clinical protocol, a chest MRI (see Section 8.2.3) may be performed if medically necessary.

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

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

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

8.2.5. Special Safety Assessment

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

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

For participants with a past history of oral or genital herpes simplex virus infection and a presentation consistent to prior infections, further laboratory analysis may be performed at the discretion of the investigator.

8.2.6. Skin Type Assessment

As part of baseline characteristics, a skin type assessment will be done at the Day 1 visit using the Fitzpatrick Skin Type assessment (see Appendix 26). This is used to classify a person's skin type by their response to sun exposure (ie, burning or tanning).

8.2.7. Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and [QTc] intervals. Refer to Appendix 5 for [QTc] withdrawal criteria. ECGs reading will be performed by a central reader who has expertise reading and interpreting ECGs in adolescents.
- All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.
- A subject's screening ECG must not demonstrate clinically significant abnormalities prior to randomization.

8.2.8. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the Schedule of activities for the timing and frequency.

- When possible, participants should abstain from all food and drink (except water and non-study medications) for an 8-hour overnight fast prior to labs that include the lipid profile panel on Day 1, Week 4, Week 12, and EOS. All other labs do not require fasting.

- Sample collection, labeling, storage, and shipping information can be found in the laboratory manual.

- 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. The laboratory reports must be filed with the source documents. 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 Pfizer clinician.
    - 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 Schedule of activities.
    - 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.

8.2.8.1. Hepatitis Testing

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

Interpretation of Hepatitis B Testing Results:

HBsAg negative and HBcAb negative: Subject is eligible for the study;

HBsAg positive and HBcAb negative: Subject is excluded from study participation;

HBsAg negative and HBcAb positive and HBsAb positive: Subject is eligible for study;

HBsAg negative and HBcAb positive and HBsAb negative: Subject is excluded from study participation.

For China, Taiwan and countries where HBV DNA testing is required (except Japan): Participants who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Participants who have HBV DNA at or above lower limit of quantification (LLQ) will be excluded. Participants who are HBV DNA negative or below LLQ may be randomized but will have repeat HBV DNA testing at Week 12 (or Early Termination).

For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all participants rather than as a reflex test. Participants with negative results for HBsAg, HBcAb and HBsAb may be eligible. Participants who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Participants who are

HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND participants who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Participants who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 (or Early Termination).

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

Interpretation of Hepatitis C Testing Results:
HCV Ab positive and HCV RNA positive: Subject is excluded from study participation.

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

Adolescent participants without documentation confirming prior VZV infection (chickenpox), or without documented evidence of having received at least a single dose of the varicella vaccine in countries where the varicella vaccine is approved and standard of care will be tested for VZV IgG Ab as described in the lab manual. Participants that lack evidence of prior exposure to VZV based on serological VZV IgG Ab testing are excluded.

8.2.8.3. Viral Studies

Blood samples will be collected at baseline, Week 4 and Week 12 for viral studies but will be analyzed only if the subject has suspected viral infection/reactivation. Additional sample collection instructions will be provided in the lab manual. The retained samples will be destroyed upon subject completion of this study or the long-term extension study.

8.2.9. Suicidal Ideation and Behavior Risk Monitoring

Participants meeting exclusionary results as described in Section 5.2 on the C-SSRS, SBQ-R and PHQ-8 should be excluded from participation; it is recommended the subject's primary care physician (PCP) should be informed, and the subject referred to a mental health professional, either by the PCP or the investigator according to their usual practice.

8.2.9.1. 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 (see Appendix 22).[38] At the screening visit, if there are "yes" answers on items 4 or 5 in the past year or on any question in the suicidal behavior section of the C-SSRS in the past 5 years, the subject will not be included in the study. Trained site staff is to administer the C-SSRS to all participants at screening and assess the subject's eligibility based on the answers.

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

The Suicidal Behaviors Questionnaire-Revised (see Appendix 23) is a patient-reported questionnaire consisting of 4 items to assess suicidal ideation, suicide attempts, threat of suicidal behavior, and likelihood of suicidal behavior. At the Screening Visit, if SBQ-R total score ≥8, the subject will not be included in the study.[39] Site staff is to administer the SBQ-R to all participants at screening and score immediately.

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

The Patient Health Questionnaire – 8 items (see Appendix 24) is a patient-reported questionnaire consisting of 8 items to assess the subject's depression level. At Screening Visit, if PHQ-8 total score ≥15, the subject will not be included in the study.[40] Site staff is to administer the PHQ-8 to all participants at screening and score immediately.

8.2.10. Pregnancy Testing

For all WOCBP, a serum pregnancy test with a sensitivity of at least 25 mIU/mL, will be performed at Screening. A urine pregnancy test, will be performed at every site visit including the follow-up visit (EOS) to confirm the participant has not become pregnant during the study. Serum and urine pregnancy test kits will be provided by the central laboratory with sample collection instructions provided in the package insert.

A negative pregnancy test result is required at the baseline visit before the participant may receive the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Participants who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory, with a sensitivity of at least 25 mIU/mL).

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

8.3. Adverse Events and Serious Adverse Events

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

AE 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 / study (see Section 7 and Appendix 5).

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 study intervention), through and including a minimum of 28 calendar days; except as indicated below after the last administration of the study intervention.

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

AEs and SAEs that begin before the start of the study intervention but after obtaining informed consent are recorded on the Medical History/Current Medical Conditions section of the case record form (CRF), not the AE section. AEs and SAEs that begin from the first administration of the study intervention are recorded on the AE CRF. SAEs are also reported on the CT SAE Report Form from the time of obtaining informed consent is signed.

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 AE or SAE 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.

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

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 study intervention must be reported to Pfizer Safety.

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

Both non-serious AEs and SAEs occurring during the active collection period as defined in Section 8.3.1. and after the start of study intervention are recorded on the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE 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 non-leading 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 a 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 (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a 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/IEC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention 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 study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention 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 study intervention;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating participant.
- Refer to Section 6.4 for examples of medication errors related to compliance with study intervention.

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

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

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

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

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 8 tablets within a 24-hour time period [+/- 2 hours] 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 Pfizer Clinician immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 3 days).
3. A plasma sample for PK analysis may be requested by the Pfizer clinician (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 Pfizer clinician based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

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

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

- At 22 hours (±30 min) after the participant's last dose taken on the day prior to the Week 8 visit (this corresponds to 2.0 hours (±30 min) pre-dose relative to the dose taken at the Week 8 visit, assuming a regular dosing schedule of once every 24 hours).
- At 2.0 hours (±30 min) post-dose at Week 12.

