CLINICAL PHARMACOLOGY PROTOCOL

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, THIRD-PARTY OPEN, PLACEBO-CONTROLLED, DOSE ESCALATING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF SINGLE AND/OR MULTIPLE INTRAVENOUS AND/OR SUBCUTANEOUS DOSES OF PF-06817024 IN HEALTHY SUBJECTS WHO MAY BE MILDLY ATOPIC, SUBJECTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS, AND SUBJECTS WITH MODERATE-SEVERE ATOPIC DERMATITIS

Compound:	PF-06817024
Compound Name:	Not Applicable
United States (US) Investigational New Drug (IND) Number:	CCI (Atopic Dermatitis IND): CCI
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number:	C0341001
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 5	22 May 2018	[redacted] • SOA Tables B, C and D: Added footnote for safety labs at extended follow-up visits for Parts 1 and 2 (cohorts currently in the study) to be done at the discretion of the PI. Rationale: to allow for follow-up of safety labs if needed. [redacted] • SoA Table E (Part 3): 4 hr post-dose PK sample collection has been eliminated. Blood volume table (Table 8) in Section 7.2.5 has been updated to reflect this change. Rationale: revision made to reduce the length of the visit. • Section 1.2.3: Nonclinical pharmacokinetics section has been updated. Rationale: revision made to align with updated IB.

Document	Version Date	Summary of Changes and Rationale
		• Section 1.2.4: Nonclinical safety section has been updated. Rationale: revision made to align with updated IB. • Section 1.2.5.1: Clinical safety section has been updated. Rationale: revision made to align with updated IB. • Section 1.2.5.2: Clinical PK section has been updated. Rationale: revision made to align with updated IB. • Sections 1.3.1.2 and 3.1.3 (Part 3)– Randomization ratio has been changed from 2:1 to 3:1 (PF-06817024: placebo). Total number of subjects in the study will be adjusted based on the emerging data from the Atopic Dermatitis cohort. Rationale: revision made to optimize the study design and minimize the number of subjects receiving placebo. • Section 1.3.1.3 (Parts 1, 2 and 3)– Language added around current guidance on discharge of subjects from the study. Rationale: to inform the sites of the current guidance for discharge of subjects from the study. • Section 1.3.2 (Parts 1, 2 and 3)–safety margins are updated based on emerging data. Rationale: to align with IB. • Figure 2 in Section 3.1 updated for Part 3.

Document	Version Date	Summary of Changes and Rationale
		Rationale: to reflect the randomization ratio of 3:1 and possible adjustment of total number of subjects. • Section 4.1.1.1 (Part 3)–Revised Inclusion criterion #2 to allow subjects between the ages of 18 and 75 years, inclusive, with Sponsor discussion for ages greater than 70. Rationale: to facilitate recruitment. • Section 4.1.1 (Part 3)–Revised Inclusion criterion #6 to allow subjects with BMI 17.5 to 40 kg/m^2. Rationale: to facilitate recruitment. • Section 4.1.1 (Part 3)– Inclusion criterion #7c has been revised to correct IGA and EASI criteria to be consistent with moderate-severe AD (defined as having an affected BSA (captured as part of EASI) ≥10%, IGA ≥3, and EASI ≥12 at the screening and baseline visits). Rationale: Typographical errors corrected. • Section 4.1.2.1 (Part 3)– Exclusion criterion #16 has been revised to permit subjects with sensitivity and/or anaphylaxis to a single avoidable allergen (eg, aspirin, penicillin, sulfadrugs, nonsteroidal anti inflammatory drugs (NSAIDs), peanuts) provided they carry appropriate treatment for anaphylaxis, know how to manage the anaphylactic reactions , and avoid the allergen. Rationale: revised to allow inclusion of subjects with sensitivity to a single avoidable allergen (eg, aspirin, penicillin, sulfadrugs, nonsteroidal anti inflammatory drugs (NSAIDs), peanuts) that would not impact the overall safety of subjects

Document	Version Date	Summary of Changes and Rationale
		participating in the trial in recognition of frequent comorbidity of these sensitivities with allergic disease. • Section 4.1.2.1 (Part 3)– Exclusion criterion #18 has been updated to exclude subjects with a positive urine drug screen except marijuana where use is permitted by local law and regulations. Rationale: to provide clarification to urine drug screen testing. • Section 4.1.2.1 (Part 3)– Exclusion criterion #24 has been updated to exclude subjects with prior or current use of anti-IL-33 targeted therapies. Section 5.9.2 Prohibited Medications for Part 3 has been updated to include Anti-IL-33 therapies. Rationale: to avoid selection bias and interference with interpretation of the results of the current study in recognition of other drugs targeting IL-33 in clinical development. • Section 4.1.2.1 (Part 3)– Exclusion criterion #24 has been revised to change the wash-out period for dupilumab from 6 months to 4 months of first dose of study drug. Rationale: adjustment based on reported PK of dupilumab. • Section 4.1.2.1 (Part 3)– Exclusion criterion #24 has been revised to change the wash-out period for steroids from 6 weeks to 4 weeks prior to first dose of study drug. Rationale: adjustment to wash-out period is based on half-life of steroids.

Document	Version Date	Summary of Changes and Rationale
		• Section 4.2 (Part 3)–Randomization ratio has been changed from 2:1 to 3:1 (PF-06817024: placebo). Total number of subjects in the study will be adjusted based on the emerging data from the Atopic Dermatitis cohort. Rationale: revision made to optimize the study design and minimize the number of subjects receiving placebo. • Section 4.3.2.4 is updated with language around sexual abstinence and use of selected and approved contraception method for a long enough period prior to dosing to ensure that the selected contraception method is effective at the time of the first dose of study drug. Contraception check and pregnancy results will be documented in the CRF. Rationale: Administrative clarification for language around sexual abstinence. Contraception check and pregnancy testing documentation in CRF added to enable monitoring of subjects for use of contraception per protocol. • Section 4.3.2.5 clarifies that the travel restrictions stipulated in Section 4.3.1.4 for Parts 1 and 2 are also applicable to Part 3. Rationale: Administrative clarification. • Section 4.3.2.6 is updated and requires that subjects to the extent possible, have all elective surgical procedures be performed before enrolling into the study or deferred as long as possible after the active dosing period is complete (and preferably until after 1 year). Rationale: to inform investigators and subjects of the unknown effects of the

Document	Version Date	Summary of Changes and Rationale
		study drug on wound healing in the event of a surgery. • Section 5.9.2.1 Rescue medications has been added with respect to subject access to standard of care treatment for the disease in the study. Rationale: To clarify that subjects have access to standard of care treatments for flares in their atopic dermatitis during the study with investigator judgment as to the judicious addition of such treatments. • Administrative changes and sentence revisions made through out the document. Rationale: Revisions made to remove inconsistencies, incorporate PACLs, correct grammatical, spelling or other errors, and provide more clarity.
Amendment 4	03 August 2017	• Addition of Atopic Dermatitis (AD) Cohort to explore safety, tolerability, CCI [redacted] in subjects with moderate – severe AD to provide data to support potential future development in AD. The following Sections of the protocol have therefore been updated: • Title. • SoA Table E. • Introduction (Section 1.1, Section 1.2.1.2, Section 1.3.1.2, Section 1.3.2.3). • Study Objectives and Endpoints (Section 2). • Study Design (Section 3.1.3). • Inclusion (Section 4.1.1.1) and

Document	Version Date	Summary of Changes and Rationale
		Exclusion (Section 4.1.2.1) Criteria. • Randomization Criteria (Section 4.2.1). • Lifestyle Guidelines (Section 4.3.2). • Removed overnight fasting of at least 10 hours for receiving IP for the AD cohort as it is not a requirement for IV administration [redacted]. • Permitted (Section 5.8.3), and Prohibited (Section 5.9.2) Concomitant Treatments. • Study Procedures (Section 6.2). • Assessments (Section 7.2). • Data Analysis/Statistical Methods (Section 9.0, Section 9.1, Section 9.4, Section 9.5). • Figure 2. • Tables 6, 8, 9, 10, 11. • Appendices 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 and 17). • References from 51-61. • An update to the preliminary estimated half-life to 90 days for Part 3 in Section 1.3.1.3 and 1.3.2.3, SOA Table E Footnote "a". • Added emerging PK and Safety Data as follows in support of inclusion of AD cohort in study (Section 1.2.5 and includes Table 1 on Emerging Clinical Pharmacokinetics Based on

Document	Version Date	Summary of Changes and Rationale
		Preliminary Draft Dataset). • CCI [redacted] • Section 9: Added language to allow for analysis and reporting of summarized unblinded preliminary safety, PK, CCI [redacted] data prior to LSLV as follows: In addition, summarizations of unblinded preliminary safety, PK, CCI [redacted] may be performed for each part after Week 12 safety, PK, CCI [redacted] data have been obtained from a majority of subjects in that Part, as applicable, but prior to the end of the study and full safety follow-up. Further details will be defined in the SAP. CCI [redacted] Rationale: allows for communication of safety and tolerability data to IRBs / ECs, FDA and other Regulatory Authorities in advance of LSLV which may be protracted due to the prolonged t½ suggested by emerging PK data. • C CCI [redacted]

