A PHASE 1 FIRST IN HUMAN, RANDOMIZED, DOUBLE BLIND, SPONSOR OPEN, PLACEBO-CONTROLLED, SINGLE- AND MULTIPLE DOSE ESCALATION, PARALLEL GROUP STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF PF-07242813 IN HEALTHY PARTICIPANTS AND PARTICIPANTS WITH ATOPIC DERMATITIS

Study Intervention Number:	PF-07242813
Study Intervention Name:	N/A
US IND Number:	148,558
EudraCT Number:	N/A
ClinicalTrials.gov ID:	NCT04668066
Protocol Number:	C4461001
Phase:	1

Short Title: A Phase 1 Study to Evaluate the Safety and Tolerability of PF-07242813 in Healthy Participants and Participants with Atopic Dermatitis.

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 2	10 July 2021	1. Schedule of Activities for Multiple Ascending Doses (MAD) in Healthy Participants, Table 2: Three (3) additional PK samples will be collected in MAD cohorts on Days 8, 19 and 33 respectively. Further, decreased the time window for PK sample collection has been narrowed, from ±3 days to ±1 day, for Day 8, Day 22 and Day 36 visits. These changes were made to better characterize the PK profile after subcutaneous administration. The immunogenicity sample noted for collection on Day 8 in MAD cohorts has been removed as it was unnecessary. 2. Section 4.1.1, Section 8.5: Flexible language added to allow additional PK sample collection and analysis, as needed and appropriate, based on emerging data. 3. Section 5.2. Exclusion Criteria 25.c. and Section 8.8.3.5: Revised Exclusion Criteria #25 to modify hormone test requirements prior to randomization such that the laboratory data are evaluated in the context of clinical signs of endocrinopathy. 4. Section 9.1: Language updated from mean change to percent change from baseline to be consistent with the analysis as described in Sections 3 and 9.4.1. 5. Sections 5.4 and 8: Delays in randomization up to 1 week due to delayed laboratory test results will not be

		considered protocol deviations. 6. Section 8.8.1.1: Clarified language regarding processing of skin punch biopsies. 7. Revisions outlined in Protocol Administrative Letters (PACLs) #1, dated 26 February 2021 and #2, dated 14 June 2021 have been incorporated. 8. Appendix 4, Section 10.4.4 Contraception Methods: Added protocol template language for contraception methods that are permitted in Part 2. 9. Minor typographical errors and inconsistencies corrected as applicable.
Amendment 1	20 November 2020	The protocol was revised to address regulatory comments from the FDA. Changes incorporated include the following: 1. Sections 1.1 and 4.1.1. Initiation of the multiple dose, 15 mg SC dose level (Cohort 10) will occur after the SAD 100 mg IV dose cohort (Cohort 6) completes. *Previously MAD Cohort 10 was planned to start after completion of the SAD 30 mg IV cohort (Cohort 5).* 2. Multiple sections (1.1, 1.2, 3.1, 4 and 8). Cohort 8 (1000 mg IV), the highest planned dose, will be conducted in healthy participants. *Previously Cohort 8 was intended initially in AD participants.* This change also affected number of participants enrolled in Part 1 SAD from 49 to 57 healthy participants, in Part 2 from 57 to 48. AD participants, and overall number of participants from 146 to 145 participants. 3. Section 7.1 and Appendix 3. Added criteria for permanent discontinuation of study intervention for any Grade 2 or higher adverse events in the blood/bone marrow or cardiac categories; or any Grade 3 or higher adverse event, as defined by

		CTCAE criteria. 4. Section 6.6.1. Revised cohort stopping criteria to stop enrollment of a cohort if 2/3 of participants in a cohort develop a defined stopping AE. *Previously criteria was 2 patients on active study drug experienced AEs possibly related to study intervention.* 5. Minor typographical errors have been corrected throughout the document.
Original Protocol	30 September 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

Synopsis

Short Title: A Phase 1 Study to Evaluate Safety and Tolerability of PF-07242813 in Healthy Participants and Participants with Atopic Dermatitis.

Rationale

This is the first time PF-07242813 will be given to humans. The purpose of the study is to evaluate the safety, tolerability, and pharmacokinetics of escalating single and repeat doses of PF-07242813 in healthy participants and participants with moderate to severe atopic dermatitis. CCI [redacted]

Objectives, Estimands, and Endpoints

Objectives and Endpoints Part 1 (Healthy Adult Participants)

Objectives	Endpoints
Primary:	**Primary:**
To evaluate the safety and tolerability of PF-07242813, following single and multiple doses in healthy adults.	Incidence of treatment-emergent adverse events (AEs and SAEs); vital signs, safety laboratory tests, cardiac telemetry (SAD only), and ECG.
Secondary:	**Secondary:**
To characterize the serum exposure of PF-07242813, following single and multiple doses in healthy adults.	PF-07242813 serum exposure as data permit: AUC_{last}, AUC_{inf}, C_{max}, T_{max} and $t_{1/2}$ after single doses; AUC_{τ}, C_{max}, and T_{max} after each repeated dose; and $t_{1/2}$ after the last repeated dose.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
CCI [redacted]	[redacted]

Objectives, Endpoints and Estimands Part 2 (Atopic Dermatitis Participants)

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To evaluate the safety and tolerability of PF-07242813 versus placebo, in participants with moderate to severe AD.	Incidence of treatment-emergent adverse events (AEs and SAEs); vital signs, safety laboratory tests, and ECG.	There is no defined estimand for these endpoints; they will be analyzed using CaPS as applicable.
Secondary:	**Secondary:**	**Secondary:**
To compare the efficacy of PF-07242813 versus placebo on percent change from baseline in Eczema Area and Severity Index (EASI) in participants with moderate to severe atopic dermatitis (AD).	Percent change from baseline in EASI total score at Week 6.	Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the study intervention on a continuous endpoint; without prohibited medications during treatment. Study Intervention: PF-07242813 or placebo. Population: Participants with moderate to severe AD as defined by the inclusion and exclusion criteria. Variable: Percent change from baseline in EASI total score at Week 6. Intercurrent Events: a. Prohibited medications – all scores in participants who receive prohibited medication post randomization to Week 6 will be omitted from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the study intervention. b. Inadequate compliance – participants data will be used as recorded. Events a and b are stated with

Objectives	Endpoints	Estimands
		precedence in descending order. Population level summary: The percent change from baseline mean difference between PF-07242813 and placebo in EASI score.
CCI		

Objectives	Endpoints	Estimands
CCI		

Objectives	Endpoints	Estimands
CCI [redacted]	[redacted]	

Overall Design

This is a first-in-human (FIH) study of PF-07242813 that will be conducted in 2 parts: Part 1 will be conducted in healthy adult participants and Part 2 will be conducted in adult participants with moderate to severe AD (see Figure 1).

Part 1 is within-cohort randomized, participant- and investigator-blind, sponsor-open, placebo-controlled investigation of the safety, tolerability, PK, and immunogenicity following single and multiple ascending doses of PF-07242813 in healthy participants. Part 1 will also include a cohort of Japanese healthy adult participants (Cohort 15) to provide safety, tolerability, and PK data in Japanese population to enable the inclusion of Japanese participants in future clinical trials.

Part 2 is a randomized, participant- and investigator-blind, sponsor-open, placebo-controlled investigation of the safety, tolerability, PK, and pharmacodynamics (including clinical effects) of PF-07242813 in adult participants with moderate to severe atopic dermatitis (AD). In Part 2, Cohort 9 will randomize (2:1, PF-07242813:placebo) 24 participants at the MTD defined in Part 1 (or maximum dose studied in Part 1 if MTD is not achieved) for the assessment of the safety, tolerability, PK, and clinical effects of PF-07242813 in AD and CCI [redacted] evaluations of pharmacodynamic activity. The number of participants enrolled in Cohort 9 will provide a sample size sufficient for statistical evaluation of the primary efficacy endpoint (placebo-corrected percent change from baseline in continuous EASI).

Number of Participants

Up to approximately 145 participants will be randomly assigned to study intervention, either PF-07242813 or placebo.

In Part 1, up to approximately 57 healthy participants, including a cohort of 5 healthy Japanese participants, will be randomly assigned to receive a single dose of study intervention (SAD). Up to approximately 40 healthy participants, including an optional cohort, will be randomly assigned to receive multiple doses of study intervention (MAD).

In Part 2, 24 participants with moderate to severe AD will be randomly assigned to a single dose of study intervention in Cohort 9. An optional cohort (Cohort 16) of up to 24 participants with AD may be enrolled to evaluate further IV or SC dosing, based on cumulative safety and PK data from Part 1 and Cohort 9.

Intervention Groups and Duration

Part 1 SAD: Within 28 days of successful completion of the screening process, eligible participants for the single ascending dose period will be enrolled and randomized to receive a single IV infusion of PF-07242813 or placebo.

As illustrated in Figure 1, healthy participants in the SAD phase of the study will be randomized sequentially into 8 single dose cohorts (Cohorts 1-8). Participants will be admitted into the clinic approximately 1 day prior to dosing and be required to stay confined in the clinic through completion of Day 5 evaluations. Participants in the single dose cohorts will return for outpatient visits up to Day 71 (or at least 4 half-lives of PF-07242813 based on observed data). For Cohort 1, the outpatient visit is up to Day 29 (±3 days). For Cohorts 2 and 3, the last follow-up visit will be determined based on emerging safety and PK data from previous cohort(s). As such, the last follow-up visit (and discharge from the study) may occur earlier than Day 71 (±3 days), but will be at least through Day 29 (±3 days).

During the SAD period, escalation to subsequent dose levels will only occur if the sponsor's review of the available safety and PK data for the previous cohorts suggest that the next dose is likely to have acceptable safety and tolerability. There will be a minimum of 10 days between cohorts for dose escalation. Dosing in SAD (up to the maximum dose of 1000 mg IV) may be adjusted depending upon the actual exposure of PF-07242813 observed in humans at lower doses. If, based on the observed data, the subsequent dose projected group mean C_{max} is >1020 µg/mL or AUC_{168H} >106000 µg.h/mL, the exposure limits pre-specified, that dose will not be explored.

In addition, a cohort of healthy Japanese adults (Cohort 15, n=5) will be enrolled to receive a single IV dose of PF-07242813 or placebo (active:placebo,=4:1). This cohort will be initiated after single dose escalation in healthy participants is complete and will enroll in parallel to Part 2.

Part 1 MAD: Four (4) escalating multiple SC dose cohorts and 1 optional multiple IV dose cohort in healthy participants are planned. Initiation of the multiple dose at 15 mg SC (Cohort 10) dose is planned to begin following the Sponsor's review of available safety data through study Day 8 and PK data through study Day 3 from the 100 mg single IV dose cohort (Cohort 6), as well as the accumulated safety data from the previous IV single dose cohorts. The starting dose for the initial multiple dose cohort may be adjusted, based on emerging safety and PK data from single dose cohorts. Doses and/or dosing regimens planned may be modified based on emerging data from earlier single and multiple dose cohorts. If the exposures in the subsequent dose is projected to exceed the exposure limits pre-specified, after repeat doses, that dose will not be explored.

Healthy participants who are enrolled into the multiple dose cohorts (Cohorts 10-14) will be randomized 3:1 to receive PF-07242813 or placebo every 2 weeks (Q2W) for a total of 3 doses. Participants will be confined to the clinical research unit starting on the day prior to dosing and through at least 96 hours after the first dose of study intervention administration and 48 hours after the second and third doses. Participants will return for outpatient visits at least through Day 99 visit (or at least 4 half-lives of PF-07242813 based on observed data).

Part 2 Atopic Dermatitis: At least 1 cohort of adult participants with moderate to severe AD (Cohort 9, n=24) will be randomized 2:1 to receive a single dose of either PF-07242813 or placebo.

Cohort 9 will be initiated following completion of all single dose cohorts evaluated in Part 1 and review of cumulative safety and PK data from Part 1. Participants in Cohort 9 will receive study intervention on Day 1 at the MTD defined in Part 1 (or the highest dose studied in Part 1 if MTD is not achieved). All study visits will be done on an outpatient basis through the last scheduled visit on Day 113 (Week 16).

An optional cohort of up to 24 moderate to severe AD participants (Cohort 16) may be enrolled as needed to evaluate further IV or SC dosing of PF-07242813, based on cumulative safety and PK data from Part 1 and Cohort 9 in Part 2.

Participants who prematurely discontinue from the study for reasons other than safety may be replaced, at the discretion of the investigator and Sponsor.

Data Monitoring Committee or Other Independent Oversight Committee: This Phase 1 study will not have a DMC or other independent oversight committee.

Statistical Methods

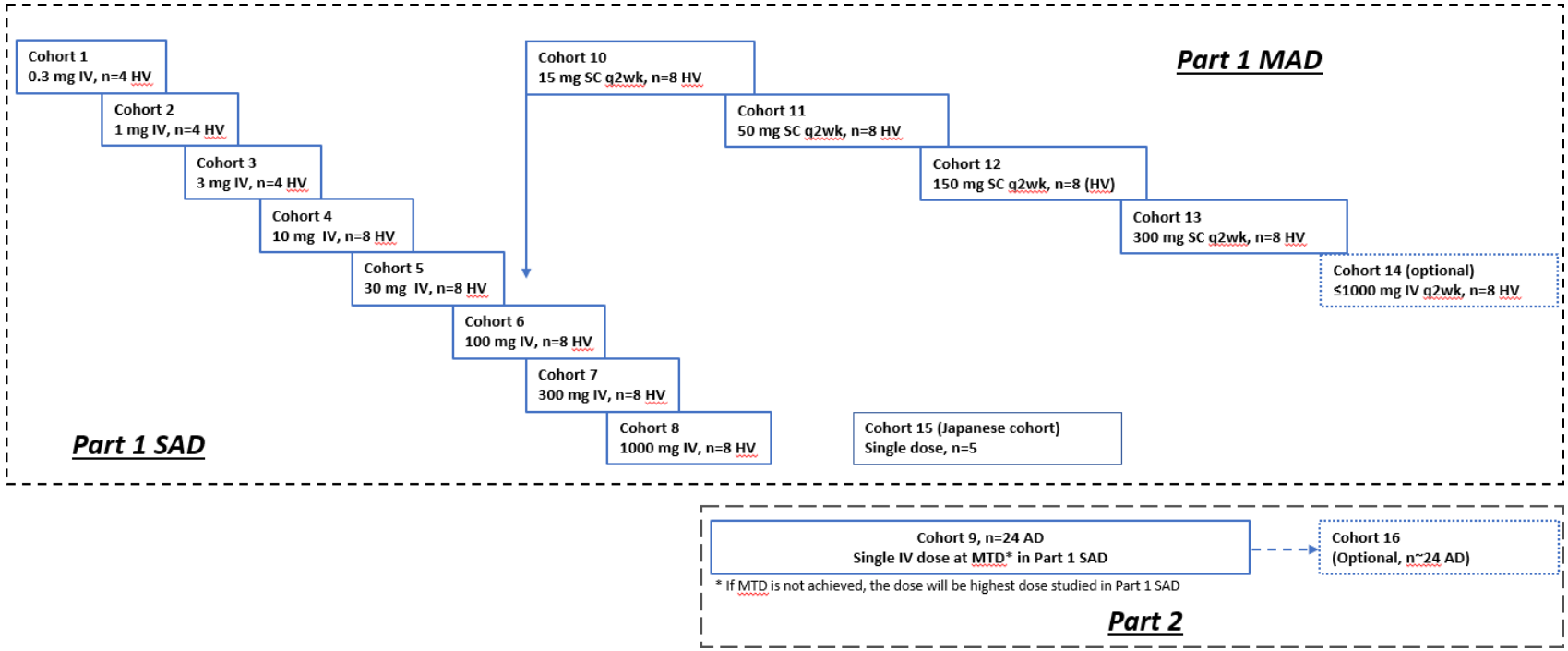
Safety data will be summarized in accordance with CDISC/CaPS. All participants who receive study intervention (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations.

In Part 2, the secondary objective will be to evaluate the effect of PF-07242813 on clinical indices of AD activity with the secondary endpoint being percent changes in EASI score from baseline at Week 6. The primary estimand will be the population average treatment effect on percent change from baseline in EASI score relative to placebo at 6 weeks in the absence of prohibited medication. All observations after the initiation of prohibited medication will be set to missing. Missing data from all causes, including post-prohibited medication use will be imputed in the PF-07242813 dose arms using a jump to control method using the distribution of the placebo group.