All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. The exact time of the sample collection is to be noted on the source document and data collection tool (eg, CRF). Samples obtained outside the windows specified in the Schedule of Activities will be considered a protocol deviation. For Early Termination (ET) visits, if the participant discontinues before Week 8 do not collect PK samples. If the ET visit occurs after Week 8, collect PK samples only if the participant takes the study intervention at the site visit.

- The plasma will be stored in appropriately labeled screw-capped polypropylene tube at approximately -20°C within 1 hour of collection.
- Further details regarding the collection, processing, storage and shipping of the blood samples will be provided in the lab manual.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.
- As part of understanding the PKs of the study intervention, CCI [redacted]

8.5.1. Shipment of Pharmacokinetic Samples

The central laboratory will provide collection materials and directions for packaging and shipment of samples and will forward samples to the contract analytical laboratory. The contract analytical laboratory will be provided with randomization codes so that only samples in the PF-04965842 treatment groups are assayed. Placebo samples may be assayed in the event of suspected error in participant randomization. Refer to the central lab vendor manual for further information.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable to the study.

9. STATISTICAL CONSIDERATIONS

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The primary estimand of the main study is a composite estimand (accounting for both treatment adherence and response), defined according to the primary objective and is in alignment with the primary endpoint. It includes the following four attributes:

- Population: Participants with moderate-to-severe AD as defined by the inclusion criteria and exclusion criteria and are randomized;
- Variable: Response based on IGA and EASI-75 at Week 12 (co-primary endpoints) and any other binary outcome measures such as response based on NRS4, % BSA < 5%, EASI-50, EASI 90, EASI-100, SCORAD50, SCORAD75. Participants who discontinue from the study treatment for any reason are considered as treatment failures or non-responders;
- Intercurrent event: The intercurrent event is captured through the variable definition;
- Population-level summary: Proportion of participants who are responders in each treatment group and differences in proportions of responders between each PF-04965842 dose and placebo at Week 12.

The secondary estimand of this study is the hypothetical estimand, which estimates the effect as if all patients maintain their randomized treatment. It includes the following four attributes:

- Population: Participants with moderate-to-severe atopic dermatitis as defined by the inclusion criteria for the double-blind phase and are randomized;
- Variable: Change from baseline to Week 12 in a continuous outcome measure such as total scores obtained from EASI, NRS, SCORAD, %BSA, PSAAD, PtGA, HADS, POEM, CDLQI, EQ-5D-Y, DFI, Peds FACIT-F;
- Intercurrent event: All data after an intercurrent event (eg discontinuation of treatment), if collected, will be censored;
- Population-level summary: Difference in least-square means between each PF-04965842 dose and placebo.

9.2. Sample Size Determination

A total sample of 225 participants, with 75 participants randomized to PF-04965842 200 mg QD, 75 participants randomized to PF-04965842 100 mg QD, 75 participants randomized to matching placebo (1:1:1 randomization) is planned. This would provide at least 80% power to detect a difference of at least 20% in IGA response rate between either dose of PF-04965842 and placebo, assuming the placebo response rate is 12% at Week 12. This will also provide at least 96% power to detect a difference of at least 30% in EASI-75 response

rate between either dose of PF-04965842 and placebo, assuming the placebo response rate is 23% at Week 12.

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

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

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Full Analysis Set (FAS)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they are randomized to.
Per-Protocol Analysis Set (PPAS)	All participants from the FAS who do not have any major protocol violations related to inclusion / exclusion criteria, compliance with randomized dosing, background therapy or visit windows and any other major protocol violation. The participants excluded from this set will be determined and documented before the study is unblinded.
Safety Analysis Set (SAF)	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

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

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, for all endpoints listed in Section 3, and procedures for accounting for missing data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

9.4.2. Testing Procedure for Multiple Comparisons

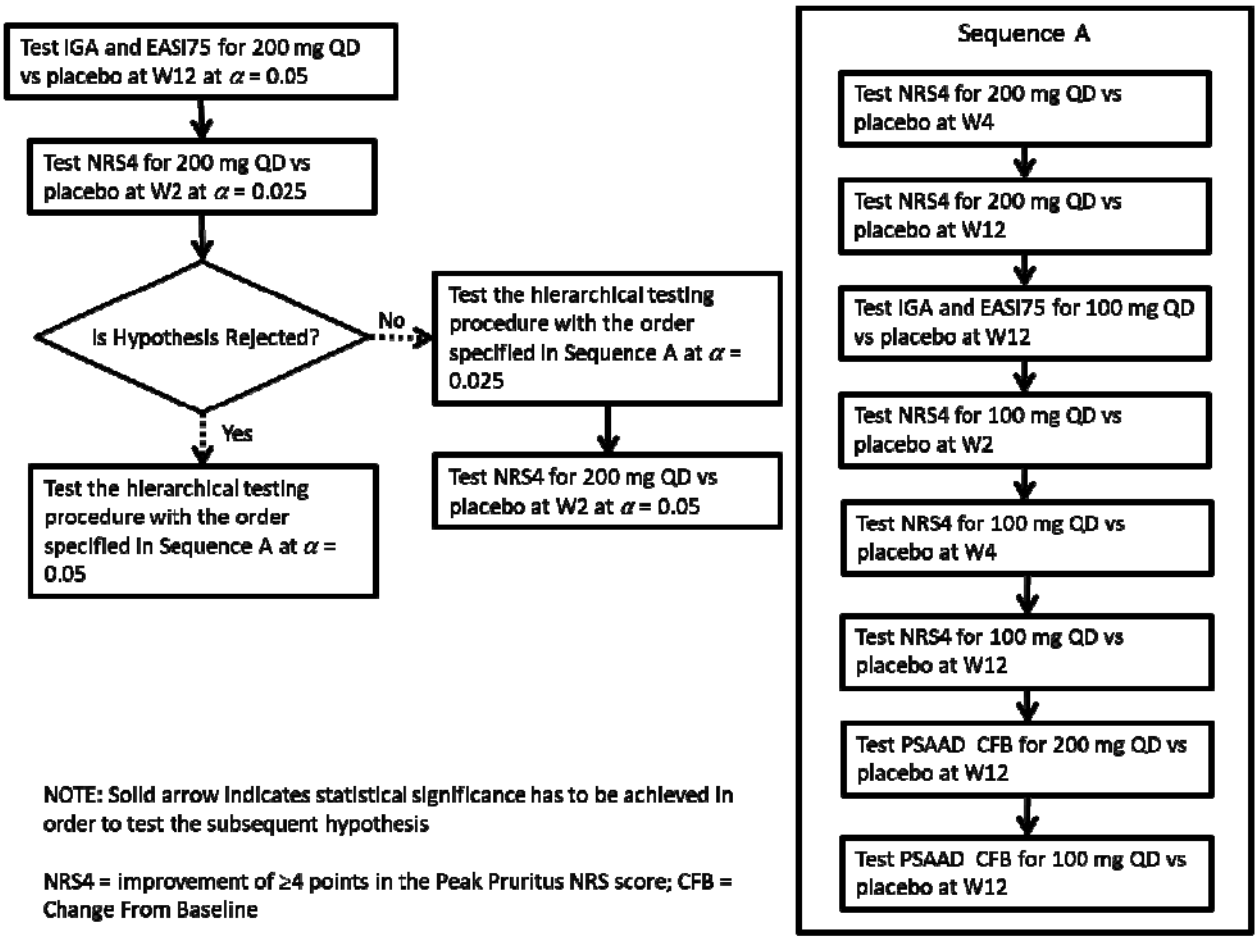
The familywise Type-I error rate for testing the co–primary and key secondary endpoints will be strongly controlled at 5% using a sequential, Bonferroni–based iterative multiple testing procedure.