Document	Version Date	Summary of Changes and Rationale
		CCI • Minor administrative changes : Updated section numbers referenced in Part 1 and 2 parts of the protocol. Rationale : Some section numbers changed due to the addition of Part 3 as follows. These are (i) Exclusion criteria 8 – Lifestyle Guidelines Section 4.3.1 updated to Section 4.3.1.5, (ii) Exclusion criteria 9 Section 7.1.1 updated to Section 7.1.1.1, (iii) Prohibited Concomitant Medication for Part 2 - Section 5.9 updated to Section 5.9.1.
Amendment 3	26 October 2016	• Revised "Extended Immunogenicity Follow-up" to "Extended Follow-up" (SoA Tables B, C, and D, and Section 6.3), and added language to specify additional follow-up visits to cover projected prolonged exposure due to the longer than expected $t_{½}$ (Tables B and D footnotes a, Table C footnote b, and Sections 1.3.1 and 6.3). Rationale: to address extended half-life predictions that increase the likelihood of additional subject visits to monitor safety and PK. C • Added visit window to Extended

Document	Version Date	Summary of Changes and Rationale
		Follow-Up (Tables B, C, and D). Rationale: operational feasiblity. • Removed "serum" from pregnancy test (Table D, Sections 6.1, 6.2.1, 6.2.3, 6.2.4, 6.2.5, 6.2.6, and 6.4). Rationale: alignment with Section 7.1.2 description of acceptable pregnancy tests. C CCI [redacted] • Revised language for the Day 0 visit for Part 2. This visit may be completed as an outpatient visit (Table D footnote w and Section 6.2.1). Rationale: operational feasibility. • Revised language in Part 2 clarifying spirometry screening procedure is for subjects with a history of asthma only (Table D footnote f, and Sections 6.1 and 7.6). Rationale: administrative clarification. • Revised objective, endpoints, and study design to clarify Cohort 7 may consist of one or more doses (Section 1.3.1, 2.1.1, 2.2.2, and 3.1). Rationale: administrative clarification to address that Cohort 7 may be one or more doses to be defined in light of emerging data. • Revised Part 2 study design by removing sequential dosing and administration of higher dose prior to lower dose (Section 3.1). Rationale: to provide flexibility for Part 2 dosing due to extended half-life predictions.

Document	Version Date	Summary of Changes and Rationale
		• Revised Part 2 study design removing strata of asthmatics and non-asthmatics and adding flexibility of randomizing Cohorts 8 and 9 at either 1:1 or 2:1 ratio (Sections 1.3.1, 3.1, 4.2, and 9.1 and Figure 1). Rationale: randomization ratio modified to enable option to conduct only 1 cohort of patients with CRSwNP while ensuring an adequate number of placebo subjects. Stratification of CRSwNP patients based on asthma comorbidity eliminated as the number of subjects recruited would be too limited to make a covariate analysis based on asthma status meaningful. • Revised Phadiatop and IgE inclusion criteria noting Cohort 1 through 4 replacement subjects were exempt (Section 4.1.1). Rationale: administrative clarification. • Revised exclusion criteria for Part 2 permitting subjects with known sensitivity and/or anaphylaxis to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) if the subject is aware of the hypersensitivity and avoids aspirin/NSAIDs (Section 4.1.2). Rationale: modification for patients with CRSwNP to remove exclusions for certain frequent comorbid conditions (eg, aspirin hypersensitivity) that do not impact overall safety of subjects participating in the trial to assist with logistical feasibility. • Revised exclusion criteria for Part 2 permitting subjects with sinus infections that have not required antibiotic treatment within 28 days prior to screening (Section 4.1.2). Rationale: modification for patients with CRSwNP to remove ambiguities (eg, with respect to nasal surgery and sinus infections) that do not

Document	Version Date	Summary of Changes and Rationale
		impact overall safety of subjects participating in the trial to assist with logistical feasiblity. • Revised exclusion criteria for Part 2 providing additional clarification for parenteral corticosteroids and limiting systemic corticosteroid steroids to 6 weeks before screening (Section 4.1.2). Rationale: administrative clarification to assist with logisticial feasibility. • Revised exclusion criteria for Part 2 regarding nasal surgeries (Section 4.1.2). Rationale:modification for patients with CRSwNP to remove ambiguities (eg, with respect to nasal surgery and sinus infections) that do not impact overall safety of subjects participating in the trial to assist with logistical feasiblity. • Revised exclusion criteria for Part 2 specifing subjects with a history of asthma, and clarifying systemic steroid treatment within 2 months prior to screening and dose of inhaled corticosteroids per day (Section 4.1.2). Rationale: administrative clarification and modification to assist with logistical feasibility. • Revised limited physical examination to include skin and gastrointestinal system (Section 7.1.3). Rationale: administrative clarification. • Revised immunogenicity language (Section 7.2.2). Rationale: company-wide updates to immunogenicity language. • Revised computerized axial tomography (CT) scan language to clarify potential to perform repeat CT scans if initial scans are unreadable (Section 7.10). Rationale:

Document	Version Date	Summary of Changes and Rationale
		to ensure collection of usable CT data while providing administrative clarification that subjects remain within the FDA limits for annual radiation exposure. • Minor administrative corrections.
Amendment 2	09 August 2016	• Revised protocol title; SoA Table A, B, and C titles; Section 1.3.1, 2.1.1, 2.1.2, and 3.1; and Figure 1 to healthy subjects may be mildly atopic (but are not required to be mildly atopic). Rationale: administrative change in alignment with alterations to inclusion criteria for Part 1 Cohorts 5 and later. • Added ECG and vital sign collection time may occur up to 10 minutes prior to investigational product infusion completion (SoA Table A footnote a, Table C footnote c, Table D footnote b, Section 6.2.2 and 6.2.8). Rationale: operational feasibility. • Revised Phadiatop collection to prior to dosing for Part 1 only (Cohorts 5 and later) (SoA Table A footnote k, Section 6.1, and Tables 3 and 5). Rationale: administrative change in alignment with alterations to inclusion criteria for Part 1 Cohorts 5 and later. • Revised IgE collections to at least two (2) pre-dose collections for Part 1 only (Cohorts 5 and later) (SoA Table A footnote o, Section 6.1, and Table 5). Rationale: administrative change in alignment with alterations to inclusion criteria for Part 1 Cohorts 5 and later. • Added post-dose time point guidance if intravenous infusion time exceeds 100 minutes (SoA Table A footnote q,

Document	Version Date	Summary of Changes and Rationale
		Table C footnote l, Table D footnote s, Section 6.2.2 and 6.2.8). Rationale: administrative change for clarification. • Revised Hepatitis B exclusion criteria starting with Cohorts 5 and later (Section SoA Table A footnote r, Table D footnote t, 4.1.2 and Table 3). Rationale: clarification for subjects testing HBsAg- and HBcAb+. • Revised Day 46 and Day 61 visit windows to ±5 days (SoA Table B, Table C, Table D (Day 61 only)). Rationale: operational feasibility. • Added guidance surrounding follow-up visits based upon second dose (Table B footnote d, Table C footnote a, and Section 6.2.7). Rationale: administrative change for clarification. • Revised second dose window to a maximum of 12 weeks (SoA Table C footnote a, Section 1.3.1, 1.3.2, and 3.1). Rationale: operational feasibility. • Altered Phadiatop inclusion criteria to include Part 1 only Cohorts 1-4 (SoA Table D, and Section 4.1.1). Rationale: operational feasibility. • Altered IgE inclusion criteria to include Part 1 only Cohorts 1-4 (SoA Table D, and Section 4.1.1). Rationale: operational feasibility. • CCI [redacted]

Document	Version Date	Summary of Changes and Rationale
		• Added number of subjects whose safety results are required as part of the second dose prerequisite (Table 2). Rationale: administrative change for clarification. • Revised times surrounding meals (Section 4.3.1). Rationale: operational feasibility. • Revised study drug administration time (Section 5.4.3). Rationale: operational feasibility. • Added language surrounding Part 2 randomized subjects receiving prohibited treatments and medications (Section 5.9). Rationale: additional information requested by regulatory agency. • Added Clinical Criteria for Diagnosing Anaphylaxis Guidance (Appendix 6, SoA Table A footnote s, Table C footnote m, and Table D footnote v). Rationale: additional information requested by regulatory agency. • Minor administrative corrections.
Amendment 1	06 May 2016	• Altered window surrounding dosing time point (section 5.4.3). Rationale: operational feasibility. • Included drug stability information (section 5.6). Rationale: additional information requested by regulatory agency. • Revised screening details to add clarity around Day 0 procedures and assessments (section 6.1). Rationale: administrative change for clarification. • Minor administrative corrections.