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

1.1. Schema

Figure 1. C4461001 Study Design with Planned Doses



Doses shown for each cohort are planned doses and may be modified based on emerging data from previous cohorts.

1.2. Schedule of Activities

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

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

Table 1. Part 1. Schedule of Activities for Single Ascending Doses in Healthy Participants, (Cohorts 1-8) and Japanese Cohort (Cohort 15)

Visit Identifier	Screening	Clinical Confinement											Outpatient Visits					EOS[i]	Early Termination
Day relative to dose (Day 1)	Day-28 to Day-2	Day -1	Day 1						Day 2	Day 3	Day 4	Day 5	Day 8 ±3	Day 15 ±3	Day 29 ±3	Day 43 ±3	Day 57 ±3	Day 71 ±3	
Hours After Dose (for clinical confinement portion)			-2 hrs to -5 min	0	End of infusion[a]	2[a]	6[a]	12[a]	24[a]	48[a]	72[a]	96[a]							
Informed consent	X																		
Demography, Medical history	X																		
Update to medical history		X																	
Physical examination[b]	X																	X	X
Height	X																		
Body Weight	X	X																	
History of Drug, Alcohol, and Tobacco use	X																		
Inclusion/Exclusion Review	X	X																	
Admission to Clinical Research Unit		X																	
Randomization[l]		X																	
Laboratory (hematology, blood chemistry, urinalysis)	X	X							X		X		X		X			X	X
Urine Drug Test	X	X																	
Serum FSH[c]	X																		
Urine Pregnancy Test[j]	X	X													X		X	X	X
HIV, HBsAg, HBcAb, HCVAb	X																		
QuantiFERON TB Gold	X																		

Visit Identifier	Screening	Clinical Confinement											Outpatient Visits					EOS[i]	Early Termination
Day relative to dose (Day 1)	Day-28 to Day-2	Day -1	Day 1						Day 2	Day 3	Day 4	Day 5	Day 8 ±3	Day 15 ±3	Day 29 ±3	Day 43 ±3	Day 57 ±3	Day 71 ±3	
Hours After Dose (for clinical confinement portion)			-2 hrs to -5 min	0	End of infusion[a]	2[a]	6[a]	12[a]	24[a]	48[a]	72[a]	96[a]							
Sample for CCI cytokine analyses (TNFα, IL-6 total, and IFNγ)[d]			[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]								
Continuous Cardiac Monitoring by Telemetry[e]			X	X	→	→	X												
12-Lead ECG[f]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X X
Vital Signs[g]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X X
Prior/Concomitant Medication	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X X
Study Intervention Administration				X															
Infusion/Injection Site Reaction Assessment					X	X	X	X	X	X	X								
PK blood sampling																			X
CCI			X		X	X	X	X	X	X	X	X	X		X	X	X	X	X
Banked Biospecimens for Genetics Prep D1[h]		X	[redacted]											[redacted]	[redacted]	[redacted]			[redacted]
Banked Biospecimens for Biomarkers Prep B2.5		X								X									
Sample(s) CCI analyses of hormone levels: HGH, IGF-1, TSH, T4 and Cortisol[k]	[redacted]	[redacted]	[redacted]						[redacted]						[redacted]				
Adverse event monitoring	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Discharge from Clinic												X							

a. Procedures should be completed within ±10% of the collection time (ie, 2 hours ±12 minutes; 6 hours ±36 minutes, etc).

b. A full PE may be done at screening or deferred to Day -1 at the discretion of the principal investigator. A limited PE will be performed at discharge; a full PE may be performed instead, at the discretion of the Investigator. At any time during the study, a limited PE may be performed at the discretion of the investigator if there is a new or ongoing AE.

c. FSH test is performed only in WONCBP at screening to confirm postmenopausal status in females who have been amenorrhoeic for at least 12 consecutive months.

d. Biospecimens for exploratory cytokine analyses will be collected pre-dose (-2 hrs to -5 min), 30 minutes (±5 min) after the end of infusion, 2, 12, 24 and 48 hours after IV infusion starts. Biospecimens will be analyzed ad hoc based on clinical signs of cytokine release syndrome.

e. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing. This may be done immediately prior to dosing or at some 2 hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Continuous cardiac monitoring will be conducted -15 minutes pre-dose through the 8 hour post dose period.

f. ECGs will be collected in triplicate approximately 2-4 minutes apart at pre-dose, and during clinical confinement at the times specified in the Schedule of Activities (Day 1 prior to dose to morning of Day 5, ie 96 hours post-dose). Single ECGs will be collected at all other designated visits.

g. Vital signs include supine blood pressure, pulse rate, respiratory rate, and temperature.

h. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

i. For Cohort 1, the follow-up visit is up to Day 29 (±3 days). For Cohorts 2 and 3, the final follow-up visit will be determined based on safety and PK data emerging from previous cohort(s), which may be earlier than Day 71 (±3 days) but will be at least through Day 29 (±3 days).

j. Pregnancy test is performed only in WOCBP.

k. Hormone samples will be collected in the morning. Beginning at baseline visit (Day -1 or predose Day 1), samples should be collected at approximately the same time in the morning.

l. Randomization may be performed Day -1, or prior to first dose on Day 1.

Table 2. Part 1. Schedule of Activities for Multiple Ascending Doses in Healthy Participants (Cohorts 10-14)

Screening to Day 8 Visits (1st Dose)

Visit Identifier	Screening	Clinical Confinement											Out-patient Visit	Early Termination
Study Day	Day-28 to Day-2	Day -1	Day 1						Day 2	Day 3	Day 4	Day 5	Day 8 ±1 day	
Hours After Dose (for clinical confinement portion)			-2 hrs to -5 min	0	End of infusion[b,e]	2[b]	6[b]	12[b]	24[b]	48[b]	72[b]	96[b]		
Informed consent	X													
Demography, Medical history	X													
Update to medical history		X												
Physical examination[c]	X													X
Height	X													
Body Weight	X	X[a]												
History of Drug, Alcohol, and Tobacco use	X													
Inclusion/Exclusion Review	X	X[a]												
Admission to Clinical Research Unit		X												
Randomization		X[a]												
Discharge from Clinic												X		X
Laboratory (hematology, blood chemistry, urinalysis)	X	X[a]							X		X		X	X
Urine Drug Test	X	X												
Serum FSH[d]	X													
Urine pregnancy test[i]	X	X												X
HIV, HBsAg, HBcAb, HCVAb	X													
QuantiFERON – Tuberculosis Gold	X													
12-Lead ECG[f]	X		X		X	X	X	X	X	X			X	X
Vital Signs[g]	X		X		X	X	X	X	X	X			X	X
Prior/Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Intervention Administration				X										
Infusion/Injection Site Assessment					X	X	X	X	X	X	X	X		
PK blood sampling			X		X	X	X	X	X	X	X	X	X	X
CCI [redacted]			[redacted]											[redacted]
Banked Biospecimens for Genetics Prep D1[h]		X												

Visit Identifier	Screening	Clinical Confinement											Out-patient Visit	Early Termination
Study Day	Day-28 to Day-2	Day -1	Day 1						Day 2	Day 3	Day 4	Day 5	Day 8 ±1 day	
Hours After Dose (for clinical confinement portion)			-2 hrs to -5 min	0	End of infusion[b,e]	2[b]	6[b]	12[b]	24[b]	48[b]	72[b]	96[b]		
Sample(s) CCI [redacted] of hormone levels: HGH, IGF-1, TSH, T4 and Cortisol[j]	CCI [redacted]	[redacted]	[redacted]						[redacted]					
Banked Biospecimens for Biomarkers Prep B2.5		X							X					
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Study procedures may be performed Day-1, or prior to first dose on Day 1.

b. Procedures should be completed within ±10% of the collection time (ie, 2 hours ±12 minutes; 6 hours ±36 minutes, etc).

c. A full PE may be done at screening or may be deferred to Day -1 at the discretion of the principal investigator. A limited PE may be performed at discharge at the discretion of the investigator. A limited PE may also be performed at the discretion of the investigator at a follow-up visit if there is a new or ongoing AE.

d. FSH test is performed only in WONCBP at screening to confirm postmenopausal status in females who have been amenorrhoeic for at least 12 consecutive months.

e. Infusion pertains *only* to the IV cohort and does not pertain to the SC Cohorts.

f. ECGs will be collected in triplicate approximately 2-4 minutes apart at pre-dose, and during clinical confinement at the times specified above. Single ECGs will be collected at all other designated visits.

g. Vital signs include supine blood pressure, pulse rate, respiratory rate, and temperature.

h. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

i. Pregnancy test is performed only in WOCBP.

j. Hormone samples will be collected in the morning. Beginning at baseline visit (Day -1 or predose Day 1), samples should be collected at approximately the same time in the morning.

Day 14 Through Day 22 Visits (2nd Dose)

Visit Identifier	Clinical Confinement									Out-patient Visit		Early Termination
Study Day	**Day 14**	**Day 15**						**Day 16**	**Day 17**	**Day 19**	**Day 22 ±1 day**	
Hours After Dose (for clinical confinement portion)		**-2 hrs to -5 min**	**0**	**End of infusion[a,b]**	**2[a]**	**6[a]**	**12[a]**	**24[a]**	**48[a]**	**96[a]**		
Admission to Clinical Research Unit	X											
Physical examination[c]												X
Laboratory (hematology, blood chemistry, urinalysis)	X							X			X	X
Urine Drug Test	X											
Urine Pregnancy Test[f]	X											X
12Lead -ECG[d]		X		X		X	X		X		X	X
Vital Signs[e]		X		X		X	X		X		X	X
Prior/Concomitant Medication	X	X	X	X	X	X	X	X	X		X	X
Study Intervention Administration			X									
Infusion/Injection Site Reaction				X	X	X	X	X	X			
Pharmacokinetic (PK) blood sampling		X		X	X	X	X	X	X	X	X	
CCI [redacted]		[redacted]										[redacted]
Sample(s) for CCI [redacted] of hormone levels: HGH, IGF-1, TSH, T4 and Cortisol[g]		[redacted] CCI						[redacted]			[redacted]	
Banked Biospecimens for Biomarkers Prep B2.5	X							X				
Adverse event monitoring	→	→	→	→	→	→	→	→	→	→	→	X
Discharge from Clinic									X			

a. Procedures should be completed within ±10% of the collection time (ie, 2 hours ±12 minutes; 6 hours ±36 minutes, etc).

b. Infusion pertains *only* to the IV cohorts and does not pertain to the SC Cohorts.

c. Physical examination prior to the second dose will be at the discretion of the investigator, based on any review of potential adverse events or other clinical signs/symptoms.

d. ECGs will be collected in triplicate approximately 2-4 minutes apart at pre-dose, and during clinical confinement at the times specified in the Schedule of Activities (Day 15 prior to dose and up to 48 hours post-dose). Single ECGs will be collected at all other designated visits.

e. Vital signs include supine blood pressure, respiratory, pulse rate, and temperature.

f. Pregnancy test is performed only in WOCBP.

g. Hormone samples will be collected in the morning, at the same time of day.

Day 28 Through Day 99 Visit (3rd Dose)

Visit Identifier	Clinical Confinement									Out-patient Visits						EOS	Early Termination
Study Day	Day 28	Day 29						Day 30	Day 31	Day 33	Day 36 ±1	Day 43 ±3	Day 57 ±3	Day 71 ±3	Day 85 ±3	Day 99 ±3	
Hours After Dose (for clinical confinement portion)		-2 hrs to -5 min	0	End of infusion[a,b]	2[a]	6[a]	12[a]	24[a]	48[a]	96[a]							
Admission to Clinical Research Unit	X																
Physical Examination[c]																X	X
Laboratory (hematology, blood chemistry, urinalysis)	X							X			X		X			X	X
Urine Drug Test	X																
Urine Pregnancy Test[f]	X												X			X	X
12-Lead ECG[d]		X		X		X	X	X	X		X	X	X	X	X	X	X
Vital Signs[e]		X		X		X	X	X	X		X	X	X	X	X	X	X
Prior/Concomitant Medication	X										X	X	X	X	X	X	X
Study Intervention Administration			X														
Infusion/Injection Site Reaction				X	X	X	X	X	X								
Pharmacokinetic (PK) blood sampling		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]		[redacted]										[redacted]		[redacted]		[redacted]	[redacted]
Sample(s) for CCI [redacted] of hormone levels: HGH, IGF-1, TSH, T4 and Cortisol[g]		[redacted]						[redacted]				[redacted]			[redacted]		
Banked Biospecimens for Biomarkers Prep B2.5	X							X									
Adverse event monitoring	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Discharge from Clinic									X								

a. Procedures should be completed within ±10% of the collection time (ie, 2 hours ±12 minutes; 6 hours ±36 minutes, etc).

b. Infusion pertains *only* to the IV cohort and does not pertain to the SC Cohorts.

c. Physical examination prior to the third dose will be at the discretion of the investigator, based on any review of potential adverse events or other clinical signs/symptoms.

d. ECGs will be collected in triplicate approximately 2-4 minutes apart pre-dose, and during clinical confinement at the times specified in the Schedule of Activities (Day 29 prior to dose and up to 48 hours post-dose). Single ECGs will be collected at all other designated visits.

e. Vital signs include supine blood pressure, respiratory rate, pulse rate, and temperature.

f. Pregnancy test is performed only in WOCBP.

g. Hormone samples will be collected at the same time of day, in the morning.

Table 3. Part 2. Schedule of Activities in AD Participants – Cohort 9

Visit Identifier	Screening	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12	EOS Week 16	ET
Day relative to dose (Day 1)	**Day-28 to Day-2**	**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 85**	**Day 113**	
Visit Window - Days			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Screening Assessments										
Informed consent	X									
Demography	X									
Medical History (including AD)	X									
Height	X									
Body Weight	X	X[a]								
Drug, Alcohol and Tobacco History	X	X[a]								
FSH[d]	X									
HIV, HBsAg, HBcAb, HCVAb	X									
QuantiFERON TB Gold	X									
Inclusion/Exclusion	X	X								
Randomization		X[a]								
Laboratory Assessments										
Safety labs (hematology, blood chemistry, urinalysis)	X	X[b]	X		X	X	X	X	X	X
Urine Drug Test	X	X[a]								
Pregnancy test[d]	X	X			X		X	X	X	X
PK blood samples		X[b]		X	X	X	X	X	X	X
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Medical Procedures										
Physical Examination[c]	X								X	X

Visit Identifier	Screening	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12	EOS Week 16	ET
Day relative to dose (Day 1)	**Day-28 to Day-2**	**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 85**	**Day 113**	
Visit Window - Days			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
12 Lead -ECG[f]	X	X[b,f]	X	X	X	X	X	X	X	X
Spirometry (FEV1, FCV)[k]	X			X	X	X	X	X	X	X
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X
Exploratory Biomarker										
Banked Biospecimens for Genetics Prep D1[h]		X[a]								
Banked Biospecimen -Prep PBMC2		X[a]	X			X		X	X	X
Banked Biospecimen -Prep R1		X[a]	X			X		X	X	X
Banked Biospecimens for Biomarkers Prep B2.5		X[a]	X			X		X	X	X
Serum IgE		X[a]	X			X		X	X	X
Serum TARC (CCL17)		X[a]	X			X		X	X	X
Plasma for Interleukin-31 (IL-31) and Interleukin-17A (IL-17A)		X[a]	X			X		X	X	X
Whole Blood for Flow Cytometry		X[a]	X			X		X	X	X
Skin Punch Biopsies -nonlesional		X								
Skin Punch Biopsies lesional		X		X		X				
Physician Assessments										
Columbia Suicide Severity Rating Scale (C-SSRS)	X									
Fitzpatrick Skin Type Assessment	X									
Eczema Area and Severity Index (EASI)	X	X[a]	X	X	X	X	X	X	X	X
CCI [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient Reported Outcomes										
Pruritus Numerical Rating Scale (Pruritus NRS)[i]		X[a]	X	X	X	X	X	X	X	X
Dermatology Life Quality Index (DLQI)		X[a]	X	X	X	X	X	X	X	X
Patient Global Assessment (PtGA)		X[a]	X	X	X	X	X	X	X	X