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

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

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

Figure 1 Schematic for Multiple Testing Procedure



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

9.4.2.1. Analysis of the Primary Endpoints

The co–primary endpoints will be analyzed using the (Cochran–Mantel-Haenszel) test adjusted by baseline disease severity group (moderate and severe) and for a given dose both must achieve statistical significance to meet the primary objective. The difference between each active group and the placebo group in the proportion of participants achieving IGA response (similarly for EASI-75) along with its 95% confidence interval (using the normal approximation for the difference in binomial proportions) will be reported. If a participant withdraws from the study, then this participant will be counted as non-responder for endpoints after withdrawal. Additional secondary analyses will utilize missing at random (MAR) and missing not at random (MNAR) approaches (eg, longitudinal mixed models and tipping point analyses).

9.4.2.2. Analysis of Secondary Endpoints

The key secondary endpoints which are expressed as proportions such as EASI-75, and the proportion of participants achieving a 4-point improvement from baseline in the severity of Peak Pruritus NRS measure will be analyzed using the same method as for the co-primary

endpoints. This would also apply to any other binary endpoint in the study, such as the proportion of participants with PtGA of AD of clear (0) or almost clear (1) and >=2 point improvement from baseline over 12 weeks. All binary secondary endpoints are based on responder definitions and the primary analysis is estimating a composite estimand. So missing responses would be defined as "non-response" while defining the binary outcomes.

For continuous endpoints, and change from baseline in the pruritus severity and frequency using the NRS measure at all scheduled time points, a mixed-effect model with repeated measures (MMRM) will be used. This model will include the factors (fixed effects) for treatment group, disease severity group, visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will be tested at the pre–specified primary time point, Week 12, as well as at the other time points by time point-specific contrasts from the MMRM model. The primary analysis of all continuous secondary endpoints is estimating a hypothetical estimand and so no imputations for missing data will be used. The MMRM methodology as mentioned above will be used under an assumption that missing data is Missing At Random (MAR).

9.4.3. Safety Analyses

All safety analyses will be performed on the Safety Population. The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- Treatment-emergent AEs and SAEs;
- Withdrawals from active treatment due to AEs;
- Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials or met other criteria that required the event be classified as serious;
- Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and lipid profiles);
- Vital signs;
- ECG parameters if applicable.

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

9.4.4. Analysis of PK Endpoints

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

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[redacted]

9.5. Interim Analyses

There are no formal interim analyses planned. There will be a program-level E-DMC (see below) who will periodically review the safety data from the study.

9.5.1. Data Monitoring Committee (DMC)

This study will use an E-DMC. The E-DMC is independent of the study team and includes only external members. The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter.

The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate. Composition of the E-DMC and processes under which the E-DMC operates will be documented in the E-DMC charter.

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 ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations, including applicable privacy laws.

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC 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/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- 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 study intervention, 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 (parent(s)/legal guardian) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent/assent 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/IEC 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/IEC 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/assent 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 ICF.
- Participants must be re-consented to the most current version of the ICF(s) and if the age of majority is reached during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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 have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.
- To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets 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. Committees Structure

External Data Monitoring Committee (E-DMC)
See Section 9.5.1.

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

10.1.6. 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 (Clinical Study Report [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.

10.1.7. 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/IEC 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 and contracts.
- 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 ICFs, 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 so 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 sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow 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 sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. 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's site.
- Data reported on the CRF or entered in the 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 the Clinical Monitoring Plan.

10.1.9. 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 CRO if requested to do so by the responsible IRB/IEC 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/IEC 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.

10.1.10. 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 one 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 submit 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 to 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.

10.1.11. 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 clinical trial management 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 study intervention identifiers, participant study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the 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. For sites other than a Pfizer CRU, 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 tests detailed in Table 6 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If such a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF. This is applicable for repeat tests.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
    1. Refer to Section 5.1 Inclusion Criteria and Section 8.2.10 Pregnancy Testing for screening pregnancy criteria.
    2. For details of timing of recommended pregnancy testing see the Schedule of Activities.

Table 6. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC RBC Morphology Reticulocyte Count	White blood cell (WBC) count with Differential: Total Neutrophils Lymphocytes Monocytes Eosinophils Basophils Coagulation Panel Activated Partial Thromboplastin Time (APTT) Prothrombin Time/International Normalized Ratio (PT/INR)	
Clinical Chemistry[1]	Blood urea nitrogen (BUN) Creatinine Creatine Phosphokinase Glucose (non-fasting) AST	ALT GGT Potassium Sodium Calcium	Chloride Uric acid Albumin Total Protein Total CO2 (bicarbonate)	Total, indirect and direct bilirubin Alkaline phosphatase Lactate dehydrogenase
Lipid Profile Panel[1]	Total cholesterol	Triglycerides	LDL	HDL
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, nitrite, leukocyte esterase by dipstick • Microscopic examination and/or culture[2]			
Other Tests	• HIV[3] • HBsAg[3] • HBcAb[3] • HBsAb[3,4] • HBV DNA[5] • HCVAb[3,4] • HCV RNA[3,4] • VZV IgG Ab[6] • Serum Pregnancy Test[3,7] • Urine pregnancy test[7] • QFT-G or PPD (if applicable) or T-SPOT®.*TB* test (Japan only)[8] • All study-required laboratory assessments will be performed by a central laboratory, with the exception of: urine pregnancy tests, which will be performed on the Day of the study visits. [redacted] CCI C [redacted]			

Table 6. Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
	CCI [redacted]