Document	Version Date	Summary of Changes and Rationale
Original protocol	14 March 2016	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

[redacted]

[redacted]

SCHEDULE OF ACTIVITIES

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

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

Table A: Part 1, Healthy Subjects Who May be Mildly Atopic Screening through Day 15

Protocol Activity	**Screen**	**Clinical Confinement**												**Follow-up Visit**	
Study Day	**-27 to -1**	**Day 0**	**Day 1[q]**								**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**
Visit Window			**-2 hrs to -5 min**	**0hr**	**.5 hr**	**1hr[a]**	**2hr**	**4hr**	**8hr**	**12hr**	**24hr**	**48hr**	**72hr**	**96hr**	**±1 day**	**±3 days**
Enrollment Procedures																
Informed Consent	X															
Demography	X															
Medical History	X	X[b]														
History of Drug, Alcohol and Tobacco use	X	X[b]														
Inclusion/Exclusion Criteria	X	X[b]														
Medical Procedures																
Physical Examination[c]	X	X												X	X	X
Weight	X	X												X	X	X
Height	X															
Chest X-ray[d]	X															
Vital Signs: supine BP, PR & oral temperature	X	X[e]	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital Sign: Respiratory Rate (RR)			X						X		X	X	X	X	X	X
Single 12-lead Electrocardiogram (ECG)	X															
Triplicate 12-lead Electrocardiogram (ECG)[f]			X			X	X		X	X	X	X	X	X		
Insert IV catheter for blood collection[g]			X													
Insert IV catheter for study drug infusion[h]			X													
Telemetry[i]			X	→	→	→	→	→	→							
Laboratory Assessments																
Urine Drug Test and Alcohol Breath Test[j]	X	X														
HIV, HBsAg, HBcAb, HCVAb, HBsAb[r]	X															

Protocol Activity	**Screen**	**Clinical Confinement**													**Follow-up Visit**	
Study Day	**-27 to -1**	**Day 0**	**Day 1[q]**								**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 15**
Visit Window			**-2 hrs to -5 min**	**0hr**	**.5 hr**	**1hr[a]**	**2hr**	**4hr**	**8hr**	**12hr**	**24hr**	**48hr**	**72hr**	**96hr**	**±1 day**	**±3 days**
QuantiFERON – Tuberculosis (TB) Gold Test	X															
Phadiatop[k]	X															
Follicle Stimulating Hormone (FSH)[l]	X															
Safety Laboratory: Hematology, Chemistry, Urinalysis (UA)	X	X[m]									X	X	X	X	X	X
[redacted]		C														
		C														
		[redacted]														
Serum Pharmacokinetic (PK)			X			X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]																
Serum IgE[o]	X	X	C													
CCI [redacted]																
Immunogenicity (ADA, NAb)			X													X
Trial Treatment Procedures																
Admission to Clinical Research Unit (CRU)		X														
Study Treatment Administration				X												
Infusion/Injection Site Reaction					X[p]	X[p]	X	X	X	X	X	X	X	X		
Discharge from Clinical Research Unit														X		
Contraception Check	X	X												X	X	X
Adverse Event Monitoring[s]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Prior/Concomitant Treatment	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

Abbreviations: → = ongoing/continuous event; ADA = antidrug antibody; BP = blood pressure; CRU = clinical research unit; CCI [redacted]; ECG = electrocardiogram; CCI [redacted] FSH = follicle-stimulating hormone; HCVAb =Hepatitis C Virus Antibodies; HBcAb = Hepatitis B Core Antibody; HBsAb = Hepatitis B Surface Antigen; HBsAg = Hepatitis B Surface Antigen; HIV = human immunodeficiency virus; IgE = Immunoglobulin E; CCI [redacted]; CCI [redacted]; IV = intravenous; NAb = neutralizing antibody; PK = pharmacokinetic; PR = pulse rate; CCI [redacted] RR = respiratory rate; SAD = Single Ascending Dose; CCI [redacted] TB = tuberculosis; UA = urinalysis.

a. The 1 hour post-dose procedures are to be implemented for all cohorts (IV and subcutaneous [SC]) as close to 1 hour as possible. For the IV Cohorts, procedures are to occur after investigational product infusion is completed (see Dosage and Administration Instructions (DAI)). ECG and vital sign procedures may be collected up to 10 minutes prior to investigational product infusion completion.

b. Updated since screening.

c. A full physical examination may be done at screening or may be deferred to Day 0 at the discretion of the principal investigator (PI). If a full physical exam is performed at screening, a limited physical exam will be performed on Day 0. Full physical examinations are required prior to dosing (screening or Day 0) and at the final study visit. A limited physical examination will be completed at all other times specified in the SoA. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

d. Chest X-ray results within 3 months of the screening visit otherwise a chest x-ray must be performed and results obtained prior to randomization.

e. On Day 0, oral temperature is the only vital sign collection required.

f. ECGs will be collected in triplicate approximately 2-4 minutes apart.

g. Site may insert IV catheter for blood sample collection up to 24 hours prior to study drug administration. IV catheter should be inserted in the extremity contra lateral to that into which test article will be administered. Heparin is not to be utilized.

h. IV cohorts only, after all pre-dose procedures have been completed, insert IV catheter for study drug.

i. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing. This may be done 2-hours 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 subject is awake. Continuous cardiac monitoring will be conducted approximately -5 minutes pre-dose through the 8 hour post-dose period.

j. Subjects may undergo a urine drug test at the discretion of the investigator at any time during the study. An alcohol breath test is not mandatory but may be given at Screening or any other time during the study at the discretion of the investigator.

k. Phadiatop historical positive test result with appropriate documentation is acceptable for Cohorts 1-4 only. Starting with Cohort 5 and later, Phadiatop is to be collected prior to dosing.

l. Serum FSH for all females who are amenorrheic for at least 12 consecutive months.

m. The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed on Day 1.

C [redacted]

o. IgE results within 6 months of the screening visit otherwise an IgE test must be performed and results obtained prior to randomization for Cohorts 1-4 only. Starting with Cohort 5 and later, at least two (2) IgE pre-dose collections are to occur.

p. Subjects will be continuously monitored for infusion site reactions (for IV administration) from start of drug administration until the end of infusion. Injection site reactions (for SC administrations) should be monitored continuously for the first 30 minutes and then at time points indicated in the SoA.

q. If any intravenous infusion time exceeds 100 minutes, the post-dose time points for Day 1 (through 24 hours) will shift out relative to the end of infusion.

r. HBsAb test if screening results for HBsAg are negative and HBcAb are positive for Part 1 (Cohort 5 and later).

s. See Appendix 6: Clinical Criteria for Diagnosing Anaphylaxis Guidance to assist with identifying cases of potential anaphylaxis while monitoring for adverse events. Any signs or symptoms of anaphylaxis should be treated according to the Investigator's standard of care and reported as an adverse event.

Table B: Part 1, Healthy Subjects Who May be Mildly Atopic, Single Dose Cohorts Day 32 through Day 211[a] (Cohorts 1, 2 and 6, and Cohorts 3 through 5 and 7 if NOT Rolled Over Into Multiple Dosing Portion of Study)[d]

Protocol Activity	Follow-up Visits								Extended Follow-up[a]
Study Day	**Day 32**	**Day 46**	**Day 61**	**Day 91**	**Day 121**	**Day 151**	**Day 181**	**Day 211**	
Visit Window	**±3 days**	**±5 days**	**±5 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±14 days**
Medical Procedures									
Physical Examination[b]	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	
Vital Signs (supine BP, PR, RR, and oral temperature)	X	X	X	X	X	X	X	X	
Single 12-lead Electrocardiogram (ECG)	X		X	X	X	X	X	X	
Laboratory Assessments									
Urine Drug and Alcohol Breath Test[c]									
Safety Laboratory: Hematology, Chemistry, Urinalysis (UA)	X	X	X	X	X	X	X	X	
CCI [redacted]									
Serum Pharmacokinetic (PK)	X	X	X	X	X	X	X	X	X
CCI [redacted]									
CCI [redacted]									
CCI [redacted]									
Immunogenicity (ADA, NAb)	X	X	X	X	X	X	X	X	X
Trial Treatment Procedures									
Contraception check	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring	→	→	→	→	→	→	→	→	→
Prior/Concomitant Treatment	→	→	→	→	→	→	→	→	→
Discharge from Study								X	X

Abbreviations: → = ongoing/continuous event; ADA = antidrug antibody; BP = blood pressure; CCI ECG = electrocardiogram; CCI IV = intravenous; NAb = neutralizing antibody; PK = pharmacokinetic; PR = pulse rate; CCI RR = respiratory rate; CCI UA = urinalysis

a. Extended follow-up visits: Subjects having an unresolved adverse event that is possibly related to ADA immune response will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit for up to 12 months after last drug administration or until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and Sponsor concurs with the investigator's assessment. Subjects may also be required to attend extended follow-up visits if the emerging data project that half-life is longer than approximately 41 days. Under these circumstances, subjects will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit to cover approximately ≥5 times the observed half-life CCI CCI OR of sufficient duration to have projected exposures decrease below ADA drug tolerance CCI . Safety labs for extended follow-up visits may be done at the discretion of the PI for cohorts currently in the study.

b. Full physical examination is required at the final study visit. A limited physical examination will be completed at all other times specified in the SoA. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

c. Subjects may undergo a urine drug test and/or alcohol breath test at any time during the study at the discretion of the investigator.

d. If a subject from Cohorts 3-5, 7, or 10-12 cannot receive a second dose within the allotted time due to unexpected circumstances (eg, scheduling), they should follow SoA Table B through the end of the study.