Visit Identifier	Screening	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 12	EOS Week 16	ET
Day relative to dose (Day 1)	**Day-28 to Day-2**	**Day 1**	**Day 8**	**Day 15**	**Day 29**	**Day 43**	**Day 57**	**Day 85**	**Day 113**	
Visit Window - Days			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Patient-Oriented Eczema Measure (POEM)		X[a]	X	X	X	X	X	X	X	X
Hospital and Anxiety Depression Scale (HADS)		X[a]	X	X	X	X	X	X	X	X
ACQ-5[k]		X[a]				X			X	X
Other Study Activities										
Contraception Check[d]	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring	X	→	→	→	→	→	→	→	X	X
Prior/Concomitant Treatment	X	→	→	→	→	→	→	→	X	X

a. Study procedures will be collected prior to first dose on Day 1.

b. Day 1 will include the following: 1) pre-dose vital signs, ECG and PK CCI [redacted], 2) post-infusion ECG, vital signs, PK blood sample, and 3) 2 hours after the start of the infusion ECG, vital signs and blood samples for PK and cytokine release analyses.

c. A full PE will be done at screening, or can be deferred to pre-dose on Day 1 at the discretion of the investigator. A limited PE will be conducted at all other timepoints indicated, or at the discretion of the investigator if clinically indicated.

d. FSH test is performed only in WONCBP at screening to confirm postmenopausal status in females who have been amenorrhoeic for at least 12 consecutive months. Contraception checks and pregnancy tests will be conducted in WOCBP.

e. Biospecimens for cytokine release labs will be collected pre-dose (-2 hrs to -5 min), 30 minutes (±5 min) after the end of infusion, and 2 hours after IV infusion starts. Biospecimens will be analyzed ad hoc based on clinical signs of cytokine release.

f. ECGs will be collected in triplicate approximately 2-4 minutes apart pre-dose, immediately after infusion prior to PK blood collection, and at 2 hours after infusion start, prior to PK blood collection. Single ECGs will be collected at all other designated visits.

g. Vital signs include supine blood pressure, pulse rate, respiratory rate, and temperature.

h. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

i. Pruritis NRS to be completed by participants every day for 14 days at home after the Day 1 dosing visit. Note that Pruritis NRS has 2 scales, one for severity and one for frequency. See Section 8.1.5.2.1 and 8.1.5.2.2.

j. Hormone samples should be collected in the morning, at the same time each day. Beginning at baseline visit (Day -1 or predose Day 1), samples should be collected at approximately the same time in the morning.

k. Spirometry measures (FEV1, FCV) will be assessed for all participants at Screening. Spirometry and ACQ-5 during active study assessments of spirometry and ACQ-5 are required for participants with asthma.

2. INTRODUCTION

PF-07242813 is an anti-CD1a antibody that is being developed as a treatment for patients with moderate to severe atopic dermatitis.

2.1. Study Rationale

This is the first time PF-07242813 will be given to humans. The purpose of the study is to evaluate the safety, tolerability, and pharmacokinetics of escalating single and repeat doses of PF-07242813 in healthy participants and in participants with moderate to severe atopic dermatitis. CCI

2.2. Background

AD is a common inflammatory skin disease, especially in children with a prevalence of 5-20% and ~11% in the total population of the US (Oyoshi et al. 2009; Williams 2005).[15,20] Current treatments for AD include emollients, and topical anti-inflammatory agents such as corticosteroids and calcineurin inhibitors. These agents have generally been unsatisfactory for the treatment of moderate to severe disease. More recently, an injectable monoclonal antibody directed against the IL-4 receptor α (dupilumab) that blocks the binding of IL-4 and IL-13 has been approved for the treatment of moderate to severe AD. While dupilumab represents a considerable advance in the treatment of AD, not all patients respond well or achieve completely clear skin. Moreover, some patients may become refractory to dupilumab with prolonged dosing. Additional treatments are needed that are complementary to currently approved drugs that increase the proportion of patients achieving complete resolution of skin inflammation and/or are effective in patients who do not respond or become refractory to dupilumab.

CD1a is an MHC class I-like molecule expressed on Langerhans cells in the skin. CD1a presents lipid antigens found in the skin which can be recognized by antigen-specific T cells, leading to subsequent T cell activation (de Jong et al. 2014).[7] Emerging data suggest that pathogenic lipids, signaling through CD1a, may be important drivers of inflammation in AD (Berdyshev et al. 2018; Cooper 1994; Cully 2016; Jarrett et al. 2016; Kim et al. 2016).[1,5,6,11,13]

PF-07242813 is a novel humanized monoclonal antibody that binds CD1a protein with high affinity and selectivity. PF-07242813 prevents CD1a from interacting with T cell receptors, leading to the inhibition of T cell activation. Therefore, PF-07242813 would be expected to inhibit T cell activation and downstream proinflammatory signaling. This mechanism would be distinct from currently available treatments that are either broadly immunosuppressive (eg, corticosteroids and calcineurin inhibitors) or specifically targeted to type 2 inflammation (eg, dupilumab).

2.2.1. Nonclinical Overview

The pharmacology and safety of PF-07242813 are supported by nonclinical studies.

2.2.1.1. Nonclinical Pharmacology

In vitro assessments using several methods have demonstrated that PF-07242813 binds to both human and cynomolgus monkey CD1a with similar high affinity. SPR analysis demonstrated high affinity binding to recombinant forms of both human and cynomolgus monkey CD1a. Flow cytometry studies showed that PF-07242813 bound surface-expressed human and cynomolgus monkey CD1a, whether exogenously expressed by transfection into CHO cells or endogenously expressed on monocyte-derived dendritic cells. PF-07242813 suppressed IL-2 secretion and upregulation of CD69 expression on Jurkat76-BK6 cells, a CD1a-restricted T cell line, during co-culture with human CD1a expressing cells. In vitro, IL-17A secretion by primary $CD3^+$ cells, isolated from either whole blood or healthy skin, in response to CD1a stimulation was suppressed by PF-07242813. Likewise, PF-07242813 was able to suppress IL-17A secretion by primary cynomolgus monkey $CD3^+$ cells when co-cultured with cells expressing cynomolgus monkey CD1a.

Additionally, PF-07242813 was shown functionally to neutralize CD1a-dependent immune responses in vivo using human CD1a transgenic mice with an HDM-induced model of skin inflammation. PF-07242813, when administered in vivo in a prophylactic dosing regime, resulted in a statistically significant decrease of all AD measurements assessed, including dermatitis score, total IgE levels, HDM-specific IgE titers, presence of inflammatory or $IL\text{-}13^+$ cells in the skin, and presence of an AD gene signature in the skin.

Taken as a whole, these data demonstrate PF-07242813 neutralizes CD1a-dependent T cell activation and inflammation supporting its development as a novel therapeutic for the treatment of AD.

2.2.1.2. Nonclinical Safety

No test article-related effects or target organs were identified following once weekly administration of PF-07242813 to cynomolgus monkeys for 13 weeks in the GLP toxicity study that would predict a safety risk for participants in early clinical studies. The NOAEL in the pivotal 13-week monkey toxicity study was the highest dose tested, 200 mg/kg/week (IV), with C_{max} and C_{av} exposures of 10200 µg/mL and 6310 µg/mL, respectively.

Staining of neuroendocrine cells with PF-07242813 in the human pituitary was observed in the TCR study. However, the risk of pituitary toxicity is considered low since CD1a is not expected to be expressed in the pituitary, PF-07242813 does not have effector function, and no toxicity was observed in the 13-week repeat-dose monkey study for other tissues that showed positive staining in the TCR study.

The in vitro cytokine release assay identified the potential for PF-07242813 to induce cytokine release; however, the clinical translation of findings from this assay has not been established.

The nonclinical program supports the progression of PF-07242813 in clinical trials of up to 3 months in duration via the SC and/or IV routes of administration.

2.2.1.3. Nonclinical PK

Non-linear PK was observed after a single IV dose in cynomolgus monkeys, consistent with TMDD. In the pivotal repeat-dose GLP study, there were no apparent sex-related differences in systemic exposure (as assessed by C_{max} and AUC), and systemic exposure increased with increasing dose and was higher after repeat dosing. CCI [redacted]

The PK of PF-07242813 in humans are expected to be the same as those of a typical therapeutic IgG mAb. Based on a site of action PK/PD model, the predicted efficacious dose of PF-07242813 in humans is 30 mg SC Q4W. The predicted steady-state human AUC_{tau} for the efficacious dose level is 1730 µg•h/mL and the predicted C_{max} and C_{av} values are 3.67 and 2.58 µg/mL, respectively.

CCI [redacted]

CCI

[redacted]

2.2.2. Clinical Overview

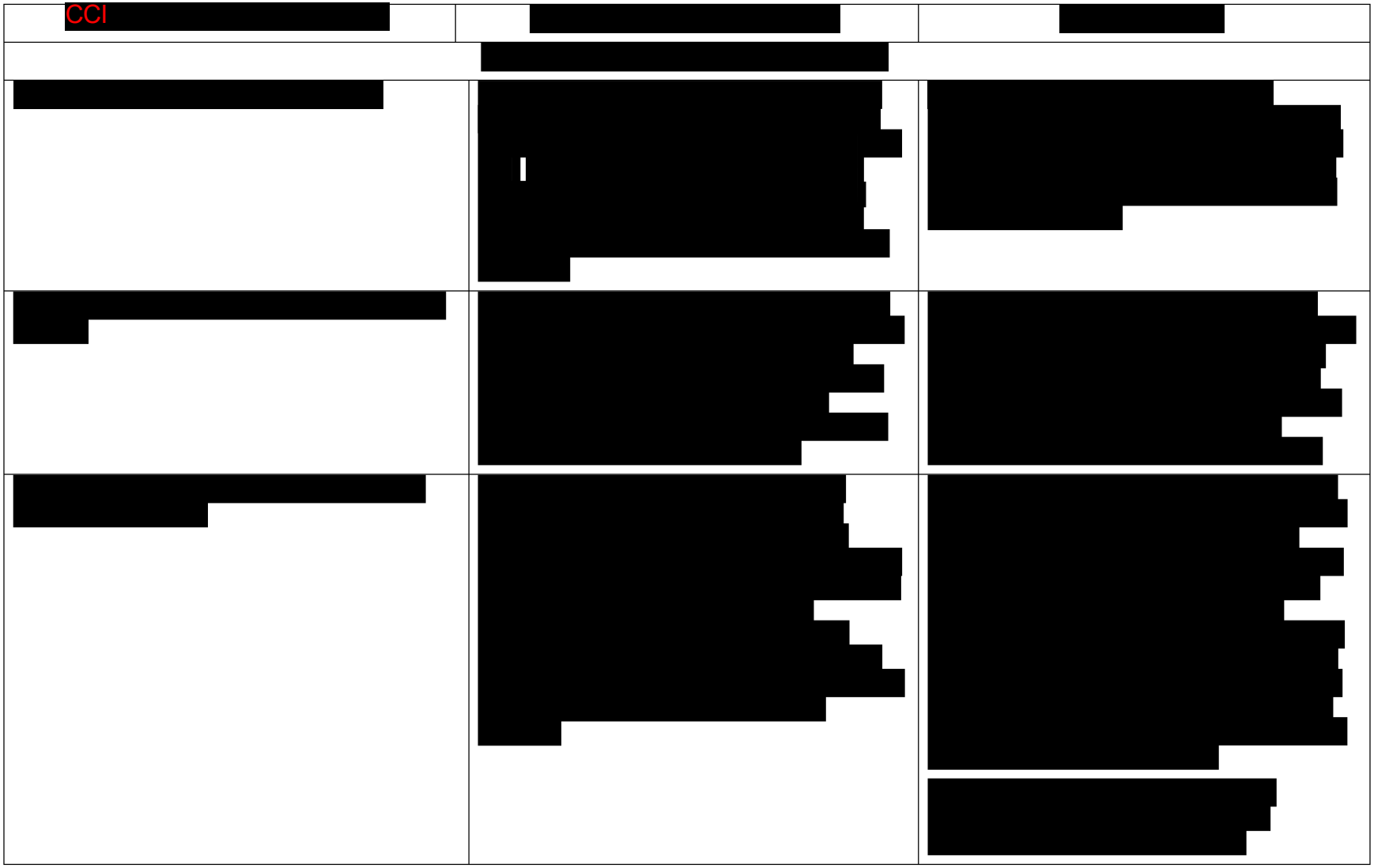
PF-07242813 has not been administered to humans. Therefore, there are no clinical safety data.

2.3. Benefit/Risk Assessment

Study C4461001 is the first time that PF-07242813 will be administered to humans. For healthy participants participating in this single and multiple doses, no clinical benefit is expected. The purpose of the study is to provide the basis for further clinical development of PF-07242813 as a potential new, pharmacological agent for the treatment of participants with AD. As to date, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2.1. The clinical impact of these potential risks will be minimized through the proposed cautious dose. The clinical impact of these potential risks will be minimized through the proposed cautious dose escalation process wherein higher doses of PF-07242813 will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile. In addition, this study includes standard, intensive, inpatient monitoring of the participants following administration of single and multiple doses of the study intervention.

The risk assessment for study participation and potential risks of PF-07242813 is provided below. More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07242813 may be found in the Investigator's Brochure, which is the SRSD for this study.

2.3.1. Risk Assessment



CCI [redacted]	[redacted]	[redacted]
Study Procedures		
CCI [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

2.3.2. Benefit Assessment

No clinical benefit is anticipated for healthy participants. However, participants may benefit society by contributing to the process of developing new therapies in an area of unmet need. Additionally, participants will benefit from Medical evaluations/assessments associated with study procedures (eg, physical exam, ECG, labs, etc.).

Similarly, while no clinical benefit may be expected for participants with AD, they may obtain potential benefit of receiving study intervention during study duration that may have clinical utility.

2.3.3. Overall Benefit/Risk Conclusion

Based on the preclinical toxicology studies, measures taken to minimize risk to participants in this study, and the ultimate potential benefit of PF-07242813 to patients with AD, the overall potential benefit/risk of PF-07242813 is favorable.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Objectives and Endpoints: Part 1 (Healthy Adult Participants)

Objectives	Endpoints
Primary:	**Primary:**
To evaluate the safety and tolerability of PF-07242813, following single and multiple doses in healthy adults.	Incidence of treatment-emergent adverse events (AEs and SAEs); vital signs, safety laboratory tests, cardiac telemetry (SAD only), and ECG.
Secondary:	**Secondary:**
To characterize the serum exposure of PF-07242813, following single and multiple doses in healthy adults.	PF-07242813 serum exposure as data permit: AUC_{last}, AUC_{inf}, C_{max}, T_{max} and $t_{1/2}$ after single doses; AUC_{τ}, C_{max}, and T_{max} after each repeated dose; and $t_{1/2}$ after the last repeated dose.
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.2. Objectives, Endpoints and Estimands: Part 2 (Atopic Dermatitis Participants)

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To evaluate the safety and tolerability of PF-07242813 versus placebo, in participants with moderate to severe AD.	Incidence of treatment-emergent adverse events (AEs and SAEs); vital signs, safety laboratory tests, and ECG.	There is no defined estimand for these endpoints; they will be analyzed using CaPS as applicable.
Secondary:	**Secondary:**	**Secondary:**
To compare the efficacy of PF-07242813 versus placebo on percent change from baseline in Eczema Area and Severity Index (EASI) in participants with moderate to severe atopic dermatitis (AD).	Percent change from baseline in EASI total score at Week 6.	Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the study intervention on a continuous endpoint; without prohibited medications during treatment. Study Intervention: PF-07242813 or placebo. Population: Participants with moderate to severe AD as defined by the inclusion and exclusion criteria. Variable: Percent change from baseline in EASI total score at Week 6. Intercurrent Events: a. Prohibited medications – all scores in participants who receive prohibited medication post randomization to Week 6 will be omitted from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the study intervention. b. Inadequate compliance – participants data will be used as recorded. Events a and b are stated with precedence in descending order. Population level summary: The percent change from baseline mean difference between PF-07242813 and placebo in EASI score.

Objectives	Endpoints	Estimands
CCI		

Objectives	Endpoints	Estimands
CCI [redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Objectives	Endpoints	Estimands
	CCI [redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a first-in-human (FIH) study of PF-07242813 that will be conducted in 2 parts: Part 1 will be conducted in healthy adult participants and Part 2 will be conducted in adult participants with moderate to severe AD (see Figure 1).