1. Lipid profile panel should be performed after at least an 8 hour fast, when possible. Lipid profile panel will be completed at Day 1, Week 4, Week 12, and EOS, and will include total cholesterol, LDL, HDL, and triglycerides.
2. Microscopy with culture performed as appropriate.
3. At Screening only. HIV testing will be performed for all participants.
4. HBsAb reflex testing only if HBsAg negative but HBcAb positive. HCV RNA is reflex testing only if HCVAb is positive. For Japan only: In addition to HBsAg and HBcAb, HBsAb testing will be performed at Screening for all participants rather than as a reflex test.
5. For China, Taiwan and countries where HBV DNA testing is required (except Japan): Participants who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Participants who have HBV DNA at or above LLQ will be excluded. Participants who are HBV DNA negative or below LLQ may be randomized and will have repeat HBV DNA testing at Week 12 (or early termination). For Japan only: Participants with negative results for HBsAg, HBcAb and HBsAb tests may be eligible. Participants who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Participants who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND participants who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have reflex testing for HBV DNA. Participants who are HBV DNA negative or below LLQ may be randomized but will have HBV DNA repeated at Week 12 (EOT/ET).
6. For participants who do not have documentation of prior VZV infection (chickenpox) or at least one dose of varicella vaccine.
7. Pregnancy testing for all WOCBP.
8. PPD results should be read within 48 to 72 hours. For Japan only: QFT-G is preferred but T-SPOT®.*TB* test may be performed instead through the site's local laboratory.
9. Results will be blinded after the screening visit.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative 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 Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs 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 pre-existing 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 AE or SAE if they fulfil 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 pre-existing 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, which 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 pre-existing 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 AE and/or SAE

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) non-serious adverse events (AEs); and (3) exposure to the study intervention 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
Non-serious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (And 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 diagnostics 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 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 a 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 and the relevant IRBs. 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 and the relevant IRBs.

- The investigator may change his/her opinion of causality in light of follow-up information and send a 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 study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor" and "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 health care 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 post-mortem 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 the sponsor 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 it becomes 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.
- Contacts for SAE reporting can be found in the investigator site file.

SAE Reporting to Pfizer Safety via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Pfizer Safety.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigator site file.

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

Definitions:

Woman of Childbearing Potential (WOCBP)
For this study, a female participant is considered fertile (ie WOCBP) starting at 12 years of age (regardless of whether they have experienced/reported menarche) unless permanently sterile (see below).

Women with one of the following are not considered WOCBP

- 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 conditions 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.

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

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

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

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

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

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

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 study intervention; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study intervention;
  - 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 study intervention 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 study intervention, 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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

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: Monitoring and Discontinuation Criteria

Monitoring Criteria

The following laboratory abnormalities require prompt retesting:

- Neutrophil counts <1000 neutrophils/mm^3; confirmed promptly by repeat testing, ideally within 3-5 days;
- Platelet counts <75,000 platelets/mm^3; confirmed promptly by repeat testing, ideally within 3-5 days;
- Any single hemoglobin value <9.0 g/dL or one that drops ≥2 g/dL below baseline; confirmed promptly by repeat testing, ideally within 3-5 days;
- Any single AST and/or ALT elevation >3 times the upper limit of normal regardless of accompanying symptoms or the total bilirubin should prompt repeat testing. This should also prompt review of Appendix 6 (Liver Safety); additional investigations must be conducted.

Temporary Interruption to Dosing

Temporary interruption to dosing is not allowed in this study, except when indicated for participant safety. Sponsor clinician must be informed when temporary interruption occurs and the duration of temporary interruption must not exceed 14 days.

Discontinuation Criteria

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

- Marked prolongation of the QTcF interval to >500 ms or >60 ms change from screening ECG.
- Serious infection (see definition for Serious Adverse Events in Section 10.3.2).
- Any bleeding event thought to be associated with a platelet count reduction per the judgement of the investigator (or, if necessary/desired, following discussion with sponsor).
- Adverse event, per judgment of the investigator, requiring discontinuation from treatment (or, if necessary/desired, following discussion with sponsor).
- Confirmed pregnancy (as described in Section 8.2.10)

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

- Two sequential platelet counts <50,000/mm^3. If the subject has a platelet count <25,000/mm^3, study intervention should be temporarily withheld pending the confirmatory retest.
- Two sequential neutrophil counts <500/mm^3.
- Two sequential lymphocyte counts <500/mm^3.
- Two sequential hemoglobin assessments <8.0 g/dL and / or a decrease of > 30% from baseline value.
- Any of the following:
  - Two sequential AST or ALT elevations >3 times the upper limit of normal with at least one total bilirubin value >2 times the upper limit of normal.
  - Two sequential AST or ALT elevations >3 times the upper limit of normal with an abnormal international normalized ratio (INR).
  - Two sequential AST or ALT elevations >3 times the upper limit of normal accompanied by symptoms consistent with hepatic injury.
  - Two sequential AST or ALT elevations >5 times the upper limit of normal, regardless of total bilirubin or accompanying symptoms.

  NOTE: Any of the above findings should prompt review of "The Potential Cases of Drug-Induced Liver Injury," Appendix 6 for which additional investigations must be conducted.
- Two sequential increases in serum creatinine that are >50% over the average of screening and baseline values AND an absolute increase in serum creatinine ≥0.5 mg/dL. At the time of study completion or discontinuation, if a subject should exhibit elevations in serum creatinine ≥33% above the average of screening and baseline values, they will be re-tested every 1 to 2 weeks until the serum creatinine elevation is fully reversed to within 10% of the average of screening and baseline values or has stabilized.

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

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

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

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

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

The threshold of laboratory abnormalities for a potential DILI case depends on the 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 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: Prohibited Concomitant Medications

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

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

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

Note 2: All CYP2C9 and CYP2C19 inducers require a period of washout of at least 5 half-lives plus 14 days prior to the first dose of study intervention. For example, the average half-life of carbamazepine after repeat dosing is 15 hours. The washout period is calculated as the sum of 5 half-lives (approximately 3 days) and an additional 14 days for a total of 17 days prior to the first dose of study intervention.

Note 3: Half-life refers to the half-life of the parent drug and its metabolites, which are inhibitors or inducers. The longest half-life should be used to calculate the period necessary to washout a medication prior to the first dose of investigational product. For example, fluoxetine and its metabolite norfluoxetine are both inhibitors of CYP2C19. The terminal half-life of fluoxetine is up to 6 days. However, norfluoxetine has a longer half-life, up to 16 days. Therefore, the washout period should be calculated based on the 5 times the half-life of norfluoxetine, for a total of approximately 80 days prior to the first dose of investigational product.