Table C: Part 1, Healthy Subjects Who May be Mildly Atopic, Cohorts Receiving Multiple Doses Day 31 through Day 241[b] (Cohorts 3 through 5 and 7 if Rolled Over Into Multiple Dose Portion of Study; Cohorts 10 through 12 if Cohorts 3 through 5 were NOT Rolled Over Into Multiple Dose Portion of Study)[a]

Protocol Activity	Clinical Confinement											Follow-up Visit								Extended Follow-up[b]
Study Day	Day 31	Day 32[l]								Day 33	Day 34	Day 46	Day 61	Day 91	Day 121	Day 151	Day 181	Day 211	Day 241	
Visit Window		-2hrs to -5min	0hr	.5 hr	1hr[c]	2hr	4hr	8hr	12hr	24hr	48hr	±5 day	±5 day	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±14 days
Medical Procedures																				
Physical Examination[d]	X										X	X	X	X	X	X	X	X	X	X
Weight	X										X	X	X	X	X	X	X	X	X	
Vital Signs (supine BP, PR, RR, and oral temperature)[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Triplicate 12-lead ECG[f]		X			X	X		X	X											
Single 12-lead ECG										X	X		X	X	X	X	X	X	X	
Insert IV catheter for blood collection[g]		X																		
Insert IV catheter for study drug infusion[h]		X																		
Telemetry[i]		X	→	→	→	→	→	→												
Laboratory Assessments																				
Urine Drug and Alcohol Breath Test[j]	X																			
Safety Laboratory: Hematology, Chemistry, Urinalysis (UA)	X									X	X	X	X	X	X	X	X	X	X	
CCI																				
Serum Pharmacokinetic (PK)		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																				
Immunogenicity (ADA, NAb)		X										X	X	X	X	X	X	X	X	X

Protocol Activity	Clinical Confinement											Follow-up Visit								Extended Follow-up[b]
Study Day	Day 31	Day 32[l]								Day 33	Day 34	Day 46	Day 61	Day 91	Day 121	Day 151	Day 181	Day 211	Day 241	
Visit Window		-2hrs to -5min	0hr	.5 hr	1hr[c]	2hr	4hr	8hr	12hr	24hr	48hr	±5 day	±5 day	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±14 days
Trial Treatment Procedures																				
Contraception Check	X											X	X	X	X	X	X	X	X	X
Admission to CRU	X																			
Study Treatment Administration			X																	
Assess Injection/Infusion Site Reaction[k]				X	X	X	X	X	X	X	X									
Discharge from CRU											X									
Adverse Event Monitoring[m]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Prior/Concomitant Treatment	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Discharge from Study																			X	X

Abbreviations: → = ongoing/continuous event; ADA = antidrug antibody; BP = blood pressure; CCI [redacted] CRU = clinical research unit; ECG = electrocardiogram; CCI [redacted] IV = intravenous; NAb = neutralizing antibody; PK = pharmacokinetic; PR = pulse rate; CCI [redacted] RR = respiratory rate; CCI [redacted] UA = urinalysis

a. Second dose will occur at a minimum of 4 weeks and at a maximum of 12 weeks after the first dose and after protocol required safety and PK review (see Section 3.3). If subjects are not admitted into the clinic for the second dose by Day 35 (Day 32+3 days), subjects should follow SoA Table B Day 32 follow-up visit; if subjects are not admitted into the clinic for the second dose by Day 51 (Day 46+5 days), subjects should follow SoA Table B Day 32 and Day 46 follow-up visits; if subjects are not admitted into the clinic for the second dose by Day 66 (Day 61 +5 days), subjects should follow SoA Table B Day 32, Day 46 and Day 61 follow-up visits. SoA Table C visits would then shift out accordingly (by days of delay for each cohort/subjects affected) ensuring 7 months of follow-up after the second dose. If a subject cannot receive a second dose within the allotted time due to unexpected circumstances (eg, scheduling), they should follow SoA Table B through the end of the study.

b. Extended follow-up visits: Subjects having an unresolved adverse event that is possibly related to ADA immune response will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit for up to 12 months after last drug administration or until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and Sponsor concurs with the investigator's assessment. Subjects may also be required to attend extended follow-up visits if the emerging data project that half-life is longer than approximately 41 days. Under these circumstances, subjects will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit to cover approximately ≥5 times the observed half-life CCI [redacted] CCI [redacted] OR of sufficient duration to have projected exposures decrease below ADA drug tolerance CCI [redacted] Safety labs for extended follow-up visits may be done at the discretion of the PI for cohorts currently in the study.

c. The 1 hour post-dose procedures are to be implemented for all cohorts (IV and subcutaneous [SC]) as close to 1 hour as possible. For the IV Cohorts, procedures are to occur after investigational product infusion is completed (see DAI). ECG and vital sign procedures may be collected up to 10 minutes prior to investigational product infusion completion.

d. Full physical examinations are required at final study visit. A limited physical examination will be completed at all other times specified in the SOA. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

e. Vitals signs include BP, PR, RR, and oral temperature. RR is to be collected at Day 32 prior to dosing (up to 2 hours prior), daily during confinement, and at all follow-up visits.

f. ECGs will be collected in triplicate approximately 2-4 minutes apart.

g. Site may insert IV catheter for blood sample collection up to 24 hours prior to study drug administration. IV catheter should be inserted in the extremity contra lateral to that into which test article will be administered. Heparin is not to be utilized.

h. After all pre-dose procedures have been completed, insert IV catheter for study drug infusion for IV administration only.

i. Telemetry may be collected after study team and investigator review safety data required prior to initiating multiple dosing per protocol Section 3.1.

j. Subjects may undergo a urine drug test and/or an alcohol breath test at any time during the study at the discretion of the investigator.

k. Subjects will be continuously monitored for infusion site reactions (for IV administration) from start of drug administration until the end of infusion. Injection site reactions (for SC administrations) should be monitored continuously for the first 30 minutes and then at time points indicated in the SOA.

l. If any intravenous infusion time exceeds 100 minutes, the post-dose time points for Day 32 (through 24 hours) will shift out relative to the end of infusion.

m. See Appendix 6: Clinical Criteria for Diagnosing Anaphylaxis Guidance to assist with identifying cases of potential anaphylaxis while monitoring for adverse events. Any signs or symptoms of anaphylaxis should be treated according to the Investigator's standard of care and reported as an adverse event.

Table D: Part 2, Chronic Rhinosinusitis with Nasal Polyps Patient Cohorts (Cohort 8 and 9)[a]

Protocol Activity	Screen	Clinical Confinement										Follow-up Visit									Extended Follow-up[a]
Study Day	**-27 to -1**	**Day 0[w]**	**Day 1[s]**								**Day 2**	**Day 5**	**Day 8**	**Day 15**	**Day 32**	**Day 61**	**Day 91**	**Day 121**	**Day 181**	**Day 211**	
Visit Window			**-2hrs to -5min**	**0hr**	**.5 hr**	**1hr[b]**	**2hr**	**4hr**	**8hr**	**12hr**	**24hr**	**96hr**	**±1 day**	**±3 days**	**±3 days**	**±5 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±14 days**
Enrollment Procedures																					
Informed Consent	X																				
Demography	X																				
Medical History	X	X[c]																			
History of Drug, Alcohol and Tobacco use	X	X[c]																			
Inclusion/Exclusion Criteria	X	X[c]																			
Medical Procedures																					
Physical Examination[d]	X	X									X	X	X	X	X	X	X	X	X	X	X
Weight	X	X									X	X	X	X	X	X	X	X	X	X	
Height	X																				
Chest X-ray[e]	X																				
Spirometry[f]	X																				
Nasal Endoscopy and Nasal Polyp Score (NPS)	X[g]	X[g]													C	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]		C C														[redacted]		[redacted]			
Vital Signs: supine BP, PR & oral temperature	X	X[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Sign: Respiratory Rate (RR)			X						X		X	X	X	X	X	X	X	X	X	X	
Single 12-lead ECG	X		X			X	X		X	X	X	X			X	X	X	X	X	X	
Insert IV catheter for blood collection[i]			X																		
Insert IV catheter for study drug infusion[j]			X																		
Telemetry[k]			X	→	→	→	→	→	→												
Laboratory Assessments																					
Urine Drug Test and Alcohol Breath Test[l]	X	X																			