Up to approximately 145 participants will be randomized to the study: in Part 1, up to approximately 57 healthy participants in SAD (including 5 Japanese participants), up to approximately 40 healthy participants, including an optional cohort in MAD, and in Part 2 up to 48 participants with moderate to severe AD.

4.1.1. Part 1: Single and Multiple Ascending Dose in Healthy Participants

Part 1 is within-cohort randomized, participant- and investigator- blind, sponsor-open, and placebo-controlled investigation of the safety, tolerability, PK, and immunogenicity following SAD and MAD of PF-07242813.

Approximately 97 healthy adult participants will be enrolled at a single study site into the proposed cohorts listed below. Participants may only participate in one cohort.

Participants in the single dose cohorts will be randomized sequentially as follows:

- Cohort 1 (n=4): 0.3 mg active (n=2) or placebo (n=2), IV;
- Cohort 2 (n=4): 1 mg active (n=2) or placebo (n=2), IV;
- Cohort 3 (n=4): 3 mg active (n=2) or placebo (n=2), IV;
- Cohort 4 (n=8): 10 mg active (n=6) or placebo (n=2), IV;
- Cohort 5 (n=8): 30 mg active (n=6) or placebo (n=2), IV;
- Cohort 6 (n=8): 100 mg active (n=6) or placebo (n=2), IV;
- Cohort 7 (n=8): 300 mg active (n=6) or placebo (n=2), IV;
- Cohort 8 (n=8): 1000 mg active (n=6), or placebo (n=2), IV.

Participants in the multiple dose cohorts, will be randomized as follows:

- Cohort 10 (n=8): 15 mg active (n=6) or placebo (n=2), SC x 3 doses Q2W;
- Cohort 11 (n=8): 50 mg active (n=6) or placebo (n=2), SC x 3 doses Q2W;
- Cohort 12 (n=8): 150 mg active (n=6) or placebo (n=2), SC x 3 doses Q2W;
- Cohort 13 (n=8): 300 mg active (n=6) or placebo (n=2), SC x 3 doses Q2W;
- Cohort 14 (n=8, optional): ≤1000 mg IV active (n=6) or placebo (n=2), SC x 3 doses Q2W.

The Japanese Participant Cohort will be randomized as follows:

- Cohort 15 (n=5): a single IV dose active (n=4) or placebo (n=1).

Within 28 days of successful completion of the screening process, eligible participants will be randomized to receive a single IV infusion of PF-07242813 or placebo. In order to mitigate any unanticipated acute safety risks within the IV infused SAD cohorts, sentinel dosing will be implemented in all SAD cohorts (ie, cohorts where the dose being tested is the highest administered in the study to date). For sentinel dosing, the first 2 participants (1 active: 1 placebo) will be dosed prior to the remaining participants in the cohort and monitored for at least 24 h to assess safety. If the dose level for the first 2 sentinel participants is determined to have an acceptable safety and tolerability profile, as judged by the investigator, the remaining participants within the cohort will be dosed. Single dose cohorts will be enrolled sequentially in a dose escalating fashion starting from the lowest proposed dose (0.3 mg). During the SAD period, escalation to subsequent dose levels will occur following the sponsor's review of available safety through study Day 8 and PK data through Day 3 for the previous cohort. There will be a minimum of 10 days between cohorts for dose escalation. Dosing in this part (up to the maximum dose of 1000 mg IV) may be adjusted depending upon the actual exposure of PF-07242813 observed in humans at lower doses. If, based on the observed data, the subsequent dose projected group mean C_{max} is >1020 µg/mL or AUC_{168H} >106000 µg.h/mL, the exposure limits determined as $1/10^{th}$ of the mean exposures observed at NOAEL in the 13-week cynomolgus monkey toxicity study, that dose will not be explored.

Participants will be admitted into the clinic approximately 1 day prior to dosing and be required to stay overnight in the study center through completion of Day 5 evaluations. Participants in the single dose cohorts will return for outpatient visits per the Schedule of Activities (Table 1), up to Day 71 visit (or at least 4 half-lives of PF-07242813 based on observed data). For Cohort 1, the outpatient visit is up to Day 29 (±3 days). For Cohorts 2 and 3, the final out-patient visit will be determined based on emerging safety and PK data from previous cohort(s). As such, the final scheduled visit may be earlier than Day 71 (±3 days), but will be at least through Day 29 (±3 days).

Four (4) multiple SC dose cohorts of PF-07242813 (15 mg to 300 mg) and 1 optional multiple IV dose cohort in healthy participants are planned. Initiation of the multiple dose (Cohort 10) will occur following the Sponsor's review of available safety data through study Day 8 and PK data through study Day 3 from Cohort 6 (100 mg single IV dose) and the accumulated safety from the previous single dose cohorts. The starting dose of 15 mg for the initial multiple dose cohort may be adjusted, based on emerging safety and PK data from the single dose cohorts. Progression to the next multiple dose may proceed after review of:

- Safety/tolerability data through Day 8 and PK data through Day 3 of the single dose that is no lower than the planned SC dose in next MAD cohort;
- Cumulative safety and PK data from the previous single dose cohorts;
- Safety/tolerability data through Day 22 (7 days following the 2nd dose) of the ongoing MAD cohort and previous MAD cohorts with lower doses.

If, based on the observed data, the subsequent dose in next cohort projected group mean C_{max} is >1020 µg/mL or AUC_{168H} >106000 µg.h/mL µg/mL following the 3rd dose, that dose will not be explored. The 5th MAD cohort (**Cohort 14**) is optional for further investigation of multiple doses as needed. The dose level for this cohort will be determined following a review of the cumulative safety and PK data up to 1000 mg IV single dose cohort and at least through Day 22 (7 days following the 3rd dose) of the ongoing 300 mg MAD cohort. The dose in this cohort will be no more than 1000 mg IV.

Healthy participants who are enrolled into the multiple dose cohorts will be randomized to receive PF-07242813 or placebo every 2 weeks (Q2W) for a total of 3 doses. Participants will be confined to the clinical research unit starting on the day prior to dosing and through at least 96 hours after the first dose of study intervention and 48 hours after the second and third doses. Participants may remain in house longer at the discretion of the PI due to operational logistics. Participants will return for outpatient visits per the (Table 2), at least through Day 99 visit (or at least 4 half-lives of PF-07242813 based on observed data). Based on emerging PK data, additional samples may be added to ensure PK is adequately characterized. Based on emerging data from previous and ongoing single and multiple dose cohorts, doses planned may be modified and other doses and/or dosing regimens (eg, Q4W) may be explored. If the exposures in the subsequent dose is projected to exceed the exposure limits pre-specified, after repeat doses, that dose will not be explored.

In addition, a cohort of healthy Japanese adults (Cohort 15, n=5) will be enrolled to receive a single IV administration of PF-07242813 or placebo (4 on PF-07242813 and 1 on placebo). This cohort will be initiated after single dose escalation in healthy participants (SAD) is complete and will enroll in parallel to Part 2.

4.1.2. Part 2: Participants with Atopic Dermatitis

Part 2 is a randomized, participant- and investigator-blind, sponsor-open, placebo-controlled investigation of the safety, tolerability, PK, and pharmacodynamics (including effects on clinical signs and symptoms) of PF-07242813 in adult participants with moderate to severe atopic dermatitis (AD).

In Part 2, Cohort 9 will randomize (2:1, PF-07242813) 24 participants at the MTD defined in Part 1 (or maximum dose studied in Part 1 if MTD is not achieved) for the assessment of the safety, tolerability, PK, and clinical effects of PF-07242813 in AD and CCI [redacted]. The number of participants enrolled in Cohort 9 will provide a sample size sufficient for statistical evaluation of the primary efficacy endpoint (placebo-corrected percent change from baseline in continuous EASI).

Cohort 9 will be initiated following completion of all single dose cohorts evaluated in Part 1 and review of cumulative safety and PK data from Part 1. Participants in Cohort 9 will receive the study intervention on Day 1 at the MTD identified in Part 1, or the highest dose studied in Part 1 if MTD is not achieved. The dose will be administered at the clinical site, and participants will return for outpatient visits per the Schedule of Activities (Table 3), up to Week 16.

An optional cohort (Cohort 16) of up to 24 moderate to severe AD participants may be enrolled as needed to evaluate further IV or SC dosing, based on cumulative safety and PK data from Part 1 and Cohort 9 in Part 2.

4.2. Scientific Rationale for Study Design

Study C4461001 represents the first time PF-07242813 will be administered to humans. Therefore, this first-in-human (FIH) study will employ an escalating dose design initially using single doses and then, once the safety and tolerability of higher single dose has been demonstrated, repeat doses. Study C4461001 will consist of 2 parts. Part 1 will be conducted in healthy participants; Part 2 will be conducted in participants with moderate to severe AD.

Human reproductive safety data are not available for PF-07242813, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.1. Study Design Rationale for Part 1

As PF-07242813 is projected to have the PK profile of a typical mAb, the single dose phase of Study C4461001 will be initiated with a dose estimated to have little pharmacologic activity (see dose rationale, Section 4.3.2, below) with dose escalation continuing until a maximally tolerated dose is identified or a dose of 1000 mg is achieved. The 1000 mg dose is predicted to provide >99% target coverage at maximal exposures, thereby assuring an adequate test of pharmacology in Part 2. The MAD phase of the study will be initiated once adequate safety data are available from a higher dose in the SAD phase of the study (see Section 4.1.1). Study C4461001 uses a placebo-controlled, blinded design to minimize bias which is justified in this early clinical study to provide a reference for safety and tolerability.

The dose escalation will be conducted in healthy participants (as defined by the inclusion/exclusion criteria) in order to establish the safety and tolerability of PF-07242813 prior to exposure in patient populations. Both adult male and female participants are eligible for enrolment in the study provided females are confirmed either to be of non-childbearing potential or, if of childbearing potential, to be using a nonhormonal form of highly effective contraception of low user dependency (such as an intrauterine device or surgical sterilization as stipulated in Appendix 4: Contraceptive Guidance). No barrier method of contraception (eg, condom) is warranted for male participants as the potential exposure to PF-07242813 via semen to partners of male participants is anticipated to be very low, as the calculated safety margin between the estimated maternal exposure due to seminal transfer at maximum dose/exposure proposed in human and the minimal anticipated biological effect level (MABEL) of PF-07242813 is in excess of 100-fold. Additionally, PF-07242813 does not have genotoxicity concerns. If emerging human PK in this study suggests the potential exposure of PF-07242813 to the partners of male participants via semen could exceed anticipated MABEL exposures at the highest proposed doses, male condom will be required for the following cohorts. As an additional safety measure, WOCBP will be required to have a negative pregnancy test prior to randomization and at pre-specified visits per the Schedule of Activities.

Healthy Japanese participants will be enrolled in a separate cohort to provide a preliminary characterization of the safety, tolerability, and PK profile of PF-07242813, to support potential inclusion of Japanese patients in future studies.

Risks to study participants will be minimized by cautious dose escalation in an inpatient setting, with careful assessment and ongoing review of emerging safety data. Given that the overall potential risk of immunogenicity with PF-07242813 has been assessed to be moderate and that the cytokine release assay has suggested a low potential for cytokine release syndrome (Section 2.2.1), sentinel dosing will be implemented in all SAD cohorts (ie, cohorts where the dose being tested is the highest administered dose in the study to date). Sentinel dosing will involve administration of PF-07242813 or placebo to the first 2 participants randomized as 1: 1 in each SAD cohort, with observation for at least 24 hours to establish adequate safety and tolerability before dosing the remaining participants in the cohort.

Together, the implementation of sentinel dosing in SAD cohorts and the dose escalation rules (Section 6.6.1) are expected to minimize the risk to study participants while providing key safety and tolerability information. As is standard for FIH studies, dose administration will be conducted in the fasting state in order to facilitate management of any adverse events that may occur shortly after dosing.

CCI [redacted]

associated safety concern at the last scheduled visits eg, Day 99 visit (~70 days after 3rd dose)
CCI [redacted]

[redacted]

Staining of neuroendocrine cells with PF-07242813 in the human anterior pituitary was observed in a tissue cross reactivity study that was not observed in the homologous cynomolgus monkey tissues (Section 2.2.1). The overall risk of pituitary toxicity in humans is considered low; however selected anterior pituitary hormones and hormones regulated by them will be monitored in SAD/MAD cohorts as a screen for potential adverse effects on the pituitary gland.

Currently, the final scheduled out-patient visits in SAD and MAD cohorts (except Cohorts 1-3 in SAD) are planned to be approximately 70 days after last dose, which is >4 times of PF-07242813 $t_{1/2}$ predicted in human (17 days). Based on emerging data, the last out-patient visit schedule may be modified in the following cohorts to cover at least 4 half-lives of PF-07242813 observed in previous cohorts.

4.2.2. Study Design Rationale for Part 2

The objectives of Part 2 of Study C4461001 are to assess the safety and tolerability of PF-07242813 at a single maximally planned or maximally tolerated dose in participants with moderate to severe AD, and to provide preliminary data on the effects of PF-07242813 on clinical signs and symptoms of AD.

Part 2 of Study C4461001 will consist of up to 2 cohorts of participants with moderate to severe AD (Cohorts 9 and optional Cohort 16). Participants in Cohort 9 will receive a single IV dose of study intervention at the MTD established in Part 1 (or the highest dose studied in Part 1 if MTD is not achieved). The sample size of approximately 24 participants with AD in Cohort 9 will support the assessment of clinical activity for the primary efficacy endpoint. This approach is justified by the accumulated single and available multiple dose safety data generated in the healthy participants, and the extended duration of high target occupancy predicted at this dose.

The optional Part 2 cohort (Cohort 16) would allow for further investigation of the safety, tolerability, PK, and pharmacodynamics of PF-07242813 at lower or repeat doses, as deemed necessary based on emerging data. As for Part 1, Part 2 of Study C4461001 will be blinded to the site personnel (with the exception of the site pharmacist and, as needed, an individual designated to administer study intervention who is not otherwise associated with the study) and placebo-controlled, with the same rationale.

As noted above, a secondary objective of Part 2 is to evaluate the potential clinical activity of PF-07242813 in patients with moderate to severe AD in order to guide future development of the molecule. The patient population defined by the inclusion/exclusion criteria, the predicted human PK profile, and the resultant predicted level and duration of target engagement is expected to provide an adequate test of the pharmacology of PF-07242813 in inhibiting CD1a proinflammatory signaling in AD. The sample size and randomization schemes is expected to be sufficient to detect clinically meaningful improvement in AD signs and symptoms (see Section 9.2.2).

Women of childbearing potential (WOCBP) will be eligible for participation if they agree and adhere to the contraception guidelines stipulated in this protocol (Appendix 4: Contraceptive), which include hormonally based contraception methods. Although reproductive safety data are not available for PF-07242813, there is no suspicion of human teratogenicity, genotoxicity, or clastogenicity based on the pharmacology of the compound that would preclude the inclusion of WOCBP using highly effective contraception into a controlled clinical trial. Compared to the contraception requirements in Part 1, the allowance for hormonal methods of contraception is justified by the accumulated safety and tolerability data from the SAD and MAD cohorts in Part 1 and will facilitate recruitment given that many patients with AD are of reproductive age and capacity. As an additional safety measure, WOCBP will be required to have a negative pregnancy test prior to randomization and at all study visits.

For both **Part 1 and Part 2**, Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

4.3.1. Prediction of Human PK and Efficacious dose

Based on the serum PK parameter values observed for PF-07242813 in nonclinical species, the predicted 2-compartment PK parameter values in humans are expected to be the same as those of a typical therapeutic IgG mAb. These values have been reported previously (Dirks and Meibohm 2010; Betts et al. 2018)[8,2] and were used for the PF-07242813 human PK predictions as follows: 3.2 L for central volume, 2.2 L for peripheral volume, 0.25 L/day for central CL, 0.45 L/day for distributive clearance, 0.26 1/day for SC absorption rate constant and 60% for SC bioavailability. The predicted volume and clearance values resulted in a 17-day $t_{½}$ and a 5.4 L V_{ss}.

As there are no validated mechanism-based biomarkers or preclinical disease/efficacy model for human AD, the efficacious dose of PF-07242813 has been projected empirically, as a dose that will achieve >95% CD1a receptor occupancy at steady state trough concentrations at the site of action (skin). A site of action model was used to link PF-07242813 exposure to CD1a receptor occupancy using the PF-07242813 K_D and the predicted human PK parameters, CD1a concentrations in skin and CD1a internalization/turnover rate. Using this approach, the predicted efficacious human dose of PF-07242813 is estimated to be 30 mg SC q4wk. The projected steady state AUC_{tau} (tau=4 weeks/672 hrs), C_{ave} and C_{max} associated with the predicted efficacious dose are 1730 µg.h/mL, 2.58 µg/mL and 3.67 µg/mL.