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

10.8. Appendix 8: Country-specific Requirements

Section 5.2:

Exclusion Criteria #6:

- A participant known to be infected with Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C (Section 8.2.8.1).
    - For China, Taiwan and countries where HBV DNA testing is required (except Japan): Participants who are HBsAg negative, HBcAb positive, and HBsAb positive will have reflex testing for HBV DNA. Participants who have HBV DNA at or above LLQ will be excluded. Participants who are HBV DNA negative or below LLQ may be randomized but will have repeat HBV DNA testing at Week 12 (or Early Termination).
    - For Japan only: Participants with negative results for HBsAg, HBcAb and HBsAb may be eligible. Participants who are HBsAg negative, HBcAb negative and HBsAb positive and provide documentation of prior HBV vaccination may be eligible and will not require HBV DNA monitoring during the study. Participants who are HBsAg negative, HBcAb negative and HBsAb positive without documentation of prior HBV vaccination AND participants who are HBsAg negative, HBcAb positive, and HBsAb positive at screening will have reflex testing for HBV DNA. Participants who are HBV DNA negative or below LLQ may be randomized but will have repeat HBV DNA testing at Week 12 (or Early Termination).

Section 1.3 Schedule of Activities and Section 8.2.2 Vital Signs:

For Germany and UK, Temperature monitoring has been added as part of the vital signs measurements.

- Temperature will be assessed pre-dose. The same method/location should be used consistently for a given subject throughout the study, based on standard local practice (e.g. oral, tympanic, rectal, axillary, skin, temporal artery). Temperatures are being collected for investigator use in assessing potential infection and will be maintained in the source documents only.

Section 5.2 Exclusion Criteria, Section 8.2.3 Chest Imaging, Section 8.2.4 Tuberculosis Testing:

For Germany, the recommendation to perform chest imaging for screening in adolescents has been removed. It is also indicated that, in addition to the use of the QFT-G test, if the use of

chest imagining is considered medically necessary to screen for active TB, chest MRI may be performed at the discretion of the Principal Investigator.

- For Germany only: Chest imaging is not required for screening in this study. In addition to the use of the QFT-G testing, if the use of chest imaging is considered medically necessary to exclude active TB, chest MRI may be performed at the discretion of the Principal Investigator for screening, unless previously performed and documented within 12 weeks prior to Study Day 1. If performed, the MRI must be read by a qualified radiologist and show no evidence of current, active TB. Documentation of the official reading must be located and available in the source documentation.

10.9. Appendix 9: Abbreviations

AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	Area under the curve
AUC_{inf}	area under the curve from time zero extrapolated to infinity
AUC_{last}	area under the curve from time zero to last quantifiable
AUC_{tau}	area under the curve over dosing interval tau
BCG	Bacille Calmette Guérin
BfArM	(German) Federal Institute for Drugs and Medical Devices
BID	twice a day
BSA	body surface area
C_{max}	maximum concentration
CD	cluster of differentiation
CDLQI	Children's Dermatology Life Quality Index
CFB	Change from baseline
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	clearance/fraction of dose absorbed
CO2	carbon dioxide
CK	creatine kinase
CRF	case report form
CsA	cyclosporine A
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CV	Coefficient of variation
DFI	Dermatitis Family Impact Questionnaire
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index
EBV	Epstein Barr virus
EC	ethics committee
ECG	electrocardiogram
eDiary	electronic diary
eCRF	electronic case report form
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency

EOS	end of study
EOT	end of treatment
ePRO	electronic Patient Reported Outcome
EQ-5D-5L	EuroQol Quality of Life 5-Dimension 5-Level Scale
EQ-5D-Y	EuroQol Quality of Life 5-Dimension Youth Scale
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FACs	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMC	geometric mean concentration
GMFR	geometric mean fold rise
HADS	Hospital Anxiety and Depression Scale
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C viral antibody
HCV RNA	hepatitis C viral ribonucleic acid
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
CCI [redacted]	[redacted]
HSV	herpes simplex virus
HTA	health technologies assessment
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	Independent Ethics Committees
IFN	interferon
IFN-α	interferon-alpha
IFN-γ	interferon-gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IgG	immunoglobulin G
IIV	inter individual variability

IL	interleukin
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive web response
JADE	Jak1 Atopic Dermatitis Efficacy and safety program
JAK	Janus kinase
JAK1	Janus kinase 1
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LDL	low-density lipoprotein
LFT	liver function test
LLQ	lower limit of quantification
LSLV	last subject last visit
LTE	long-term extension
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	mixed-effect model with repeated measures
MNAR	missing not at random
MRI	magnetic resonance imaging
MTX	methotrexate
N/A	not applicable
NB-UVB	narrowband ultraviolet B light
NRS4	numerical rating scale 4 points improvement from baseline
NRS	numerical rating scale
OTC	over-the-counter
PCD	primary completion date
PCP	primary care physician
PDE4	phosphodiesterase type 4
PEER Study	Pediatric Eczema Elective Registry Study
Peds-FACIT-F	Pediatric Functional Assessment of Chronic Illness Therapy Fatigue Scale
PRN	pertactin
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PGx	Pharmacogenomics
PHQ-8	Patient Health Questionnaire - 8 items
PK	Pharmacokinetics
POC	proof of concept
POEM	Patient-Oriented Eczema Measure

PPAS	per-protocol analysis set
PPD	purified protein derivative test
PRO	patient reported outcome
PSAAD	Pruritus and Symptoms Assessment for Atopic Dermatitis
PT	prothrombin time
PtGA	Patient Global Assessment
QD	once daily
QFT-G	QuantiFERON®-TB Gold
QT	Q wave interval
QTc	corrected Q wave interval
QTcF	Fridericia corrected Q wave interval
R_{ac}	accumulation ratio
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBQ-R	Suicide Behaviors Questionnaire-Revised
SCORAD	Scoring Atopic Dermatitis
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
t½	Half-life
T_{max}	time to maximum absorption
TB	tuberculosis
TBili	total bilirubin
TCI	topical calcineurin inhibitors
TCS	Topical corticosteroids
Tdap	tetanus, diphtheria and acellular pertussis combination vaccine
TdP	Torsade de Pointes
TYK2	tyrosine kinase 2
UK	United Kingdom
ULN	upper limit of normal
US	United States
UVA	ultraviolet A light
UVB	ultraviolet B light
VAS	visual analog scale
V/F	volume of distribution/fraction absorbed
VZV	varicella zoster virus
WBC	white blood cell
WOCBP	women of childbearing potential

10.10. Appendix 10: Diagnostic Criteria for Atopic Dermatitis

Per Inclusion Criterion 2, a subject is to have a clinical diagnosis of AD according to the criteria of Hanifin and Rajka.[20]

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

10.11. Appendix 11: Immunogenicity Sub-study

A STUDY OF IMMUNOGENICITY FOLLOWING ADMINISTRATION OF TETANUS, DIPHTHERIA AND ACELLULAR PERTUSSIS COMBINATION VACCINE (TDAP) IN ADOLESCENT PARTICIPANTS 12 TO <18 YEARS OF AGE WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS RECEIVING PF-04965842 OR PLACEBO

Objective:

To evaluate the effect of PF-04965842 on immunogenicity to Tdap vaccine in adolescent participants 12 to < 18 years of age with moderate-to-severe AD.