Protocol Activity	Screen	Clinical Confinement										Follow-up Visit									Extended Follow-up[a]
Study Day	**-27 to -1**	**Day 0[w]**	**Day 1[s]**								**Day 2**	**Day 5**	**Day 8**	**Day 15**	**Day 32**	**Day 61**	**Day 91**	**Day 121**	**Day 181**	**Day 211**	
Visit Window			**-2hrs to -5min**	**0hr**	**.5 hr**	**1hr[b]**	**2hr**	**4hr**	**8hr**	**12hr**	**24hr**	**96hr**	**±1 day**	**±3 days**	**±3 days**	**±5 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±14 days**
HIV, HBsAg, HBcAb, HCVAb, HBsAb[t]	X																				
QuantiFERON – Tuberculosis (TB) Gold Test	X																				
Follicle Stimulating Hormone (FSH)[m]	X																				
Pregnancy Test[n]	X	X									X	X	X	X	X	X	X	X	X	X	
Safety Laboratory: Hematology, Chemistry, Urinalysis (UA)	X	X[o]									X	X	X	X	X	X	X	X	X	X	
[redacted]		C																			
		C																			
		I																			
Serum Pharmacokinetic (PK)			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]																					
Immunogenicity (ADA, NAb)			X											X	X	X	X	X	X	X	X
Assessments																					
CCI [redacted]																					
Trial Treatment Procedures																					
Admission to CRU		X																			
Study Treatment Administration				X																	
Infusion Site Reaction[r]					X	X	X	X	X	X	X	X									
Discharge from CRU											X										
Contraception Check	X	X									X	X	X	X	X	X	X	X	X	X	X

Protocol Activity	Screen	Clinical Confinement										Follow-up Visit									Extended Follow-up[a]
Study Day	-27 to -1	Day 0[w]	Day 1[s]								Day 2	Day 5	Day 8	Day 15	Day 32	Day 61	Day 91	Day 121	Day 181	Day 211	
Visit Window			-2hrs to -5min	0hr	.5 hr	1hr[b]	2hr	4hr	8hr	12hr	24hr	96hr	±1 day	±3 days	±3 days	±5 days	±7 days	±7 days	±7 days	±7 days	±14 days
Adverse Event Monitoring[v]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Prior/Concomitant Treatment	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Discharge from Study																				X	X

Abbreviations: → = ongoing/continuous event; CCI [redacted] ADA = antidrug antibody; BP = blood pressure; CCI [redacted] CRU = clinical research unit; CT = computerized axial tomography; ECG = electrocardiogram; CCI [redacted] FSH = follicle-stimulating hormone; HCVAb = Hepatitis C Virus Antibodies; HBcAb = Hepatitis B Core Antibody; HBsAb = Hepatitis B Surface Antibody; HBsAg = Hepatitis B Surface Antigen; HIV = human immunodeficiency virus; CCI [redacted] IV = intravenous; NAb = neutralizing antibody; CCI [redacted] PK = pharmacokinetic; PR = pulse rate; CCI [redacted] RR = respiratory rate; CCI [redacted] TB = tuberculosis; UA = urinalysis; CCI [redacted].

a. Extended follow-up visits: Subjects having an unresolved adverse event that is possibly related to ADA immune response will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit for up to 12 months after last drug administration or until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and Sponsor concurs with the investigator's assessment. Subjects may also be required to attend extended follow-up visits if the emerging data project that half-life is longer than approximately 41 days. Under these circumstances, subjects will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit to cover approximately ≥5 times the observed half-life CCI [redacted] CCI [redacted] OR of sufficient duration to have projected exposures decrease below ADA drug tolerance CCI [redacted]. Safety labs for extended follow-up visits may be done at the discretion of the PI for cohorts currently in the study.

b. The 1 hour post-dose procedures are to be implemented as close to 1-hour as possible. For the IV Cohorts, procedures are to occur after investigational product infusion is completed (see DAI). ECG and vital sign procedures may be collected up to 10 minutes prior to investigational product infusion completion.

c. Updated since screening.

d. A full physical examination may be done at screening or may be deferred to Day 0 at the discretion of the principal investigator (PI). If a full physical exam is performed at screening, a limited physical exam will be performed on Day 0. Full physical examinations are required prior to dosing (screening or Day 0) and at the final study visit. A limited physical examination will be completed at all other times specified in the SoA. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

e. Chest X-ray results within 3 months of the screening visit otherwise a chest x-ray must be performed and results obtained prior to randomization.

f. Spirometry required for subjects with a history of asthma. Spirometry results acceptable within 3 months of screening visit otherwise a spirometry must be performed and results obtained prior to randomization.

g. The screening nasal endoscopy including assessment of Nasal Polyp Score (NPS) is to be completed after all other screening criteria have been verified. If a subject is eligible for the study, they will undergo nasal endoscopy including assessment of NPS, and CT scan to assess the Lund-Mackay CT score, ideally on Day 0. However, the baseline NPS and Lund-Mackay CT score may be determined up to 5 days prior to Day 0. Thus, if a subject is screened and found eligible for the study based on NPS no more than 5 days prior to Day 0, the NPS from screening may be used as the Day 0 NPS. The baseline/Day 0 CT scan cannot be completed until it has been determined the subject is eligible for the study regardless of when the CT scan occurs.

h. On Day 0, oral temperature is the only vital sign collection required.

i. Site may insert IV catheter for blood sample collection up to 24 hours prior to study drug administration. IV catheter should be inserted in the extremity contra lateral to that into which test article will be administered. Heparin is not to be utilized.

j. After all pre-dose procedures have been completed, insert IV catheter for study drug infusion for IV administration only.

k. To establish a baseline, telemetry should be recorded for at least 2 hours before dosing. This may be done 2-hours 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 subject is awake. Continuous cardiac monitoring will be conducted approximately-5 minutes pre-dose through the 8 hour post-dose period.

l. Subjects may undergo a urine drug test at the discretion of the investigator at any time during the study. An alcohol breath test is not mandatory but may be given at Screening or any other time during the study at the discretion of the investigator.

m. Serum FSH for all females who are amenorrheic for at least 12 consecutive months.

n. To be completed for female subjects of childbearing potential with either documented bilateral tubal ligation or bilateral salpingectomy-see Section 7.1.1.2.

o. The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed on Day 1.

C CCI [redacted]

r. Subjects will be continuously monitored for infusion site reactions (for IV administration) from start of drug administration until the end of infusion.

s. If any intravenous infusion time exceeds 100 minutes, the post-dose time points for Day 1 (through 24 hours) will shift out relative to the end of infusion.

t. HBsAb test if screening results for HBsAg are negative and HBcAb are positive.

C CCI [redacted]

v. See Appendix 6: Clinical Criteria for Diagnosing Anaphylaxis Guidance to assist with identifying cases of potential anaphylaxis while monitoring for adverse events. Any signs or symptoms of anaphylaxis should be treated according to the Investigator's standard of care and reported as an adverse event.

w. Day 0 may be an outpatient visit (at the discretion of the investigator). If Day 0 is an outpatient visit, the subject should be carefully instructed about fasting, avoidance of dietary/alcohol indiscretions, and avoidance of strenuous exercise. Additional baseline safety laboratory samples will need to be collected at Day 1 (-2 hours to -5 minutes).

Table E: Part 3, Moderate to Severe Atopic Dermatitis Subject Cohort (Cohort 13)

Study Day	Screening: Day -41 to Day 0	Day 1[c,dd] / Week 0			Day 8/ Week 1	Day 29[c,dd]/ Week 4			Day 57[c,dd]/ Week 8		
Visit Window[y]					±2 days	±3 days			±3 days		
Time		Pre-dose[b]	0 hr	1.5 h[d]		Pre-dose[b]	0 hr	1.5 h[d]	Pre-dose[b]	0 hr	1.5 h[d]
Enrollment Procedures											
Informed Consent	X										
Demography	X										
Medical History	X	X[e]									
Atopic Dermatitis History including other atopic diseases	X	X[e]									
History of illegal Drug, Alcohol and Tobacco use	X	X[e]									
Inclusion/Exclusion Criteria	X	X[e]									
Medical Procedures											
Physical Examination[f]	X	X			X	X			X		
Weight	X	X				X			X		
Height	X										
Chest X-ray[g]	X										
Spirometry[h]	X										
Vital Signs: supine BP, PR & temperature	X	X[p]		X	X	X[p]		X	X[p]		X
Vital Sign: Respiratory Rate (RR)		X[p]		X[aa]		X[p]		X[aa]	X[p]		X[aa]
Single 12-lead ECG	X	X[p]		X		X[p]		X	X[p]		X
Insert IV catheter for blood collection[j]		X				X			X		
Insert IV catheter for study drug infusion[k]		X				X			X		
Laboratory Assessments											
Urine Drug Test and Alcohol Breath Test[l]	X	X									
HIV, HBsAg, HBcAb, HCVAb, HBsAb[m]	X										
QuantiFERON – Tuberculosis (TB) Gold Test	X										
Follicle Stimulating Hormone	X										