4.3.2. Dose Rationale for Part 1

The nonclinical safety profile of PF-07242813 has been adequately characterized to support development into human clinical studies of up to 3 months in duration. No test article-related effects or target organs were identified following once weekly administration of PF-07242813 in a pivotal 13-week cynomolgus monkey toxicity study with the NOAEL defined as the highest dose tested, 200 mg/kg/week (IV). In this study, the C_{max} and AUC_{168H} exposure limit for dose escalation are set to be 1020 µg/mL and 106000 µg/mL, respectively, determined as $1/10^{th}$ of the mean exposures observed at NOAEL in the monkey toxicity study.

A starting dose of 0.3 mg PF-07242813 IV is planned. The predicted PF-07242813 C_{max} and AUC_{168H} at the 0.3 mg single dose are approximately 10890-fold and 11150-fold, respectively, below the exposure limits pre-defined for PF-07242813 dose escalation (see Table 4). The predicted exposures at the 0.3 mg single dose are approximately 39- and 82-fold below the steady-state exposure at projected efficacious dose (30 mg SC Q4W) for C_{max} and AUC_{tau} (tau=4 weeks/672 hrs), respectively. The maximum CD1a receptor occupancy at skin, the site of action after 0.3 mg IV single dose is predicted to ~29%, at which level little pharmacological effect is expected as PF-07242813 is an antagonist of CD1a target engagement. The starting dose selection is consistent with the EMA guideline on first-in-human study (EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products) and a recent white paper on FIH starting dose selection by the IQ consortium (Leach et al. 2020).[14] The highest proposed IV infusion dose of 1000 mg is estimated to provide an exposure margin of 3.3-fold for both C_{max} and AUC_{168H}, relative to the exposure limits.

Table 4. Projected Exposures, Maximum CD1a Receptor Occupancy and Safety Margins Following Single IV Doses of PF-07242813[a]

DOSE (mg)	C_{max} (µg/mL)	AUC_{168H} (µg·h/mL)	SM_C_{max}[b] (fold)	SM_AUC[b] (fold)	RO[c] (%)
0.3	0.09368	9.51	10890	11150	29.3
1	0.3111	31.65	3279	3349	59.2
3	0.9332	94.95	1093	1116	81.2
10	3.111	316.5	328	335	93.8
30	9.332	949.5	109	112	97.9
100	31.11	3165	33	33	99.4
300	93.32	9495	11	11	99.8
1000	311.1	31650	3.3	3.3	99.9

a. Human PK was predicted using 2-CM model with IV infusion and linear PK. For dose <1 mg, infusion over 10 min, otherwise, infusion over 1 hour. Vc=3.2 L, Vp=2.2 L, CL=0.25 L/day, Q= 0.45 L/day. For dose <1 mg, it is assumed that infusion over 10 min, otherwise, infusion over 1 hour.
b. SM= safety margin, which is calculated relative the exposure limit (C_{max} = 1020 µg/mL and AUC_{168H}=106000 µg.h/mL), determined as $1/10^{th}$ of the mean exposure at NOAEL of 200 mg/kg/week IV in pivotal 13-week cynomolgus monkey toxicity study.
c. A site of action model was used to predict CD1a receptor occupancy at skin with the predicted human PK.

The dose range of 15 mg to 300 mg SC administered every two weeks (Q2W) in total of 3 doses were selected for dose escalation in 4 MAD cohorts (Table 5). The dosing regimen of every two weeks (Q2W) was selected to achieve high exposures of PF-07242813 with fewer doses compared to monthly dosing for adequate safety assessment. The multiple dose period is planned to be initiated at the 15 mg SC dose level with the C_{max} and AUC_{168H} following 3 repeated doses, each dose predicted to be 424- and 287-fold below the exposure limits pre-defined. The predicted exposures following 3 repeated doses at 15 mg SC are also below the steady-state exposures at projected efficacious dose (30 mg SC Q4W) for both C_{max} (2.405 vs 3.67 µg/mL) and AUC_{tau} (1144 vs 1730 µg.h/mL over 4 weeks/672 hrs). At the highest dose proposed (1000 mg IV) in an optional MAD cohort, the predicted margins for C_{max} and AUC_{168H}, relative to the exposure limits, are 2.3- and 2.1-fold, respectively (Table 5).

Table 5. Projected Exposures, Maximum CD1a RO and Safety Margins After the 3rd Dose of Multiple SC or IV Doses of PF-07242813[a]

DOSE (mg q2wk)[b]	C_{max} (µg/mL)	T_{max} (hr)	AUC_{168H} (µg·hr/mL)	C_{ave}[c] (µg/mL)	SM_C_{max}[d] (fold)	SM_AUC[d] (fold)	SM_C_{ave}[d] (fold)	Max RO[e] (%)
15	2.405	96	369.4	2.092	424	287	302	96.3
50	8.017	96	1231	6.973	127	86	91	98.7
150	24.05	96	3694	20.92	42	29	30	99.6
300	48.1	96	7388	41.84	21	14	15	99.8
1000 IV	441.6	1	50640	245	2.3	2.1	2.6	99.9

a. Human PK was predicted using 2-CM model with S.C. in which Vc=3.2 L, Vp=2.2 L, CL=0.25 L/day, Q=0.45 L/day, 0.26 1/day for SC absorption rate constant and 60% for bioavailability were used. PK parameters after the 3rd dose are presented.
b. Dose is given q2wk with 3 doses in total. All the doses are given as subcutaneously except 1000 mg which is given IV over 1 hr infusion.
c. $C_{ave}=AUC_{tau}/336$ (tau=336 hours for q2wk dosing in MAD cohorts).
d. SM=safety margin, which is calculated relative the exposure limits of C_{max}=1020 µg/mL and AUC_{168H}=106000 µg.h/mL, determined as $1/10^{th}$ of the mean exposure at NOAEL of 200 mg/kg/week IV in pivotal 13-week cynomolgus monkey toxicity study. C_{ave} used for safety margin calculation is exposure limit of AUC_{168H} divided by 168 hr.
e. A site of action model was used to predict CD1a receptor occupancy at skin with the predicted human PK.

4.3.3. Dose Rationale for Part 2

A single dose of study intervention is planned in 24 adult participants with AD (Cohort 9), at the maximum tolerated dose (MTD) observed in Part 1 or the highest dose studied in Part 1 if MTD is not achieved (eg, the planned maximum dose of 1000 mg). Following a 1000 mg single IV dose of PF-07242813, the predicted CD1a receptor occupancy would be saturated and remain high (>95%) for greater than 16 weeks. An optional cohort (Cohort 16) may be used to evaluate further IV or SC dosing of PF-07242813, based on cumulative safety and PK data from Part 1 and Cohort 9 in Part 2.

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 the End-of-Study visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

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

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

5.1. Inclusion Criteria

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

Age and Sex:

1. **Part 1 only:** Adult male or female participants between 18 to 55 years of age, inclusive, at the time of signing the ICD.

    - Refer to Appendix 4 for reproductive criteria for males (Section 10.4.1), females of non-child bearing potential (Section 10.4.2), and females of child-bearing potential (Section 10.4.3).

    OR

    Part 2 only: Male or female participants, who at the time of screening, are between the ages of 18 and 65 years, inclusive.

    - Refer to Appendix 4 for reproductive criteria for male participants (Section 10.4.1), females of non-child bearing potential (Section 10.4.2), and females of child-bearing potential (Section 10.4.3).

Type of Participant and Disease Characteristics:

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

3. **Part 1 only:** Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, vital sign assessments, temperature, 12-lead ECGs, laboratory tests.

4. **Part 1, Japanese cohort:** Healthy adults of Japanese descent, where parents and grandparents are Japanese.

5. **Part 2 only:** Must meet the following atopic dermatitis criteria:

   a. Have a clinical diagnosis of chronic atopic dermatitis (also known as atopic eczema) for approximately 1 year prior to Day 1 and have the diagnosis of AD confirmed (Hanifin and Rajka criteria of AD).[10]

   b. Either have had an inadequate response to treatment with topical medications (for at least 4 consecutive weeks within 1 year of the first dose of the study drug).

      OR

      Have a documented reason why topical treatments are considered medically inappropriate (eg, because of important side effects or safety risks) within the last year.

   c. Have moderate to severe AD (defined as having an affected BSA (captured as part of EASI) ≥10%, IGA ≥3, and EASI ≥12 at both the screening and baseline visits).

   d. Have an otherwise healthy medical evaluation (other than signs and symptoms of AD) including medical history, physical examination, vital sign assessments, temperature, 12-lead ECGs, laboratory tests.

      Note: Controlled comorbid diseases (ie, controlled diabetes not requiring insulin, controlled hypertension), are acceptable, so long as they do not require administration of prohibited medications.

   e. Mild or moderate asthma that is well-controlled (not requiring high dose inhaled corticosteroids, systemic [oral or parenteral] corticosteroids, or biologic asthma treatments).

Weight:

6. **Part 1:** BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lbs);
   Part 2: BMI of 17.5 to 40 kg/m^2; and a total body weight >50 kg (110 lbs).

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence of active, latent, or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by both of the following:

   a. A positive QuantiFERON-TB Gold In-tube or equivalent test.

   b. History of either untreated or inadequately treated latent or active TB infection, or current treatment for the same.

2. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C antibody (HCVAb). Hepatitis B vaccination is allowed. As an exception a positive HBsAb test due to hepatitis B vaccination is permissible.

   Testing for SARS-CoV-2 will be at the discretion of the investigator, based on local infection rates, patient exposure history, and reported signs or symptoms of COVID-19.

3. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

   - *Part 2 only:* At Screening Visit, if there are "yes" answers on items 4, 5 in the past year or on any question in the suicidal behavior section of the Columbia-Suicide Severity Rating Scale (C-SSRS) in the past 6 months, the participant will not be included in the study.

4. Known history of or evidence of current endocrine disease.

5. 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.

6. Recent exposure to live or attenuated vaccines within 28 days of the screening visit.

7. 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.

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

9. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, immunological/rheumatological.

10. **Part 1 only:** allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

Additional Exclusionary Medical Criteria for Part 2 (Atopic Dermatitis Cohorts)

11. **Part 2:** Currently have active forms of other inflammatory skin diseases.

12. **Part 2:** Have history of or current evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, lupus) at the time of Day 1 that would interfere with evaluation of atopic dermatitis or response to treatment.

13. **Part 2:** Have active chronic or acute skin infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to Day 1, or superficial skin infections within 1 week prior to Day 1.
NOTE: potential participants may be rescreened after infection resolves.

14. **Part 2:** Score of >5 on the Fitzpatrick Skin Type Assessment.

15. **Part 2:** History of anaphylaxis with the following exceptions: participants with sensitivity and/or anaphylaxis only to a single, avoidable allergen (eg, aspirin, penicillin, sulfadrugs, nonsteroidal anti-inflammatory drugs [NSAIDs], peanuts) may be enrolled, if in the opinion of the investigator, the participant is aware of the hypersensitivity and avoids -the problematic allergen. Participants must carry appropriate treatment for anaphylaxis and must know how to manage anaphylactic reactions.

Prior/Concomitant Therapy:

16. Participation in any other cohort of this study: participants can only be randomized once into this study and be assigned to 1 cohort only.

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

18. **Part 1 only**: Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives-(whichever is longer) prior to the first dose of PF-07242813. (Refer to Section 6.5.1 for additional details).

19. **Part 2 only:** Have received any of the treatment regimens within the specified timeframes as outlined in Section 6.5.2.2 (Prohibited Treatments and Medications During the Study).

Prior/Concurrent Clinical Study Experience:

20. Treatment with an investigational drug within 28 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study treatment (whichever is longer).

21. **Part 2 only:** Any investigational or experimental therapy taken or procedure performed for AD, psoriasis, psoriatic arthritis, rheumatoid arthritis or other inflammatory diseases in the previous 1 year should be discussed with the Pfizer Medical Monitor (or designee).

Diagnostic Assessments:

22. A positive urine drug test (please refer to Section 10.2).

23. **Part 1:** Screening supine blood pressure ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) 1 for healthy adults.

    Part 2: Screening supine blood pressure ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic), following at least 5 minutes of supine rest.

    For Part 1 and Part 2, if blood pressure (BP) meets the criteria above for a given single measurement, the BP should be repeated two more times and the average of the three BP values should be used to determine the participant's eligibility.

24. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTc interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

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

    a. **Part 1:** AST **or** ALT level >1.2 × ULN;
    Part 2: AST **or** ALT level ≥3 × ULN

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

    c. History or current evidence of anterior pituitary disorders Screening test results CCI [redacted]

Other Exclusions:

26. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) or 4 (female), or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).

27. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

28. History of sensitivity to heparin or heparin-induced thrombocytopenia.

29. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

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

31. Pregnant female participants, breastfeeding female participants, male participants with partners currently pregnant, or male or female participants pursuing artificial reproductive technologies including but not limited to sperm/egg donation (see Section 5.3).

32. Use of tobacco/nicotine containing products more than 5 cigarettes/day.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and at least 8 hours prior to dose administration. Water is permitted without restriction.

Part 1: The following requirements apply **ONLY** to Part 1, while the participants are confined in CRU:

- Breakfast will not be provided on Day 1.
- Noncaffeinated drinks may be consumed with meals and the evening snack.
- Lunch will be provided approximately 4 hours after dosing on Day 1. Dinner will be provided approximately 9 to 10 hours after dosing on Day 1.
- An evening snack may be permitted.
- The total daily nutritional composition, while confined, should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Alcohol, Caffeine and Tobacco

- All participants will abstain from alcohol for 24 hours prior to all outpatient visits. All participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator. Participants in **Part 1** will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol during clinical confinement at the CRU. Participants may undergo an alcohol breath test at the discretion of the investigator.
- All participants will abstain from caffeine-containing products for 24 hours prior to all outpatient visits till the completion of infusion of the IP and necessary activities such as ECG, vitals, respiratory rate (RR). **Participants in Part 1** will abstain from caffeine-containing products for 24 hours prior to admission to the CRU and during confinement in the CRU.
- All participants will abstain from the use of tobacco- or nicotine-containing products for 6 hours prior to all outpatient visits and through the completion of infusion of the IP and necessary activities such as ECG, vitals, respiratory rate (RR). **Participants in Part 1** will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to admission to the CRU and during confinement in the CRU.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each study visit requiring blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- **Part 1:** Participants will be confined to the procedure room for the first 4 hours after dosing on Day 1 during continuous cardiac monitoring, except to use the bathroom. After this, if the equipment setup allows, participants may be ambulatory during the ECG monitoring period, but should not engage in strenuous activities. If equipment does not allow ambulation, appropriate accommodations will be made by the investigator site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate participants' excretory needs).

5.3.4. Contraception

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

In Part 1, females of childbearing potential enrolled are required to use a low user dependency, nonhormonal form of highly effective contraception for contraception method (such as an intrauterine device or surgical sterilization, as stipulated in Appendix 4 Section 10.4.4).

5.4. Screen Failures

Part 1: Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported to the clinical database. Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. However, for participants who have met the criteria for participation during screening but the screening falls outside 28-day window, they can be rescreened in this case.

Part 2: Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details,

eligibility criteria, and any SAE must be documented in source and recorded in the CRF. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice.

Delays in randomization of a participant (up to 1 week) related to receipt of primary or repeat laboratory results will not be considered protocol deviations.

6. STUDY INTERVENTION

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

For the purposes of this protocol, study intervention refers to PF-07242813 and placebo, administered either intravenously or subcutaneously.

6.1. Study Intervention(s) Administered

Intervention Name	**PF-07242813**	**Placebo**
Type	**Active Drug**	**Placebo**
Dose Formulation	PF-07242813 100 mg/mL vial	Vial
Route of Administration	IV SC	IV SC
Use	Active	Placebo
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.
Packaging and Labeling	Study intervention will be provided in vials.	Study intervention will be provided in vials.

6.1.1. Administration

PF-07242813 and placebo will be administered intravenously or subcutaneously.