Endpoints (as secondary endpoints for study B7451036)

- Mean fold increase from baseline in concentrations of IgG against tetanus toxoid, diphtheria toxoid, pertussis toxoid, pertactin (PRN), filamentous hemagglutinin (FHA), and fimbriae types 2 and 3 (FIM) at 4 weeks post-vaccination.

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Table 11-1. Immunogenicity Sub-study Additional Procedures

Sub-study Activity	Baseline	Follow-up 4 weeks after baseline	Notes
Visit number	Visit 7 (Week 8)	Visit 8 (Week 12)	Same as main study
Informed Consent	X		Separate informed consent from main study required
Review Inclusion/Exclusion criteria for sub-study	X		
Collect pre-vaccination blood samples for IgG concentrations	X		
Administer Tdap vaccine	X		
Collect post-vaccination blood samples for IgG concentrations		X	

INTRODUCTION

Global guidelines of vaccination recommend administration of various vaccines in adolescents[1,2]. PF-04965842 affects signaling of several cytokines thought to be important in humoral and cellular immunity. The effect of PF-04965842 on immunogenicity after vaccination in adolescents has not been evaluated. Findings of the sub-study will inform whether vaccination during PF-04965842 treatment would impair the immunogenicity to Tdap. The sub-study findings will also be useful for evaluating the overall risk-benefit of PF-04965842 in adolescents, and for supporting development of PF-049658042 in children <12 years of age.

This sub-study will assess immune response to Tdap vaccination in adolescent participants with AD undergoing treatment with PF-04965842 or placebo in Study B7451036.

Current information for PF-04965842 is provided in the IB. Safety information on the Tdap vaccines can be found in the product labels.

Rationale of Study Design

Tdap is chosen due to its widespread use as a booster in adolescents, the inclusion of multiple antigens that would allow evaluation of immunogenicity to a broad variety of antigens, and durable immune response.[3] The elevated IgG concentrations against the respective antigens peaked on Day 14 after Tdap vaccination and the response stabilized afterwards.[3] Therefore, IgG concentrations measured in blood samples collected 4 weeks after Tdap vaccination are expected to be representative of a durable immune response.

Available literature data do not suggest an effect of Tdap vaccine on AD disease activity or disease course.[4,5] It is therefore considered suitable to add the vaccine sub-study to the main study.

Benefit/Risk of Immunogenicity Sub-Study

The administration of the tetanus, diphtheria and pertussis combination vaccine Tdap as a booster in adolescents is consistently recommended in vaccination guidelines worldwide. Vaccination of adolescent participants with Tdap is expected to provide protection from tetanus, diphtheria and pertussis. It is expected that the findings on immunogenicity to Tdap can be extrapolated to co-administration of PF-04965842 with other vaccines due to the broad array of T-dependent antigens contained in Tdap. These findings will be useful for evaluating the overall benefit-risk of PF-04965842 in adolescents, and to provide support for developing PF-049658042 in children <12 years of age.

In the Tdap product information, injection site reactions reported in adolescents within 14 days following vaccination include pain, swelling and erythema, and systemic reactions reported in adolescents within 14 days following vaccination include headache, body ache or muscle weakness and tiredness.[6] Other than the risks described in the Tdap product information, no unique risks to adolescents related to Tdap administration are expected. Administration of the Tdap vaccine during PF-04965842 treatment may result in reduced immunogenicity to Tdap. Concentrations of antibodies against specific vaccine antigens will be measured to evaluate the effect of PF-04965842 on immunogenicity. Furthermore,

available literature data do not suggest an effect of Tdap vaccine on AD disease activity or disease course.[4,5] Overall, the benefit-risk of the immunogenicity sub-study in adolescent participants is considered favorable.

STUDY DESIGN OF SUB-STUDY

This is an optional sub-study evaluating immunogenicity to vaccine antigens following Tdap administration in participants with moderate-to-severe AD participating in study B7451036.

Up to approximately 90 eligible participants may enroll in this sub-study. The sub-study participants will remain in their treatment groups as previously randomized in the main study; up to approximately 30 participants of each treatment groups will be enrolled. Study participants are required to provide a separate informed consent (with consent by the legal guardian and assent by the adolescent, as appropriate). All eligible participants participating in the sub-study must continue with all study assessments of the main study per the Schedule of Activities.

The sub-study schedule is integrated into Visits 7 and 8 of the main study.

PARTICIPANT SELECTION

The following eligibility criteria are designed to select participants for whom participation in the sub-study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this sub-study is suitable for a particular participant.

Sub-Study Inclusion Criteria

Participant eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before participants are included in the sub-study. Participants need to maintain eligibility in the B7451036 main study. In addition, participants must meet all of the following inclusion criteria to be eligible for enrollment into the sub-study:

1. Participants are expected to continue participation in the main study from Weeks 8 to 12 as scheduled;

2. No safety issues, eg clinically significant thrombocytopenia from laboratory testing at Week 4 of the main study, and no other safety concerns at Week 8 of the main study;

3. Evidence of a personally signed and dated informed consent document indicating that the participant and his/her parent(s)/legal guardian, if applicable, has been informed of all pertinent aspects of the sub-study. A separate informed consent and assent, if applicable (from the main study consent/assent) is required. (see Appendix 10.1.3 for informed consent process);

4. Participants who are willing and able to comply with scheduled sub-study, procedures.

Sub-Study Exclusion Criteria

Participants presenting with any of the following will not be included in the study:

1. Received any prior tetanus, diphtheria or pertussis vaccine within the last 5 years of Visit 7.
2. History of any severe adverse reaction associated with a vaccine.
3. Hypersensitivity to any component of the Tdap vaccine.
4. History of Guillain-Barre syndrome.
5. A history of Arthus-type hypersensitivity reactions after a previous dose of tetanus, diphtheria or pertussis vaccine.
6. A history of encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) not attributable to another identifiable cause, within 7 days of administration of a previous dose of pertussis-containing vaccine.
7. Progressive or unstable neurological conditions.
8. Any clinical conditions that would make the participant not suitable for receiving Tdap, based on the Tdap product information.

STUDY TREATMENTS

All enrolled participants will receive a single dose of Tdap vaccine per product label.