Study Day	Screening: Day -41 to Day 0	Day 1[c,dd] / Week 0			Day 8/ Week 1	Day 29[c,dd]/ Week 4			Day 57[c,dd]/ Week 8		
Visit Window[y]					±2 days	±3 days			±3 days		
Time		Pre-dose[b]	0 hr	1.5 h[d]		Pre-dose[b]	0 hr	1.5 h[d]	Pre-dose[b]	0 hr	1.5 h[d]
(FSH)[n]											
Pregnancy Test[o]	X	X			X	X			X		
Safety Laboratory: Hematology, Chemistry, Urinalysis (UA)	X	X			X	X			X		
Immunogenicity (ADA, NAb)		X			X	X			X		
CCI											
Physician Assessments of Disease Activity											
Fitzpatrick Skin Type Assessment		X									
Eczema Area and Severity Index (EASI)	X	X			C						
CCI											
Investigator's Global Assessment (IGA)	X	X			C						
CCI											

Study Day	**Screening: Day -41 to Day 0**	**Day 1[c,dd] / Week 0**			**Day 8/ Week 1**	**Day 29[c,dd]/ Week 4**			**Day 57[c,dd]/ Week 8**		
Visit Window[y]					**±2 days**	**±3 days**			**±3 days**		
Time		**Pre-dose[b]**	**0 hr**	**1.5 h[d]**		**Pre-dose[b]**	**0 hr**	**1.5 h[d]**	**Pre-dose[b]**	**0 hr**	**1.5 h[d]**
CCI [redacted]		[redacted]			[redacted]	[redacted]			[redacted]		
[redacted]		[redacted]				[redacted]			[redacted]		
[redacted]		[redacted]				[redacted]			[redacted]		
Trial Treatment Procedures											
Study Treatment Administration			X				X			X	
Assessment for Infusion Site Reaction[u]			X	X			X	X		X	X
Other study activities											
Contraception Check[i]	X	X			X	X			X		
Adverse Event Monitoring[v]	X	X	→	X	X	X	→	X	X	→	X
Prior/Concomitant Treatment	X	X	→	X	→	→	→	X	→	→	X
Discharge from Study[t]											

CONTINUATION OF TABLE E

Study Day	Day 85/ Week 12[c,dd]			Day 113/ Week 16	Day 141 /Week 20 FU	Day169 /Week 24 FU	Day 253/ Week 36 FU	Day 337/ Week 48 FU	Extended FU[a]	EW	EOS[bb]
Visit Window[y]	±3 days			±3 days	±7 days	±7 days	±7 days	±7 days	±7 days		
Time	**Pre-dose**[b]	**0 hr**	**1.5 h**[d]								
Medical Procedures											
Physical Examination[f]	X			X	X	X	X	X	X	X	X
Weight	X			X	X	X	X	X	X	X	
Vital Signs: supine BP, PR &temperature	X[p]		X	X	X	X	X	X	X	X[cc]	X[cc]
Vital Sign: Respiratory Rate (RR)	X[p]		X[aa]								
Single 12-lead ECG	X[p]		X	X	X		X			X[z]	
Insert IV catheter for blood collection[j]	X										
Insert IV catheter for study drug infusion[k]	X										
Laboratory Assessments											
Pregnancy Test[o]	X			X	X	X	X	X	X	X	X
Safety Laboratory: Hematology, Chemistry, Urinalysis (UA)	X			X			X	X	X	X	X
Immunogenicity (ADA, NAb)	X			X			X	X	X	X	X
CCI											

Study Day	Day 85/ Week 12[c,dd]			Day 113/ Week 16	Day 141 /Week 20 FU	Day169 /Week 24 FU	Day 253/ Week 36 FU	Day 337/ Week 48 FU	Extended FU[a]	EW	EOS[bb]
Visit Window[y]	±3 days			±3 days	±7 days	±7 days	±7 days	±7 days	±7 days		
Time	**Pre-dose**[b]	**0 hr**	**1.5 h**[d]								
Physician Assessments of Disease Activity											
CCI											
Trial Treatment Procedures											
Study Treatment Administration		X									
Infusion Site Reaction[u]		X	X								
Additional study activities											
Contraception Check[i]	X			X	X	X	X	X	X	X	X
Adverse Event Monitoring[v]	X	→	X	X	X	X	X	X	X	X	X
Concomitant Treatment	→	→	X	→	→	→	→	→	→	X	X
Discharge from Study[t]											X

Abbreviations: → = ongoing/continuous event; CCI ADA = antidrug antibody; BP = blood pressure; CCI CRU = clinical research unit; CCI CT = computerized axial tomography; CCI ECG = electrocardiogram; EW = Early Withdrawal; FSH = follicle-stimulating hormone; CCI HCVAb = Hepatitis C Virus Antibodies; HBcAb = Hepatitis B Core Antibody; HBsAb = Hepatitis B Surface Antibody; HBsAg = Hepatitis B Surface Antigen; HIV = human immunodeficiency virus; CCI IV = intravenous; NAb = neutralizing antibody; CCI PR = pulse rate; RR = respiratory Rate; CCI TB = tuberculosis; UA = urinalysis.

a. Extended follow-up visits: Subjects having an unresolved adverse event that is possibly related to ADA immune response will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit for up to 12 months after last drug administration OR until the adverse event (or its sequelae) resolve (or stabilize) at a level acceptable to the investigator and sponsor concurs with the investigator's assessment. Subjects will be followed for at least 1 year after the last dose (at Week 12), which is ≥3 times the preliminary estimated half-life of approximately 90 days and >80% exposure (AUC) based on emerging data for the earlier cohorts of healthy subjects, which is adequate to estimate the elimination half-life. Subjects may also be required to attend extended follow-up visit(s) if the emerging data project pharmacologically relevant exposure will extend significantly longer than 1 year. Under these circumstances, subjects will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last planned regular visit to cover approximately ≥5 times the observed half-life CCI CCI OR of sufficient duration to have projected exposures decrease below ADA drug tolerance CCI
b. Pre-dose activities on Day 1, Day 29, Day 57, Day 85 may be performed, at the discretion of the investigator, on the day preceding each dosing visit (ie, on Day 0, Day 28, Day 56, Day 84) as inpatient in clinical site or outpatient. These include medical history, atopic dermatitis history including atopic disease history, history of illegal drug, alcohol and tobacco use, inclusion/exclusion criteria, physical examination, weight, urine drug test and alcohol breath test, pregnancy test, safety laboratory (hematology, chemistry, urinalysis), CCI clinical assessments (Fitzpatrick skin type, EASI, CCI , IGA), CCI CCI For dosing visits performed as outpatient visits, the subject should be carefully instructed about fasting, avoidance of dietary/alcohol indiscretions, and avoidance of strenuous exercise. See Section 4.3.2. Pre-dose vitals and ECG measurements will be recorded as 0 hr measurements. Pre-dose samples collected for PK, Immunogenicity, CCI will be recorded as 0 hr samples. Pre-dose safety labs for the purposes of Inclusion/Exclusion criteria may be done 2 days prior to dosing on Day 1.
c. If any intravenous infusion time exceeds 1.5 hour, the post-dose (1.5 hour) time points for the visits at which subject receives IP will shift out relative to the end of infusion and will be done after the infusion of the IP is completed. The actual times need to be documented in the CRF.
d. The 1.5 hour post-dose procedures are to be implemented as close to 1.5 hours after the start of the infusion as possible but after the infusion of the IP is completed. Procedures are to occur after investigational product infusion is completed (see DAI).
e. Updated since screening.
f. A full physical examination may be done at screening or may be deferred to Day 1 at the discretion of the principal investigator (PI). If a full physical exam is performed at screening, a limited physical exam will be performed on Day 1. Full physical examinations are also required at the final study visit and early

withdrawal visit. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE. A limited physical examination will be completed at all other times specified in the SoA.