Following an overnight fast of approximately 8 hours, participants will receive study intervention (start time of infusion) at approximately 0800 hours (plus or minus 3 hours). For planned IV dosing (Cohorts 1-9 and 14), study intervention will be administered as an intravenous infusion over 15-30 min for dosing solution ≤10 mL and 60 min for dosing solution >30 mL. In the case of mild infusion reactions, at the discretion of the investigator, the infusion may be interrupted and restarted at a slower infusion rate not to exceed a total administration duration of 90 minutes. The start and stop time of the infusion will be recorded in source document and CRF. Time 0 is the time when the study intervention infusion begins. The infusion rate and amount of volume infused will be recorded. For Cohorts 10-13, study intervention is planned to be administered subcutaneously. Each injection should occur at a different site on the abdomen, approximately 1 cm apart.

6.2. Preparation/Handling/Storage/Accountability

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

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

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

5. Study interventions should be stored in their original containers.

6. Staff will instruct participants on the proper storage requirements for take-home study intervention.

7. See the IP Manual for storage conditions of the study intervention, once diluted.

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

9. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in a blinded fashion to the participants.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

The investigator will assign participant numbers sequentially to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number. It will also appear on the study medication containers. Study intervention will be dispensed at the study visits summarized in the SoA.

Healthy participants will be randomized (once) into the SAD period, at which time, they will receive treatment assignment (PF-07242813 or placebo) for both the SAD and MAD periods. Participants will receive the same blinded treatment assignment (ie, the same dose level of PF-07242813 or placebo) throughout, in both the SAD and MAD cohorts.

- The randomization ratio for the cohorts in the healthy participant SAD/MAD segment will be 3:1 (PF-07242813:Placebo) with the exception of Cohorts 1-3, which will be randomized 1:1.

- The overall randomization ratio for the atopic dermatitis cohorts will be 2:1 (PF-07242813:Placebo) for Cohort 9.

Investigators, all participants and all study personnel involved in the study, with the exception of the pharmacist who prepares the study treatment and, as needed, an individual designated to administer study intervention who has no other involvement with study conduct, personnel, or participants, will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party will be responsible for the preparation and dispensing of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense or visual presentation following randomization.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site to verify that randomization/dispensing has been done accurately.

6.3.2. Breaking the Blind

The method for breaking the blind in this study will be manual. A sealed envelope that contains the study intervention assignment(s) for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF/DCT.

Once the study is complete, all envelopes (sealed and opened) must be inventoried and retained until authorization for destruction has been provided.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The site will complete the required dosage Preparation Record located in the IP manual. The use of the Preparation Record is preferred, but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose. This may be used in place of the Preparation Record after approval from the sponsor and/or designee.

6.5. Concomitant Therapy

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study investigational product will be documented as a prior treatment. Treatments taken after the first dose of study investigational product will be documented as concomitant treatments.

6.5.1. Concomitant Treatments in Part 1

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤2.5 g/day.

Females taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study.

6.5.2. Concomitant Treatments in Part 2

6.5.2.1. Permitted During Study

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. All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. Any new concomitant medications or dose changes to current concomitant medications should be evaluated for potential new or worsening adverse events.

Treatments taken within 28 days before the first dose of study investigational product will be documented as a prior treatment. Treatments taken after the first dose of study investigational product will be documented as concomitant treatments.

The following concomitant therapies are permitted during the study:

- Oral antihistamines (excluding H4 antagonists) for allergies.
- Stable dose of leukotriene antagonists/modifiers.
- Corticosteroid inhalers at allowed doses (exclusive of high doses of inhaled corticosteroids) is permitted for stable asthma.
- Non-medicated emollient and sunscreen are the only topical products permitted to be used on atopic dermatitis skin during the study. Participants are recommended not to switch the emollient or sunscreen during the study.

A participant who is receiving a permitted concomitant medication for any reason must be on a locally-approved medication and dose for the treated indication, and this must be documented in the CRF. Participants are not allowed any other investigational drugs or treatments during the study.

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

Acetaminophen may be used intermittently (not to exceed 2.5 g/day). Vitamin and mineral supplements of standard potency are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis).

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

Unless a prohibited medication or treatment, participants may be administered any other medications necessary for the treatment of concomitant medical disorders as deemed necessary by the treating physician. Following Day 1, addition of concomitant medications or any change in the dosage should be limited to those considered medically essential.

6.5.2.2. Prohibited Treatments and Medications During the Study

Participants are required to discontinue and avoid using certain medications and treatments. 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. Prohibited medications include:

a. Systemic Corticosteroids:

   - Participants receiving systemic corticosteroids within 4 weeks prior to first dose of study intervention or scheduled to receive systemic corticosteroids during the study period for another condition.

   - Participants receiving doses of depot preparations of parenteral corticosteroids within 6 weeks of the predicted end of release of the corticosteroid from the depot are excluded.

   - An inhaled dose of greater than 1000 µg fluticasone, or an equivalent inhaled corticosteroid, per day.

b. Leukotriene antagonists/modifiers:

   - Asthmatic participants taking stable doses of leukotriene antagonists/modifiers for at least 28 days prior to first dose of study drug may be included.

c. Prior or current use of anti-IL-33 targeted therapies.

d. Current or anticipated use of protein therapeutics.

e. Benralizumab within 12 months of first dose of study intervention, or at any time during the study.

f. Prior use of the following drugs within 6 months of first dose of study intervention, or at any time during the study:

- Prior or current use of anti-IL-4 and/or IL-13 targeted therapies (eg, lebrkizumab, tralokinumab).
- Anti-IL-5 targeted therapies (eg, mepolizumab or reslizumab).
- Any cell-depleting agents including but not limited to rituximab: within 6 months of first dose of study drug or 5 half-lives (if known), or until lymphocyte count returns to normal, whichever is longer.

g. Prior use of dupilumab within 4 months of first dose of study intervention, or at any time during the study.

h. Within 12 weeks of first dose of study intervention, or at any time during the study:

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

i. Within 4 weeks of first dose of study intervention, or at any time during the study:

- Use of oral immune suppressants (eg, cyclosporine A [CsA], azathioprine, MTX, Celcept, mycophenolate-mofetil, interferon-gamma (IFN-γ) within 4 weeks of first dose of study drug or within 5 half-lives (if known), whichever is longer.
- Any Janus Kinase (JAK) inhibitors, including participation in any clinical studies in which a JAK inhibitor was a possible study treatment.
- Investigational drugs.
- Live, attenuated or mRNA vaccines.
- Oral or topical phosphodiesterase (PDE) 3 or PDE4 antagonists (eg, apremilast, crisaborole); oral/topical histamine H4 antagonists: within 28 days or 5 half-lives whichever is longer prior to first dose of study drug.
- Phototherapy (NB-UVB) or broad band phototherapy.
- Regular use (more than 2 visits per week) of a tanning booth/parlor. Use of bronzing creams, gels or sprays within the last 2 weeks.

j. Within 1 week of first dose of study intervention, or at any time during the study:

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

A protocol deviation is to be completed for any participant that takes a prohibited treatment or medication during the study and the sponsor is to be notified. The participant may be replaced at the discretion of the sponsor if prohibited treatments have been taken prior to Week 6.

All medications and treatments that could affect atopic dermatitis must be discontinued except permitted concomitant therapies (eg, oral antihistamines). Due to the potential to affect atopic dermatitis with ultraviolet light exposure, participants must also avoid prolonged exposure to the sun and avoid the use of tanning booths, sun lamps or other ultraviolet light sources during the study.

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

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

Participants should refrain from having any vaccinations during the course of study participation.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in Part 2 participants who are WOCBP (see Appendix 4).

6.5.3. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07242813; standard medical supportive care must be provided to manage the AEs.

Part 2 only: Participants randomized into the study are allowed to take other treatments for their disease as prescribed by the investigator, provided they are not included among the prohibited concomitant medications (noted in Section 6.5.2.2) and the concomitant drugs and doses are maintained unchanged throughout the first 16 weeks of the study. Although no specific rescue treatment is recommended, participants randomized into the study may have access to standard of care therapy, that may include prohibited treatments and medications defined in Section 6.5.2.2, if deemed necessary by the investigator to treat their underlying disease. Since there is no information on drug interactions, the general guidance is, if possible, to defer initiation of treatment until after the primary AD assessments are complete

at Week 6, to start with topical before systemic treatments, and to use fewer immunosuppressing treatments before progressing to more immunosuppressing treatments.

6.6. Dose Modification

6.6.1. Dose Escalation and Stopping Rules (Part 1)

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the study intervention.

The dose escalation will be terminated based on the following criteria:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance.

- If two-thirds of participants at a given dose level develop an individual participant stopping AE (see Section 7.1).

- Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.

- Other findings that, at the discretion of the study team and investigator, indicate that dose escalation should be halted.

- If, at any dose level, the average exposure reaches or exceeds the PK stopping limits, C_{max} of 1020 µg/mL and AUC_{168H} of 106000 µg.h/mL

- If, based on the observed data, the group mean C_{max} or AUC (based on total serum concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND OF STUDY PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for a minimum of 4 half-lives (approximately 70 days) after last dose. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following:

- Any participant who develops Grade 2 or higher adverse events for cardiac and blood/bone marrow categories and Grade 3 or higher adverse events in all other categories according to criteria defined in CTCAE, v. 5 will be discontinued from treatment, and followed until resolution of the adverse event(s).

- If a participant experiences symptoms typical of an allergic reaction, the study drug administration should be discontinued immediately and permanently;

- ECG changes (see below);

- Unacceptable toxicity;

- Pregnancy.

ECG Changes

A participant who meets the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from the study intervention.

- QTcF >500 msec.

- Change from baseline: QTc >60 msec.

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

7.1.1. Temporary Discontinuation

If a participant experiences symptoms typical of infusion reactions (eg, lightheadedness, nausea, chills, fever), the study intervention infusion should be stopped. At the discretion of the investigator, the infusion can be restarted at a slower rate if symptoms are resolved within 1 hour after the stop of infusion. If symptoms return, then the study intervention administration should be discontinued immediately and permanently.

In the event that there is an infusion interruption, the entire duration of drug infusion, from the initial start of infusion to the completion of infusion, should not exceed 3 hours. The start and stop time of the infusion and the infusion rate and amount of volume infused in the event of an interruption will be recorded. Participants will receive appropriate treatment at the discretion of the investigator.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

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

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible.

The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

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

The following actions must be taken if a participant fails to attend 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.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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

All screening evaluations (defined as assessments conducted prior to first dose) 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 within 28 days prior to administration of the study intervention to confirm that they meet the eligibility criteria for the study. If the time between screening and dosing exceeds 28 days (up to 1 week) due to delays related to receipt of primary or repeat laboratory results, this will not constitute a protocol deviation.

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

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

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

The total blood sampling volume for individual participants in the Part 1 SAD cohort is approximately 325 mL, for the MAD cohort is approximately 480 mL, and in Part 2 for Cohort 9 is approximately 510 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety and/or PK assessments at times

specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Assessments of Clinical Effect (Participants with Atopic Dermatitis [Part 2])

8.1.1. Fitzpatrick Skin Type Assessment

As part of baseline characteristics, a skin type assessment will be done at the Screening visit using the Fitzpatrick Skin Phototype assessment (Appendix 8: Fitzpatrick Skin Type). This is used to classify a person's skin type by their response to sun exposure (ie, burning or tanning).

8.1.2. Eczema Area and Severity Index (EASI)

The EASI quantifies the severity of a participant's atopic dermatitis based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring by the atopic dermatitis clinical evaluator of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body (Hanifin et al. 2001).[10] (See Appendix 9: EASI).

CCI [redacted]

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

Columbia suicide severity rating scale is a validated tool to evaluate suicidal ideation and behavior (Appendix 15: Columbia Suicide Severity Rating Scale (C-SSRS)) (Posner et al. 2007).[17]

At Screening Visit, if there are "yes" answers on items 4, 5 in the past year or on any question in the suicidal behavior section of the C-SSRS in the past 6 months, the participant will not be included in the study.

8.1.5. Patient Reported Outcome Measures

All patient reported outcome measures must be completed by the participant prior to significant contact between the participant and site personnel, and before all other activities listed above. These include:

8.1.5.1. POEM

The POEM is a 7-item PRO measure used to assess the impact of AD over the past week (Appendix 11: Patient-Oriented Eczema Measure (POEM)). The POEM should be completed per the Schedule of Activities (Charman et al. 2004).[4]

8.1.5.2. Pruritus Numerical Rating Scale (Pruritus NRS)

The Pruritus NRS (Appendix 12: Pruritus NRS, Severity and Frequency) consists of 2 assessments: of pruritus severity and of pruritus frequency as detailed below. Pruritus NRS will be completed by participants every day for 14 days (either while at home or confined in the clinic) after the Day 1 dosing visit and per the Schedule of Activities (Part 2 only). NRS assessment for Day 8 visit will be administered at the site. NRS assessments completed prior to Day 8 visit should be returned to the clinical site at the Day 8 visit. NRS assessments completed at home prior to Day 29 visit should be returned to the clinical site on the nominal Day 29 visit (including the Day 2-Day 8 NRS assessments if not previously returned to the clinical site) (Phan et al. 2012).[16]

8.1.5.2.1. Severity of Pruritus

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

8.1.5.2.2. Frequency of Pruritus

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

The pruritus NRS should be completed per the Schedule of Activities (Part 2 only).

8.1.5.3. Patient Global Assessment (PtGA)

The PtGA asks the participant to evaluate the overall cutaneous disease at that point in time on a single item-, 5-point scale (Appendix 13: Patient Global Assessment (PtGA)). The same category labels used in the Investigator 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 per the Schedule of Activities. The 5-point scale for PGA is: 0, "clear"; 1, "almost clear"; 2, "mild"; 3, "moderate"; 4 "severe".

8.1.5.4. Dermatology Life Quality Index (DLQI)

The DLQI (Appendix 17: Dermatology Life Quality Index (DLQI)) is a general dermatology questionnaire that consists of 10 items that assess participant health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment). It has been extensively used in clinical trials for atopic dermatitis. The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to be responsive to change. The minimally important difference for the DLQI has been estimated as a 2 to 5 point improvement from baseline.

8.1.5.5. Hospital and Anxiety Depression Scale (HADS)

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

8.1.5.6. Asthma Control Questionnaire, 5 Item Version (ACQ-5) (Asthmatic Participants only)

The 5-question version of the ACQ is a validated questionnaire to evaluate asthma control. The 5-item version of the ACQ differs from the full ACQ (7 question version) in that the question about short-acting bronchodilator use and FEV_1 score are excluded. Participants will complete the ACQ questionnaire per the Schedule of Activities A physician, trained physician's assistant, nurse practitioner, or study coordinator as acceptable according to local regulation will review the assessment for thoroughness. A copy of the ACQ is provided in Appendix 19: Asthma Control Questionnaire.[12]

8.1.6. Rater Qualifications

Investigators participating in this study should be experienced in the conduct of inflammatory disease clinical trials and have prior training and experience in the required protocol-specific AD participant clinical evaluations. **The same rater should evaluate the same participant(s) whenever possible.**

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance including skin (specific attention to infusion and injection site reactions), the respiratory, gastrointestinal, and cardiovascular systems, as well as towards participant reported symptoms.

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

8.2.2. Vital Signs

Temperature will be measured by oral, tympanic, or temporal artery method, provided the same method is used consistently throughout the study. No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

Respiratory rate will be measured after approximately 5 minutes rest in supine position by observing and counting the respirations of the participant for 30 seconds and multiplied by 2. When blood pressure is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before blood pressure measurement. Post-dose respiratory rate measurements to be done at Investigator's discretion.

Blood pressure and pulse rate will be measured at times specified in the Schedule of Activities. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Blood pressure should not be taken from the arm with an intravenous infusion. Participants should be instructed not to speak during measurements. If a single measurement is >140 mm systolic and/or >90 mm diastolic in healthy participants, or >160 mm systolic and/or >100 mm diastolic in atopic dermatitis participants, the blood pressure assessment should be repeated two more times, and the average of the three BP values recorded in the CRF and noted in source documents.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

8.2.3. Electrocardiograms

12-Lead Standard Electrocardiograms (ECGs) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR interval, QT interval, QTc intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected before dose administration on Day 1 of each cohort will serve as each participant's baseline QTc value.