The main study treatment will remain blinded. Tdap administration will not be blinded.

Drug Supplies

Intervention Name	Tdap
Type	Vaccine
Dosage Form	Injectable
Dose Strength	See local product information
Dosage	See local product information
Route of Administration	Intramuscular*
Sourcing	Provided locally by the sponsor
Packaging and Labeling	Provided in its commercial package

* Unless contraindicated or an alternative route is required in the product information.

Administration

A single dose of Tdap vaccine will be administered at Visit 7 (Week 8 of the main study). A locally approved vaccine product containing tetanus, diphtheria and pertussis must be used. The Tdap vaccine is to be administered by the intramuscular route (unless contraindicated or an alternative route is required by the product label). For complete instructions regarding storage and administration please refer to the product label.

Compliance

Administration of Tdap will be verified by review of source documents by the study monitors. Participants will continue with the protocol-specified procedures in the main study.

STUDY PROCEDURES

The study procedures for the sub-study are described below.

Enrollment

- Review the inclusion and exclusion criteria.
- A separate informed consent and assent if applicable will be required for the sub-study prior to any procedure of the sub-study.
- Participant enrollment will be recorded on the CRF.

Study Period

- The sub-study is integrated into the last 4 weeks of the main study intervention period. See Schema.
- Sub-study baseline visit (Visit 7 [Week 8] in main study): Pre-vaccination blood samples will be collected for measurement of concentrations of IgG against various vaccine antigens. A single dose of Tdap vaccine will then be administered.
- Sub-study follow-up visit (Visit 8 in main study): Blood samples will be collected 4 weeks post-vaccination at Visit 8 (Week 12 of the main study) for measurement of concentrations of IgG against various vaccine antigens.

ASSESSMENTS

Continue assessments described in the main study Schedule of Activities.

ADVERSE EVENT REPORTING

See Section 8.3 and Appendix 3 of the main study.

DATA ANALYSIS/STATISTICAL METHODS

Data analysis for the immunogenicity sub-study will be carried out when all enrolled participants have completed or have withdrawn from this sub-study. Results from this analysis are considered final for the sub-study.

Methodologies for summary and statistical analyses of data collected in this sub-study are summarized here and further detailed in a statistical analysis plan (SAP), which will be dated and maintained by Pfizer.

The SAP may modify what is outlined in the protocol; however, any major modifications of the endpoint definitions or their analyses will also be reflected in a protocol amendment.

Sample Size Determination

With 30 participants per arm, there is about 80% power to detect a ratio of geometric mean concentrations (GMCs) (at 4 weeks post-vaccination) between PF-04956842 200 mg QD and placebo of up to 23% (which means the GMC for 200 mg QD is at least 77% lower than the GMC for placebo). The Type-I error is set at 5%.

This sample size also provides a 95% confidence interval for the ratio of GMCs with an upper limit of ~3.15 times the estimated ratio with 95% chance.

Under an assumption of no difference, there is approximately 81% chance to rule out ratios (of GMCs 200 mg QD relative to placebo) of less than 0.64.

Similar statements apply to the 100 mg QD versus placebo comparison.

Analysis of Immunogenicity Endpoints

The primary immunogenicity analysis will be descriptive in nature; there will be no formal hypothesis testing, though 95% two-sided confidence intervals will be formed.

The IgG concentration data will be considered as continuous variables and logarithmically transformed for analysis. The results from the analysis will be reported in their original scale by back transformation. For the fold increase 4 weeks post-vaccination the ratio (post:pre) of concentration values will be calculated. Ratio values will be logarithmically transformed for analysis purposes. The geometric mean fold rise (GMFR) and geometric standard deviation of these fold rises will be calculated for each treatment arm. A 95% CI for this GMFR will be constructed by back transformation of the CI for the logarithmically transformed GMFRs computed using the Student's *t* distribution.

Binary endpoints based on proportions will be reported using number and percent. In addition to the number and percent, the Clopper-Pearson exact method will be used to compute the associated 95% confidence interval (CI) for each treatment. To assess the treatment effect on vaccine immunogenicity, the difference between the two binomial proportions (each

PF-04965842 dose – placebo), along with the exact 95% CI, computed using the unconditional exact method proposed by Chan and Zhang[7] will be reported.

Safety Analysis

All safety data from this sub-study will be reported using a similar approach and methods as the main study (see Section 9.4.3).

Interim Analysis

No interim analysis is planned for this sub-study.

REFERENCES FOR VACCINE SUB-STUDY

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3. Halperin BA, Morris A, MacKinnon-Cameron D, et al. Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in woman of childbearing age and postpartum women. Clin Infect Dis 2011; 53(9):885-92.

4. Nakajima K, Dharmage SC, Carlin JB, et al. Is childhood immunisation associated with atopic disease from age 7 to 32 years? Thorax 2007; 62(3):270-75.

5. Bernsen RM, de Jongste JC, Koes BW, et al. Diphtheria tetanus pertussis poliomyelitis vaccination and reported atopic disorders in 8-12-year-old children. Vaccine 2006; 24 (12):2035-42.

6. Adacel® [USPI]. Swiftwater, PA: Sanofi Pasteur Inc; 2005.

7. Chan IS, Zhang X. Text-based exact confidence intervals for the difference of two binomial proportions. Biometrics 1999; 55(4):1202-9.

10.12. Appendix 12: Peak Pruritus NRS

Protocol ID: _____

CENTER | SUBJECT ID

DATE: dd - MMM - yyyy

PEAK PRURITUS NRS

Language administered: ☒ (44) English for USA

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

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

Simpson E, Beck L, Abhijit G, et al. Defining a responder on the Peak Pruritus Numerical Rating Scale (NRS) in patients with moderate-to-severe atopic dermatitis: Detailed analysis from randomized trials of dupilumab J Am Acad of Dermatol 2017; 76:AB93.

Yosipovitch G, Reaney M, Mastey V, et al. Validation of the peak pruritus numerical rating scale: Results from clinical studies of dupilumab in adult patients with moderate to severe atopic dermatitis. J Am Acad of Dermatol 2017; 76:AB278.

10.13. Appendix 13: Frequency of Pruritus NRS

Frequency of Pruritus

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

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

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

10.15. Appendix 15: Patient Global Assessment (PtGA)

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

Choose only ONE response.