g. Chest X-ray results within 3 months of the screening visit otherwise a chest x-ray (standard posterior-anterior and lateral views) must be performed and results obtained prior to randomization.
h. Spirometry required for subjects with a history of asthma. Spirometry results acceptable within 3 months of screening visit; otherwise spirometry must be performed and results obtained prior to randomization. Post screening spirometry may be performed at investigator discretion to assess potential changes in lung function.
i. Contraception check is for WOCBP and/or male subjects who are able to father children and are sexually active and whose partners are at risk for pregnancy.
j. Site may insert IV catheter for blood sample collection up to 24 hours prior to study drug administration only for subjects who will be admitted to the clinical site a day prior to dosing. IV catheter for blood sampling may be replaced with phlebotomy procedures at the investigator's discretion. All blood samples for laboratory testing must be drawn from the extremity contralateral to that into which test article will be administered. If an indwelling catheter is used, heparin is not to be utilized to maintain patency.
k. After all pre-dose procedures have been completed, insert IV catheter for study drug infusion for IV administration only.
l. Subjects may undergo a urine drug test or alcohol breath test at the discretion of the investigator at any time during the study. An alcohol breath test is not mandatory but may be given at Screening or any other time during the study at the discretion of the investigator.
m. HBsAb test if screening results for HBsAg are negative and HBcAb are positive.
n. Serum FSH for all females who are amenorrheic for at least 12 consecutive months.
o. To be completed for female subjects of childbearing potential. Urine pregnancy tests must be done at home by female subjects of childbearing potential every month between the scheduled follow-up visits (these includeWeek 28, Week 32, Week 40 and Week 44) and every month between the scheduled extended visit follow-up visits. PI must be informed immediately if pregnancy test is positive and must see the PI for retesting (see Section 7.2.1.2).
p. Vital signs (Supine BP, PR, temperature), RR and ECG must be performed as close to the dosing time as possible.
C [redacted]
t. Per SOA or as required; see Section 1.3.1.3.
u. Subjects will be frequently monitored for infusion site reactions from start of drug administration until the end of infusion.
v. See Appendix 6: Clinical Criteria for Diagnosing Anaphylaxis Guidance to assist with identifying cases of potential anaphylaxis while monitoring for adverse events. Any signs or symptoms of anaphylaxis should be treated according to the Investigator's standard of care and reported as an adverse event.
CCI [redacted]
y. Visit windows defined from Day 1 (applies to all activities unless otherwise noted).
z. Only if before Week 16.
aa. post-dose RR measurements at Investigator's discretion.
bb. EOS visit if needed. See Section 6.2.7.
cc. At investigator's discretion.
dd. Inpatient subjects will be admitted to the clinic day prior to the dosing visits (Day 1, Day 29, Day 57, Day 85).

1. INTRODUCTION

1.1. Mechanism of Action/Indication

1.1.1. Mechanism of Action

PF-06817024 is a humanized antibody against interleukin-33 (IL-33). IL-33 is a member of the IL-1 family of cytokines, which has been shown to drive a broad range of Type 2 inflammatory mediators.[1,2] By binding IL-33, PF-06817024 prevents IL-33 from binding to its receptor, IL1RL1 (aka ST2, IL-33Ra, IL-1R4[1,3]), and thereby precludes downstream signaling. Type 1 inflammation drives phagocytic activity, is essential for anti-viral, anti-bacterial, and anti-fungal host defense, and is characterized by IL-2, IL-12, IL-18, IFNg, TNFa, and LTa.[4] Type 2 inflammation mediates anti-helminth host defense, but is also the immune response central in the development and persistence of atopic and allergic diseases, and is characterized by IL-4, IL-5, IL-9, and IL-13.[4,5]

IL-33 plays an important role in amplifying immune responses via its release from epithelial and endothelial cells and through its action on multiple target cells of both the innate and adaptive immune subsystems.[1,2] The IL-33 receptor is expressed on mast cells, basophils, eosinophils, T lymphocytes (Th2), natural killer T-lymphocytes (NKT), natural killer cells (NK) and innate lymphoid cells (ILCs, specifically type 2 ILCs, referred to as ILC2s), and accordingly drives a predominantly type 2 response. IL-33 induces cytokines such as IL-5, IL-9, IL-13, and granulocyte-macrophage colony stimulating factor (GM-CSF) in many of these cells types,[2] and induces IL-4 in basophils,[6,7] and IL-31 in T-cells.[8,9] Many chemokines are also induced by IL-33 which, in turn, rapidly recruits myeloid cells, both monocytic and granulocytic, to these surface tissues.[1,2] The release of IL-33 is triggered by many stimuli that often lead to cell death or damage, such as exposure to allergens with proteolytic activity, physical damage to the epithelium, viruses that infect the epithelium, as well as exposure to bacteria and fungi that are common at the body surfaces. Central to IL-33's role in atopic diseases is this sequence of events: damage to the epithelium leading to release of IL-33; released IL-33 acting on local, IL-33 receptor bearing immune cells; and those cells in turn producing cytokines that drive a type 2 inflammatory response.

Given IL-33's role in driving Type 2 inflammatory response and key disease related cytokines, IL-33 blockade represents a compelling approach to the treatment of atopic and allergic diseases including chronic rhinosinusitis with nasal polyps (CRSwNP) and atopic dermatitis (AD).

1.1.2. Indication

PF-06817024 is being developed for the treatment of CRSwNP and other allergic diseases including atopic diseases such as AD, given its potential for broadly inhibiting type-2 inflammation.

1.2. Background

1.2.1. Drug Development Rationale

1.2.1.1. Chronic Rhinosinusitis (CRS)

Chronic rhinosinusitis (CRS) is clinically defined as inflammation of the nose and paranasal sinuses, manifest in at least 8-12 weeks of symptoms including nasal obstruction/congestion, nasal discharge, facial pain/pressure, and reduction of or loss of sense of smell.[10,11] In a subset of these patients, inflamed mucosa protrudes into the nasal and sinus passages, and this subset is termed chronic rhinosinusitis with nasal polyposis. Due to the symptoms of CRS detailed above, and additional issues including sleep disturbance and headache, patients with CRSwNP have a significantly lower quality of life than that enjoyed by healthy peers.[11,12]

Surgery is the mainstay of treatment of CRSwNP, with 46% of CRSwNP patients in the US undergoing surgery within 4.7 months of diagnosis.[13] While surgery provides significant relief from symptoms and improvement in quality of life,[12,14] post-surgical recurrence of disease is common, with approximately 20% of patients experiencing regrowth of polyps within 3 years.[11,15] In a 20-year follow-up study of patients who had undergone surgery for nasal polyposis, 85% of patients had nasal polyposis on endoscopy at the end of the study, indicating nasal polyps recur in the vast majority of patients over time.[16] Although intranasal corticosteroids are approved by the Food and Drug Administration (FDA) for the treatment of nasal polyps, the high rates of surgery, which is reserved for disease refractory to medical treatment, suggest that intranasal corticosteroids are inadequately efficacious in the treatment of CRSwNP. Thus at present, there is significant unmet medical need for new therapies to treat CRSwNP.

While the exact causes of CRS and CRSwNP are not completely elucidated at present, significant progress has been made in understanding CRSwNP.[17,18] Work over the last several decades has refined our understanding of the inflammatory response driving CRSwNP. In 80% of CRSwNP patients in the United States (US) and Europe, the inflammatory infiltrate in CRSwNP is dominated type 2 inflammation.[18,19] As detailed in Section 1.1.1, IL-33 drives type 2 inflammation by inducing key disease-related cytokines (IL-4, IL-5, IL-13, and others).[2,6,7,8,9] Taken together, the established importance of type 2 cytokines in CRSwNP,[18,20,21] the role of IL-33 in driving type 2 inflammation,[1,2] the genetic association between variants in the IL-33 and IL1RL1 loci and allergic diseases,[22-25] and the observed release of IL-33 and presence of IL1RL1 positive cells in CRSwNP[26] support the hypothesis that blockade of IL-33 would be beneficial in CRSwNP.

1.2.1.2. Moderate to Severe Atopic Dermatitis

Atopic dermatitis (AD), also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in the quality of life. The lifetime prevalence of AD in children is 10-20% with 70% of cases occurring in children <5 years of age. Most cases (approximately 75%) improve by adulthood, while approximately 25% of AD subjects have symptoms throughout their life. The majority of studies conducted across multiple age groups suggest a continued decrease in

prevalence with older age.[54] Although less common, adult-onset AD occurs. The prevalence of AD in adults is estimated to be 10%.[55]

The complex pathophysiology of AD is still not completely understood. However, it has been established that the pathophysiology of AD includes a defective skin barrier function, allergic responses, defective antimicrobial immune defense, and a genetic predisposition. The predominant symptom of AD, pruritus and the resulting scratching typically sets off an amplification cycle of atopic skin inflammation. Activation of T lymphocytes, dendritic cells, macrophages, keratinocytes, mast cells, and eosinophils results in a release of numerous pro-inflammatory cytokines and chemokines. This amplification cycle sustains the inflammatory responses characteristic of the AD lesions.[56] Acute AD lesions have been associated with the type 2 helper T cell (T_H2) phenotype, showing dominance of IL-4, -5, -13, and -31 secretion.[56,57,58] Recent evidence supports IL-31's role in pruritus and inflammation in AD.[57,58] IL-33 is an important upstream regulator of these pro-inflammatory cytokines.

There are a limited number of treatments available for AD. Current treatments for mild to moderate AD include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. Additional treatments generally reserved for severe AD include phototherapy (eg, ultraviolet A light [UVA] with or without psoralen, ultraviolet B light [UVB] narrowband or broadband) and systemic agents (eg, corticosteroids, cyclosporine, recombinant IFN-γ, mycophenolate mofetil, methotrexate [MTX], azathioprine, intravenous immunoglobulin.[59] Of the currently available therapies, none offers a cure. Therefore, the main aims of existing treatments are to reduce the occurrence of acute flares, to reduce the extent and severity of involved eczematous skin, and to reduce pruritus and the resulting sleep disturbance.[60,61]

Currently available therapies for the treatment of AD have multiple limitations. The topical therapies have drawbacks related to the duration of use due to the potential for local and systemic side effects (eg, corticosteroid use is limited to 2 to 4 weeks) and to the body regions of use (eg, mid-high potency corticosteroids are not approved for use on the face and/or intertriginous areas). For AD subjects not responding to topical therapies and phototherapy, off-label use of systemic agents, which include both oral corticosteroids and oral immunosuppressants, remain the last viable treatment option. Systemic therapy options are associated with potentially severe adverse effects and require careful monitoring. The risk of toxicity and side effects remain a concern when systemic agents are used. For these reasons the use of these agents is limited to short courses or intermittent therapy. Therefore, the predominant unmet medical need in the treatment of AD is an effective therapeutic agent without restrictions on long-term or continuous use without significant side effects.