When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection, blood pressure and pulse rate.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTc interval for single ECG collections is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator); or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

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

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

8.2.3.1. Continuous Cardiac Monitoring by Telemetry

Telemetry will be collected in Part 1 SAD Cohorts (Cohorts 1-8). All abnormal rhythms will be recorded and reviewed by the study physician for the presence of rhythms of potential clinical concern. The time, duration, and description of the clinically significant event will be recorded in the CRF/DCT. In addition, a printed record of the tracing(s) of the clinically significant rhythm(s) will be made and retained with other source documents.

Telemetry should be collected using a centralized system that also allows for the storage and advanced analysis of all recorded data in order to preserve important events for future evaluations. Holter monitoring should not be used in parallel with continuous telemetry, unless it is the only means of data storage available at the investigator site, or verifiable arrhythmia quantification is required.

To establish a baseline, telemetry should be recorded for at least 2 hours prior to dosing. This may be done immediately prior to dosing or at some 2-hour continuous interval in the 24 hours prior to dosing, as long as the recording is performed when the participant is awake. Telemetry may be stopped within a reasonably short period of time prior to dosing, in order to avoid interference with study operations conducted immediately before dosing. However, it is expected that the telemetry leads will be in place and the system connected prior to dosing. Post-dose telemetry will continue for 8 hours after dosing.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol required- laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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

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

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

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL and the results be available prior to the administration of investigational treatment. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant’s receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

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

8.2.6. Infusion and Injection Site Reaction Assessment

Participants will be monitored for signs of any infusion or injections site reactions, including but not limited to erythema, swelling, bruising, pain or pruritus at times specified in the SoA.

Any signs or symptoms related to either an infusion or injection site reaction should be treated according to the Investigator's standard of care and reported as adverse events. All anaphylactic reactions will be assessed according to Sampson's criteria.

8.3. Adverse Events and Serious Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

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 the final scheduled visit (or at least 4 half-lives of PF-07242813, whichever is longer), after the last administration of the study intervention.

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

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

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness 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.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the 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

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy.
- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant, 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. Details of the pregnancy will be collected after the start of study intervention and until 28 days after last dose, or 5 terminal half-lives after the last dose, whichever is longer.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the 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.

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

Abnormal pregnancy outcomes are considered SAEs. 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, 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 including 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.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so 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.

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, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. 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. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Not applicable in Part 1. For Part 2 participants that do not gain clinical benefit following study intervention administration, lack efficacy should be captured as an AE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. 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 study participant.

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

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the 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 PF-07242813 greater than 1000 mg within a 24-hour time period will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07242813 (whichever is longer). Closely monitor the participant for any AEs/SAEs.

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

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

5. Obtain a blood sample for PK analysis within 28 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

8.5. Pharmacokinetics

Blood samples of approximately 4 mL will be collected for measurement of serum concentrations of PF-07242813 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times for PK assessment may change, and if needed, additional PK samples may be taken at times specified by Pfizer, provided the total serum volume taken during the study does not exceed 550 mL during any period of 60 consecutive days. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

CCI [redacted]

Genetic analyses will not be performed on these blood samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of serum concentrations of PF-07242813 will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

8.6. Pharmacodynamics

CCI [redacted]

8.6.1. Skin Biopsies

CCI [redacted] Briefly, index lesion sites may be located on the torso (upper and mid back, chest), abdomen, buttocks, upper arms, and upper legs. Index lesions may not be located on the scalp, face, elbows, knees, lower legs, genital area and inguinal area, intertriginous areas and lower back. Punch biopsies of the lesional and nonlesional- skin will be obtained at the time points specified in the Schedule of Activities, processed, and shipped according to the instructions to be provided in a separate study manual. Skin biopsies will be sent to designated laboratories for analysis following a schedule to be determined. The shipment address and laboratory contact information will be provided to the investigator.
CCI [redacted]

As skin biopsies may be associated with risk of bleeding or infection, participants will be instructed to contact the investigator or other designated site staff if they experience bleeding, warmth, swelling, tenderness, or erythema at the biopsy site; an unscheduled visit may be required for clinical assessment.

8.7. Genetics

8.7.1. Specified Genetics

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

8.7.2. Banked Biospecimens for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and atopic dermatitis or other inflammatory skin condition. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5: Genetics for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.8. Biomarkers

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Serum to monitor select anterior pituitary hormones and hormones under anterior pituitary regulatory control (Parts 1 & 2);
- Plasma to monitor for potential cytokine release (Parts 1 & 2);
- Serum or plasma for total IgE, TARC/CCL17, IL-31, IL-17A (Part 2 only);
- Whole blood for potential assessment of lymphocyte subsets (Part 2 only);
- Non-lesional and lesional skin biopsies for histology and RNA (Part 2 only).

8.8.1. Specified Gene Expression (RNA) Research

8.8.1.1. Skin Biopsies for RNA Analysis

Four (4) mm punch biopsies will be collected from non-lesional and lesional skin according to the times outlined in the Schedule of Activities. The samples will be processed and preserved in buffers appropriate for bulk and single cell RNA Sequencing. CCI [redacted]

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

Samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study.

8.8.2. Specified Cellular Research

8.8.2.1. Skin Biopsies for Histopathology and Immuno-histopathology

Four (4) mm punch biopsies will be collected from non-lesional and lesional skin according to the times outlined in the Schedule of Activities. The samples will be preserved in formalin and embedded in paraffin. Tissue sections will be stained and CCI research into changes in tissue pathology and infiltrating cell types.

Samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study.

8.8.2.2. Lymphocyte Subsets

A 10-mL blood sample for measurement of lymphocyte subsets by flow cytometry will be collected according to the times outlined in the Schedule of Activities. CCI Lymphocyte subsets may include T cells, B cells, NK cells, T cell subsets (Th1, Th2, Th17) and CD1a-restricted T cells.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

Samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study.

8.8.3. Specified Protein Research

CCI

[redacted]

8.8.3.5. Anterior Pituitary Hormones and Hormones under Anterior Pituitary Regulatory Control

CCI

[redacted]

Banked Biospecimens will be collected as local regulations and IRB/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and atopic dermatitis or other inflammatory skin conditions. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5: Genetics for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the lab manual.

CCI

[redacted]

8.10. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Estimands and Statistical Hypotheses

The primary estimand (for secondary endpoint EASI) will be the population average treatment effect on percent change from baseline in EASI score relative to placebo at Week 6 in the absence of prohibited medication. All observations after the initiation of prohibited medication will be set to missing. Missing data from all causes, including post-prohibited

medication use will be imputed in the PF-07242813 dose arms using a jump to control method using the distribution of the placebo group. Participants with inadequate compliance will have their recorded EASI scores used as-is in the analysis. The population based treatment effect will be the differences in the percent change from baseline in each treatment arm compared to the corresponding vehicle.

The secondary estimand CCI will be the estimated population average treatment effect on the rates of IGA response (participants with a score of 0 or 1 and a 2 point or greater decrease from baseline) at time points specified in Schedule of Activities. This is a composite estimand where success is defined as achievement of an IGA response as defined above while remaining on study, providing data and not taking prohibited medication; lack of compliance or adverse events will not be counted as a failure. The population based treatment effect will be the differences in the proportions of success in each treatment arm compared to the placebo. EASI-50, EASI-75, EASI-90 and other EASI scores will be treated in a similar manner.

CCI

9.2. Sample Size Determination

9.2.1. Healthy Participant Single Ascending and Multiple Dose (Part 1)

A sample size of approximately 52 healthy participants in 8 SAD cohorts (36 randomized to single PF-07242813 dose and 16 randomized to placebo) and up to 40 healthy participants in 5 MAD cohorts (30 randomized to multiple doses of PF-07242813 and 10 randomized to placebo) is not based on statistical considerations. The sample size was based on the clinical consideration to provide safety and tolerability information and on the need to minimize exposure to healthy participants at each dose level. In addition, 1 cohort of approximately 5 healthy Japanese participants (4 PF-07242813: 1 placebo) will be included and this sample size has been judged sufficient to obtain preliminary evaluation of safety, tolerability and PK data in this population. No formal inferential statistics will be applied to the safety, pharmacodynamic or pharmacokinetic data.

Participants who discontinue prior to completion of the study for other than safety reasons may be replaced, at the discretion of the investigator and sponsor.

9.2.2. Atopic Dermatitis Cohorts (Part 2)

The sample size calculation is based on the secondary endpoint (percent change from baseline in EASI score at Week 6). A total of 24 randomized participants with a randomization ratio of 2:1 into the treatment and placebo group will provide approximately 80% power to detect a difference of 50 in percent change from baseline with a common standard deviation 46% between PF-07242813 and the placebo arm with 1-sided alpha=0.05.

Cohort 9 will enroll 24 adult participants with moderate to severe AD.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

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

Defined Population for Analysis	Description
Modified Intention to Treat (mITT)	All participants randomly assigned to study intervention and who apply at least 1 dose of study intervention.
PK concentration set	All enrolled participants who applied at least one dose of PF-07242813 and in whom at least once concentration value is reported.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses (Part 2 Only)

Endpoint	Statistical Analysis Methods
Secondary (percent change from baseline)	A landmark analysis using analysis of covariance of percent change from baseline in EASI, adjusting for the baseline EASI score, to estimate the effect of the initially randomized treatment in the absence of prohibited medication. The analysis will use the mITT analysis set. Missing data due to any cause including censoring due to initiation of prohibited medication will be imputed using the corresponding vehicle arm, missing data in a vehicle arm will be imputed using data from the vehicle arm assuming data are missing at random (MAR). The analysis will combine the results from the multiple imputations using Rubin's rule's as implemented in SAS PROC MIANALYZE.
CCI	[redacted]
[redacted]	[redacted]

[redacted]

9.4.2. Safety Analyses

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

[redacted]

9.4.2.1. Electrocardiogram Analyses

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

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

Safety QTc Assessment

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

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

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTc value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTc value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.

CCI [redacted]

9.4.3. Pharmacokinetics Analyses

9.4.3.1. Analysis Population

The PK concentration population is defined as all randomized participants who received a dose of PF-07242813 and in whom at least 1 serum concentration value is reported. The PK parameter analysis population is defined as all randomized participants who received a dose of PF-07242813 and who have at least 1 of the PK parameters of interest calculated.

9.4.3.2. Derivation of Pharmacokinetic Parameters

9.4.3.2.1. Pharmacokinetic Parameters for Part 1

The PK parameters to be assessed, their definition, and method of determination are listed in Table 6**.** Actual PK sampling times will be used in the derivation of PK parameters.

Table 6. Serum PK Parameters for Part 1

Parameter	Definition	Method of Determination
Single Dose		
AUC_{last}	Concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last}/Dose
AUC_{inf}[a]	Area under the serum concentration time- profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted serum concentration at the last quantifiable time point estimated from the log-linear regression analysis
CCI [redacted]	[redacted]	[redacted]
C_{max}	Maximum serum concentration	Observed directly from data
C_{max}(dn)	Dose normalized C_{max}	C_{max}/Dose
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{1/2}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where kel is the terminal phase rate constant calculated by a linear regression of the loglinear -concentration time- curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
CCI [redacted]	[redacted]	[redacted]
Multiple Doses		
AUC_{τ}	Area under the serum concentration time- profile over the dosing interval τ where τ=2 weeks/336 hours	Linear/Log trapezoidal method
CCI [redacted]	[redacted]	[redacted]
C_{max}	Maximum serum concentration	Observed directly from data
CCI [redacted]	[redacted]	[redacted]

Parameter	Definition	Method of Determination
$t_{1/2}a$	Terminal elimination half-life	$Log_e(2)/k_{el}$, where kel is the terminal phase rate constant calculated by a linear regression of the loglinear -concentration time- curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression
CL/F and CL[a]	Apparent clearance for SC dosing (CL/F) and Systemic clearance (CL) for IV dosing	$Dose/AUC_t$, if steady state is achieved
Vz/Fa	Apparent volume of distribution following SC dosing	$Dose/AUC_{inf}*k_{el}$
F	Apparent bioavailability of SC injection	AUCt (SC, sd)/$AUC_{14\ days}$ (IV, sd)

[a] If data permit.

9.4.3.3. Statistical Methods for PK Data

No formal inferential statistics will be applied to the pharmacokinetic data.

9.4.3.3.1. PK Data in Part 1

The serum concentration of PF-07242813 will be listed and descriptively summarized by nominal PK sampling time and treatment group. Individual subject and median profiles of the serum concentration-time data will be plotted by treatment group using actual (for individual) and nominal (for median) times respectively. Median profiles will be presented on both linear and log scales.

The PK parameters in Table 6 will be summarized descriptively by treatment group in healthy and AD participants in accordance with Pfizer data standards. Summary statistics will also include the geometric mean and coefficient of variation for all parameters except T_{max}.

Where data permit, dose normalized (to a 1 mg dose) C_{max}, AUC_{inf}, AUC_{last} and/or AUC_{τ}, will be plotted against dose and administration route, as appropriate for single dose and multiple doses (using a logarithmic scale). The plot will include individual subject values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose and/or administration route.

The PK data from Japanese participants will be summarized separately.

9.4.3.3.2. PK data in Part 2

The serum concentration of PF-07242813 for Part 2 will be listed and summarized with descriptive statistics by nominal time and visit for each cohort.

A population PK modeling may be performed by combining Part 1 and Part 2 PK data to estimate specific PK parameters and/or exposures in individual participants in Part 2. In addition, a relationship between exposures and clinical efficacy/safety endpoints may be evaluated using population PK/PD approach. Any population analyses conducted will not be part of the CSR and may be reported separately.

CCI [redacted]

9.4.5. Other Analyses

CCI [redacted]

Patient recorded outcomes (PROs) will be listed and reported in tabular and graphical displays as required. The handling of item non-response and other missing data issues will be handled on a case by case basis as specified by the authors of the instruments in order to preserve the validity of the instruments.

CCI [redacted]

9.5. Interim Analysis

No formal interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessments, facilitating dose-escalation decisions, PK/PD modeling, and/or supporting clinical development.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a Data Monitoring Committee (DMC).

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 CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

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

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

The investigator will be responsible for the following:

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the 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 subinvestigators 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 and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

A copy of the ICD(s) must be provided to the participant.

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

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff 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 will 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 participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the 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 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 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. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are 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 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 contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.6. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.7. Source Documents

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

Data reported on the CRF or entered in the eCRF that are 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.

Description of the use of computerized system is documented in eCRF Completion Guidelines.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant’s first visit and will be the study start date.

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;

- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

10.1.9. Publication Policy

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

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

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

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

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

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

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Study Binder.

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

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 7. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	At screening only: • FSH[b] • Hepatitis B surface antigen[d] • Hepatitis C antibody[e] Screening and as indicated • Pregnancy test (β-hCG)[c] • Urine drug screening[f]

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. Serum; For confirmation of postmenopausal status only.
c. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential provided results are available prior to dosing at the randomization and each study visit thereafter.
d. HBsAb test if screening results for HBsAg are negative and HBcAb are positive.
e. HCV RNA test will be done as a reflex for positive HCVAb test.
f. Urine drug testing requirements: amphetamines, benzodiazepines, cocaine, methadone, opiates, propoxyphene, THC.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

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

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  • Is associated with accompanying symptoms.
  • Requires additional diagnostic testing or medical/surgical intervention.
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
• Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
• New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of SAE

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

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

baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the 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
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.	All AEs/SAEs associated with exposure during pregnancy or breastfeeding. Occupational exposure is not recorded.	All (and EDP supplemental form for EDP). Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

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

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

AEs in the cardiac and blood/bone categories will be evaluated applying Common Terminology Criteria for Adverse Events (CTCAE) Version 5. For reporting purposes, CTCAE severity grades are to be interpreted as follows:

- Grade 1 events correlate to Mild.
- Grade 2 events correlate to Moderate.
- Grade 3 and higher events correlate to 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 IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form

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

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

10.4.2. Female Participant Reproductive Inclusion Criteria

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

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

  OR

- For Part 1: Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency and not hormonally based, as described below during the intervention period and for at least 60 days (7 x terminal half-life) after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- For Part 2: Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency (including hormonally based methods), or, is using contraceptive method that is highly effective (with a failure rate of <1% per year) that is not of low user dependency (including hormonally based methods) together with a barrier method as described below during the intervention period and for at least 60 days (7 x terminal half-life) after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen containing hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation. (*Prohibited for Part 1 healthy participants. Permitted only for Part 2 AD participants.)*
2. Intrauterine device.