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

10.16. Appendix 16: European Quality of Life 5 Dimension Youth Scale (EQ-5D-Y)

Describing your health TODAY

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

Mobility (walking around)

I have no problems walking around ❑

I have some problems walking around ❑

I have a lot of problems walking around ❑

Taking care of myself

I have no problems taking a bath or shower by myself or getting dressed by myself ❑

I have some problems taking a bath or shower by myself or getting dressed by myself ❑

I have a lot of problems taking a bath or shower by myself or getting dressed by myself ❑

Doing usual activities (for example, going to school, hobbies, sports, playing, doing things with family or friends)

I have no problems doing my usual activities ❑

I have some problems doing my usual activities ❑

I have a lot of problems doing my usual activities ❑

Having pain or discomfort

I have no pain or discomfort ❑

I have some pain or discomfort ❑

I have a lot of pain or discomfort ❑

Feeling worried, sad, or unhappy

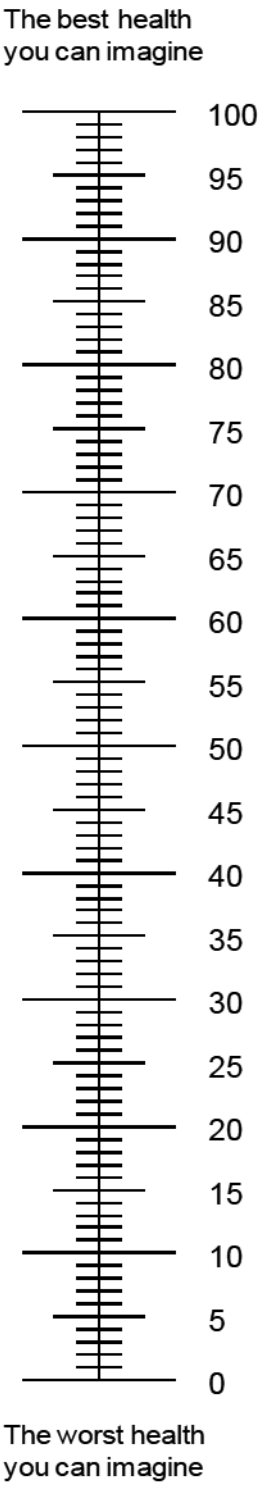
I am not worried, sad, or unhappy ❑

I am a little worried, sad, or unhappy ❑

I am very worried, sad, or unhappy ❑

How good is your health TODAY

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



10.17. Appendix 17: Children's Dermatology Life Quality Index (CDLQI)

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?** → **If school time**: Over the last week, how much did your skin problem affect your **school work**?	Prevented school Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐
	OR		
	was it **holiday time?** → **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	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.

10.18. Appendix 18: 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): .....

10.19. Appendix 19: Hospital Anxiety and Depression Scale (HADS)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10. I have lost interest in my appearance

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

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

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

12. I look forward with enjoyment to things

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

13. I get sudden feelings of panic

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

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

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

Now check that you have answered all the questions

10.20. Appendix 20: Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) Symptom Diary

Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Sleep & Usual Activities Questions

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

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

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

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

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

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

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

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

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

10.21. Appendix 21: Peds-FACIT-F

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

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

		None of the time	A little bit of the time	Some of the time	Most of the time	All of the time
pF1	I feel tired	0	1	2	3	4
pF2	I have energy (or strength)	0	1	2	3	4
pF3	I could do my usual things at home	0	1	2	3	4
pF4	I had trouble starting things because I was too tired	0	1	2	3	4
pF5	I had trouble finishing things because I was too tired	0	1	2	3	4
pF6	I needed to sleep during the day	0	1	2	3	4
pF7	I got upset by being too tired to do things I wanted to do	0	1	2	3	4
pF8	Being tired made it hard for me to play or go out with my friends as much as I'd like	0	1	2	3	4
pF9	I needed help doing my usual things at home	0	1	2	3	4
pF10	I feel weak	0	1	2	3	4
pF11	I was too tired to eat	0	1	2	3	4
pF12	Being tired made me sad	0	1	2	3	4
pF13	Being tired made me mad (angry)	0	1	2	3	4

10.22. Appendix 22: C-SSRS – Columbia Suicide Severity Rating Scale

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT dd - MMM - yyyy

Visit: _____

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

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

SUICIDAL IDEATION

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

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.	Most Severe	Most Severe
Lifetime - *Most Severe Ideation:* ____ *Type # (1-5)* _____ *Description of Ideation*		
Past X Months - *Most Severe Ideation:* ____ *Type # (1-5)* _____ *Description of Ideation*		
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in a week (4) Daily or almost daily (5) Many times each day	____	____

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

DATE OF VISIT [ ][ ] - [ ][ ][ ] - [ ][ ][ ][ ]
dd MMM yyyy

Visit: _____

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

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

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

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT dd - MMM - yyyy

Visit: _____

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

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

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

10.23. Appendix 23: SBQ-R – Suicide Behaviors Questionnaire-Revised

Protocol ID: _____ CENTER SUBJECT ID

DATE OF VISIT dd - MMM - yyyy

Visit: _____

SUICIDAL BEHAVIORS QUESTIONNAIRE-REVISED (SBQ-R)

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

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

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

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

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

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

10.24. Appendix 24: Patient Health Questionnaire - 8 items

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

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

Visit: _____

PATIENT HEALTH QUESTIONNAIRE (PHQ-8)

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

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

10.25. Appendix 25: Dermatitis Family Impact Questionnaire

"Dermatitis Family Impact Questionnaire"

Child's Name: **Mother/Father/Carer** **Date:** **Score** ☐

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

1.	Over the last week, how much effect has your child having eczema had on **housework**, e.g. washing, cleaning.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how much effect has your child having eczema had on **food preparation** and **feeding**.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much effect has your child having eczema had on the **sleep of others in family**.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
4.	Over the last week, how much effect has your child having eczema had on **family leisure activities**, eg swimming.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
5.	Over the last week, how much effect has your child having eczema had on **time spent on shopping for the family.**	Very much A lot A little Not at all	❒ ❒ ❒ ❒
6.	Over the last week, how much effect has your child having eczema had on your **expenditure**, eg costs related to treatment, clothes, etc.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
7.	Over the last week, how much effect has your child having eczema had on causing **tiredness** or **exhaustion** in your child's parents/carers.	Very much A lot A little Not at all	❒ ❒ ❒ ❒

8.	Over the last week, how much effect has your child having eczema had on causing **emotional distress** such as depression, frustration or guilt in your child's parents/carers.	Very much A lot A little Not at all	❒ ❒ ❒	❒
9.	Over the last week, how much effect has your child having eczema had on **relationships** between the **main carer and partner** or between the **main carer and other children** in the family.	Very much A lot A little Not at all	❒ ❒ ❒	❒
10.	Over the last week, how much effect has **helping with your child's treatment** had on the main carer's life.	Very much A lot A little Not at all	❒ ❒ ❒	❒

Please check you have answered EVERY question. Thank you

10.26. Appendix 26 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

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