3. Intrauterine hormone-releasing system. (*Prohibited for Part 1 healthy participants. Permitted only for Part 2 AD participants.)*

4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

Highly Effective Methods That Are User Dependent

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

    - Oral;

    - Intravaginal;

    - Transdermal.

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

    - Oral;

    - Injectable.

8. Sexual abstinence:

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to PF-07242813 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for banking will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

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

Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/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/paracetamol (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol 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: ECG Findings of Potential Clinical Concern

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

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

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Fitzpatrick Skin Type

Phototype	Sunburn and tanning history (defines the phototype)
I	Burns easily, never tans
II	Burns easily, tans minimally with difficulty
III	Burns moderately, tans moderately and uniformly
IV	Burns minimally, tans moderately and easily
V	Rarely burns, tans profusely
VI	Never burns, tans profusely

10.9. Appendix 9: EASI

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

Lesion Severity by Clinical Signs: The basic characteristics of atopic dermatitis lesions erythema, induration/papulation, excoriation, and lichenification- provide a means for assessing the severity of lesions. Assessment of these four main clinical signs is performed separately for four body regions: head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks). Average erythema, induration/papulation, excoriation, and lichenification- are scored for each body region according to a 4 point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Morphologic descriptors for each clinical sign severity score are shown in Table 8.

Table 8. Clinical Sign Severity Scoring Criteria for the Eczema Area and Severity Index (EASI)

Score		Description*
Erythema (E)		
0	Absent	None; may have residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation)
1	Mild	Light pink to light red
2	Moderate	Red
3	Severe	Deep, dark red
Induration/Papulation (I)		
0	Absent	None
1	Mild	Barely palpable to slight, but definite hard thickened skin and/or papules
2	Moderate	Easily palpable moderate hard thickened skin and/or papules
3	Severe	Severe hard thickened skin and/or papules
Excoriation (Ex)		
0	Absent	None
1	Mild	Slight, but definite linear or picked scratch marks or penetrating surface injury
2	Moderate	Moderate linear or picked scratch marks or penetrating surface injury
3	Severe	Severe linear or picked scratch marks or penetrating surface injury

Lichenification (L)		
0	Absent	None
1	Mild	Barely perceptible to slight, but definite thickened skin, fine skin markings, and lichenoid scale
2	Moderate	Moderate thickened skin, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale

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

Percent BSA with Atopic Dermatitis: The number of handprints of skin afflicted with atopic dermatitis in a body region can be used to determine the extent (%) to which a body region is involved with atopic dermatitis (Table 9). When measuring, the handprint unit refers to the size of each individual participant's hand with fingers in a closed position.

Table 9. Handprint Determination of Body Region Surface Area (BSA)

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

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

The extent (%) to which each of the four body regions is involved with atopic dermatitis is categorized to a numerical Area Score using a non-linear scaling method according to the following BSA scoring criteria (Table 10).

Table 10. 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 11 Table 9).

Table 11. Eczema Area and Severity Index (EASI) Body Region Weighting

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

* No adjustment for body regions excluded for assessment

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

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

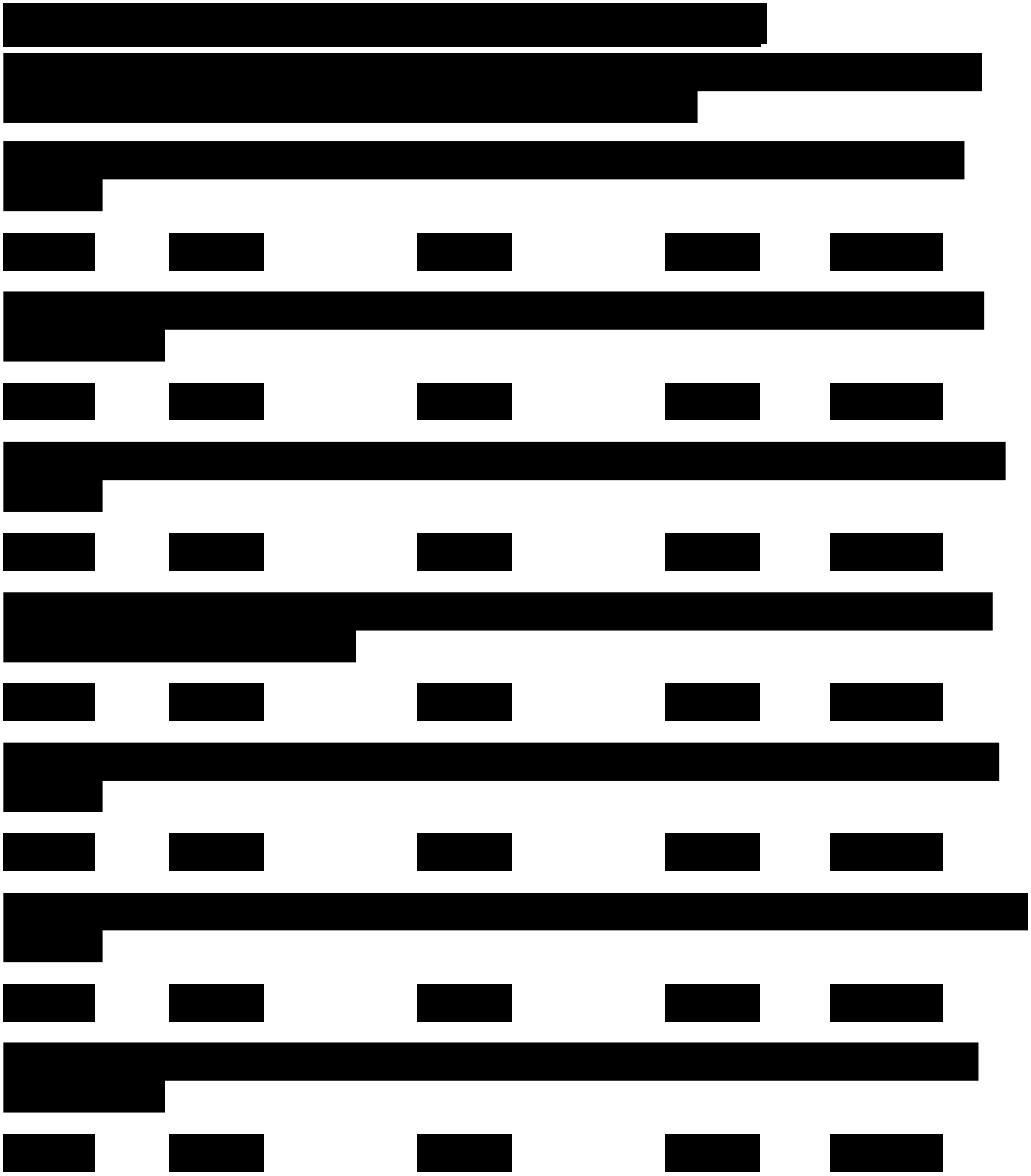
A = Area Score; E = erythema; I = induration/papulation; Ex = excoriation;
L = lichenification; h = head and neck; u = upper limbs; t = trunk; l = lower limbs

The EASI score can vary in increments of 0.1 and range from 0.0 to 72.0, with higher scores representing greater severity of atopic dermatitis. The EASI should be completed per the Schedule of Activities.

CCI [redacted]

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

[redacted]



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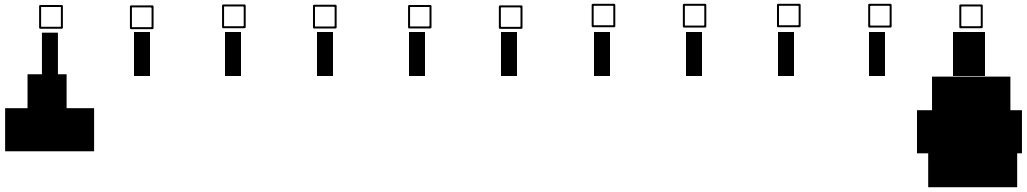
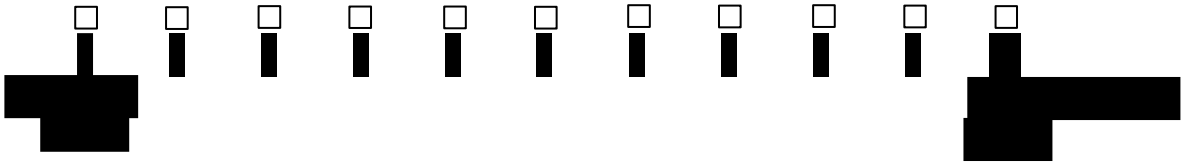


[redacted]



CCI [redacted]

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

Choose only ONE response.

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

[redacted]

CCI [redacted]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CCI [redacted]

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

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

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

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

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

CCI [redacted]

Major Criteria (must have at least three)

Pruritus

Typical morphology and distribution:

Adults: flexural lichenification or linearity

Children and infants: involvement of facial and extensor surfaces

Chronic or relapsing dermatitis

Personal or family history of atopy

Minor Criteria (must have at least three)

Xerosis

Icthyosis/keratosis pilaris/palmer hyperlinearity

Immediate (type 1) skin test reactivity

Elevated serum IgE

Early age at onset

Tendency to skin infections (Staphylococcus aureus, herpes simplex)/impaired cellular immunity

Hand/foot dermatitis

Nipple eczema

Cheilitis

Conjunctivitis

Dennie-Morgan fold

Keratoconus

Anterior subcapsular cataracts

Orbital darkening

Facial pallor/erythema

Pityriasis alba

Anterior neck folds

Itch when sweating

Intolerance to wool and lipid solvents

Perifollicular accentuation

Food intolerance

Course influenced by environmental/emotional factors

White dermographism/delayed blanch

CCI [redacted]

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

[redacted]

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula):

   AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure *to a <u>likely</u> allergen for that patient* (minutes to several hours):

   c. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).

   d. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

   e. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).

   f. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3. Reduced BP after exposure to *<u>known</u> allergen for that patient* (minutes to several hours):

   g. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*.

   h. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 X age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

CCI [redacted]

Please answer Questions 1-5

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

1. On average, during the past week, how often were you woken by your asthma during the night?

   0 Never

   1 Hardly ever

   2 A few times

   3 Several times

   4 Many times

   5 A great many times

   6 Unable to sleep because of asthma

2. On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?

   0 No symptoms

   1 Very mild symptoms

   2 Mild symptoms

   3 Moderate symptoms

   4 Quite severe symptoms

   5 Severe symptoms

   6 Very severe symptoms

3. In general, during the past week, how limited were you in your activities because of your asthma?

   0 Not limited at all

   1 Very slightly limited

2 Slightly limited

3 Moderately limited

4 Very limited

5 Extremely limited

6 Totally limited

4. In general, during the past week, how much shortness of breath did you experience because of your asthma?

0 None

1 A very little

2 A little

3 A moderate amount

4 Quite a lot

5 A great deal

6 A very great deal

5. In general, during the past week, how much of the time did you wheeze?

0 Not at all

1 Hardly any of the time

2 A little of the time

3 A moderate amount of the time

4 A lot of the time

5 Most of the time

6 All the time

10.20. Appendix 20: Abbreviations

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

Abbreviation	Term
β-HCG	Beta-human chorionic gonadotropin
Abs	absolute
ACQ-5	5-item version of the asthma control questionnaire
AD	atopic dermatitis
CCI [redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	area under the curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{504}	area under the concentration-time curve from time 0 to 504 hours
AUC_{inf}	area under the concentration-time profile from time zero to infinity
AUC_{last}	area under the concentration-time profile from time zero to the time of the last quantifiable concentration
AUC_{tau}	area under the concentration–time curve within dosing interval
AV	atrioventricular
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BSA	body region surface area
BUN	blood urea nitrogen
CaPS	Clinical analysis of Pfizer Standards
C_{av}	average concentration over dosing interval
CCL17	chemokine (C-C motif) ligand 17
CDISC	Clinical data interchange standards consortium
CDRs	complementarity-determining regions
CHO	Chinese hamster ovary
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CCI [redacted]	[redacted]
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID	coronavirus
CPT	current procedural terminology
CRA	Clinical Research Associate

Abbreviation	Term
CRF	case report form
CRO	clinical research organization
CRS	chronic rhinosinusitis
CRSwNP	chronic rhinosinusitis with nasal polyps
CRU	clinical research unit
CsA	cyclosporine A
CSR	clinical study report
[redacted]	[redacted]
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DCT	data collection tool
DILI	drug induced liver injury
CCI	[redacted]
dn	dose normalized
DNA	deoxyribonucleic acid
EASI	eczema area and severity index
EBV	Epstein-Barr virus
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EMA	European Medicines Agency
EOS	end of study
EU	European Union
EudraCT	European Clinical Trials Database
[redacted]	[redacted]
FCV	forced vital capacity
FDA	Food and Drug Administration (United States)
FEV1	forced expiratory volume in one second
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transpeptidase
GLP	good laboratory practice
HADS	Hospital and Anxiety Depression Scale
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C antibody
HDM	house dust mite
HED	Human equivalent dose

Abbreviation	Term
CCI	[redacted]
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HV	healthy volunteer
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
CCI	[redacted]
CCI	[redacted]
IgE	immunoglobulin E
CCI	[redacted]
IgG1	Immunoglobulin Gamma 1
CCI	[redacted]
IL1RL1	Interleukin 1 Receptor-Like 1
ILCs	innate lymphoid cells
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ISR	injection site-reactions
IUD	intrauterine device
IV	intravenous
JAK	Janus Kinase
K_2EDTA	Potassium salt ethylenediaminetetraacetic acid
LBBB	left bundle branch block
LFT	liver function test
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MAD	multiple ascending dose
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple dose
MedDRA	medical dictionary for regulatory activities
MHC	major histocompatibility process
mm2	IL-33 amino acids 112-270 with 4 cysteines changed to serine
mRNA	messenger ribonucleic acid
MRT	mean residence time

Abbreviation	Term
CCI	[redacted]
MTX	methotrexate
n *or* N	number
N/A	not applicable
NAb	neutralizing antibody
NB-UVB	Narrow Band Ultraviolet B
ND	not determined
NHANES III	Third National Health and Nutrition Examination Survey
NK	natural killer cells
NKT	natural killer T-lymphocytes
NOAEL	no observed adverse effect level
NPS	Nasal polyp score
NRS	numerical rating scale
NSAIDs	nonsteroidal anti-inflammatory drugs
PACL	Protocol Administrative Change Letter
PBMC	peripheral blood mononuclear cell
Pbo	placebo
PD	pharmacodynamics
PDE	phosphodiesterase
PE	physical examination
PF	PF-06817024
PI	principal investigator
PK	pharmacokinetics
pM	Picomolar
CCI	[redacted]
PR	pulse rate
CCI	[redacted]
CCI	[redacted]
PT	prothrombin time
CCI	[redacted]
CCI	[redacted]
Q2W	every 2 weeks
Q4W	every 4 weeks
QTc	corrected QT
QTcF	Federicia's corrected QT
Rac	accumulation ratio
RBC	red blood cell
RNA	ribonucleic acid
RR	respiratory rate
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SCORAD	scoring atopic dermatitis
SCr	serum creatinine
SD	single dose
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
CCI [redacted]	[redacted]
SoA	Schedule of Activities
SOC	System Organ Classes
SOP	Standard Operating Procedure
SPR	Surface plasmon resonance
SRSD	Single reference safety document
$t_{½}$	terminal half-life
T4	thyroxine test
TARC	thymus and activation regulated chemokine
TB	tuberculosis
Tbili	total bilirubin
TCR	T-cell receptor
TEAEs	treatment emergent adverse events
Th2	T lymphocytes
THC	tetrahydrocannabinol
TK	toxicokinetics
T_{max}	time to reach maximum concentration
TMDD	Target-mediated drug disposition
CCI [redacted]	[redacted]
ULN	upper limit of normal
UPSIT	University of Pennsylvania smell identification test
US	United States
UVA	Ultraviolet A
UVB	Ultraviolet B
CCI [redacted]	[redacted]
WBC	white blood cell
WOCBP	women of child-bearing potential
WONCBP	women of non-childbearing potential
Wt	wild-type

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Document Approval Record

Document Name:	C4461001 Protocol Amendment 2 Clean 10 July 2021
Document Title:	C4461001 Protocol Amendment 2 Clean 10 July 2021

Signed By:	Date(GMT)	Signing Capacity
PPD		
PPD		