Dupilumab is a recently approved, fully human monoclonal antibody that blocks the activity of IL-4 and IL-13 signaling, that has shown efficacy in subjects with moderate - severe AD.[53] Systemic treatment with dupilumab in adults with moderate to severe AD resulted in marked reductions in signs and symptoms of AD, and associated levels of type 2 inflammatory biomarker, such as thymus- and activation-reguated chemokine (TARC)/chemokine

(C-C motif) ligand 17 (CCL17). Since cytokines such as IL-5, IL-17, IL-22, and IL-31 have been implicated in the pathophysiology of AD in addition to IL-4 and IL-13, inhibition of IL-33 has the potential to suppress more of the Th2 inflammatory process than therapies targeting just IL-4 and IL-13. IL-33 therefore represents an attractive therapeutic target for AD and has the potential for superior efficacy compared to dupilumab due to a broader inhibition of the underlying inflammation.

Although the breadth of IL-33 mediated Type 2 inflammation provides the rationale for drug development in CRSwNP and other atopic/allergic diseases such as AD, it should be noted that IL-33 does not play an essential role in clearing viral and bacterial infections[1,2] suggesting a favorable safety profile. In addition, as with any antagonist of Type 2 inflammation (ie, anti-IL-5, anti-IL-13, anti-IL-4/13), there is a potential risk of increased susceptibility to parasitic infections, specifically to helminths, with IL-33 blockade.[5]

1.2.2. Nonclinical Pharmacology

PF-06817024 is a humanized monoclonal antibody that binds to human IL-33 and blocks the interaction of IL-33 with suppression of tumorigenicity 2 (ST2). PF-06817024 binds IL-33 with high affinity, measured by surface plasmon resonance to be 70 picomolar (pM) on reduced wild-type (wt) IL-33 and 13 pM on IL-33 (mm^2), a form of IL-33 that is maintained in an active state by mutation of its four cysteine residues to serine.[27] PF-01687024 does not bind with any significant affinity to the oxidized (inactive) forms of IL-33(wt) or to other IL-1 family cytokines tested (IL-1α, IL-1β, IL-18, IL-36α, IL-36γ). PF-06817024 binds to cynomolgus monkey IL-33(mm^2) with an affinity of 10 pM.

PF-06817024 blocks the binding of purified IL-33 receptor (ST2) to IL-33 and correspondingly inhibits the activity of IL-33 in multiple cell-based assay formats. PF-06817024 inhibits the activity of IL-33 on human mast cells with an half maximal inhibitory concentration (IC_{50}) of 64 pM and demonstrates neutralizing activity in other cell based formats, including human whole blood, peripheral blood mononuclear cells, and recombinant cell lines overexpressing the receptor with IC_{50s} ranging from 1 pM to 1000 pM. PF-06817024 is also shown to bind to native IL-33 using human cell lysates and in in vivo toxicity studies with cynomolgus monkeys.

PF-06817024 is a humanized Immunoglobulin Gamma 1 (IgG1)/kappa molecule. The variable-domain sequences of PF-06817024 outside the complementarity-determining regions (CDRs) are identical to those of the human germlines VH3 DP-54 and VK1 DPK9, and overall the molecule is 95% human. PF-06817024 has been further engineered to have an extended half-life and minimal interaction with Fcγ receptors and complement while retaining full IL-33 neutralization activity.

1.2.3. Nonclinical Pharmacokinetics

After a single intravenous (IV) dose of PF-06817024 to cynomolgus monkeys, the mean clearance (CL), volume of distribution at steady state (V_{ss}), and terminal half-life ($t_{½}$) values were 0.058 mL/h/kg, 56 mL/kg, and approximately 18 days, respectively. Additionally, single dose toxicokinetics (TK) were evaluated after IV or subcutaneous (SC) dosing in an exploratory toxicity study. Systemic exposure increased with increasing dose in the IV dose groups and sex-related differences in exposure were not observed. SC bioavailability was approximately 78%. No anti-drug antibodies (ADA) were detected following a single IV dose to cynomolgus monkeys.

After repeat IV or SC administration of PF-06817024 to cynomolgus monkeys in 13- and 27-week toxicity studies, systemic exposure (as assessed by the highest drug concentration observed in serum [C_{max}] and area under the serum drug concentration-time curve from 0 to 504 hours [AUC_{504}]) increased with increasing dose in the IV dose groups. Accumulation was observed with mean Area under the C_{urve} (AUC) ratios ranging from 1.4 to 3.2 between Day 1 and Day 64 or 169. There were no apparent sex-related differences in systemic exposure observed. The incidence of antidrug antibody (ADA) induction to PF-06817024 was 42% across all-repeat dose groups in the 13-week study and 33% in the 27 week study. Exposures (as assessed by maximum observed concentration (C_{max}) and AUC_{504}) were generally similar in ADA-positive animals compared to ADA-negative animals.

Based on the pharmacokinetics (PK) observed in cynomolgus monkeys, the PK of PF-06817024 in humans is predicted based on allometric scaling and the PK of PF-06817024 in humans is assumed to be linear. The projected PK parameters include absorption rate constant of 0.18 day^{-1}, SC bioavailability of 78%, plasma CL of 0.082 L/day, inter-compartmental CL of 0.39 L/day, V_{ss} of 2.1 L (central) and 2.4 L (peripheral), and a $t_{½}$ of 41 days.

1.2.4. Nonclinical Safety Data

The toxicity of intravenously or subcutaneously administered PF-06817024 has been evaluated in a single dose exploratory study, and pivotal 13-week and 27-week (chronic) repeat-dose studies in sexually mature and sexually immature cynomolgus monkeys respectively. The IV and SC routes of administration were selected for these studies since they are the intended routes of clinical administration. Separate safety pharmacology studies were not conducted with PF-06817024, but safety pharmacology endpoints (electrocardiogram measurements) evaluating the potential effects of PF-06817024 on the cardiovascular (CV) system were included in the 13- and 27-week repeat-dose toxicity studies in cynomolgus monkeys. Administration of PF-06817024 to cynomolgus monkeys once every 3 weeks for 13 weeks or 27 weeks at doses of 20 (IV), 200 (IV), 300 (IV), 80 (SC), or 90 (SC) mg/kg did not produce any effects on safety pharmacology endpoints, including waveform morphology, heart rate, or RR-, PR-, QRS-, QT-, or QTc- intervals. No target organ toxicity or adverse effects were identified in cynomolgus monkeys in either study via IV or SC administration. In the 13-week toxicity study in sexually mature monkeys, no effects were seen in reproductive tissues.

Additional studies conducted to support nonclinical development, including a human cytokine release assay and a tissue cross-reactivity study, did not identify specific human risks. Although ADA induction was observed across all IV and SC PF-06817024-dosed groups following repeat-dose administration serum exposures (as assessed by C_{max} and AUC_{504}) were generally similar in ADA-positive animals compared to ADA-negative animals, indicating ADA induction did not affect exposure. No ADA induction was detected following a single IV dose to monkeys.

Given the lack of target organ toxicity or adverse effects observed in either study, the no-observed-adverse-effect-levels (NOAELs) in the 13-week study were the highest doses tested, 300 mg/kg/dose (IV) and 90 mg/kg/dose (SC). The NOAELs in the 27-week study were the highest doses tested, 300 mg/kg/dose (IV) and 80 mg/kg/dose (SC). As the no observed adverse effect levels (NOAELs) are the maximum doses evaluated in the 13 and 27 week good laboratory practice (GLP) toxicity studies in monkeys, the PK exposure limit in humans will be established based on the exposures achieved in the 13 week GLP toxicity study, as this study produced lower steady state exposures than the 27 week study. Thus, the human exposure limits will be set to be C_{av} of 442.0 µg/mL (calculated as AUC_{504} of 2230000 µg•h/mL divided by 504 hours), which is $1/10^{th}$ of the mean C_{av} at the IV NOAEL dose in the 13 week GLP toxicity study in monkeys. In the 13-week study, at 300 mg/kg/dose IV, C_{max} and C_{av} safety margins relative to the highest planned clinical IV dose of 600 mg (every 4 weeks) are 27x and 12x, respectively.

Collectively, the nonclinical program supports the chronic use of PF-06817024 in clinical trials in both males and females (including women of childbearing potential with use of appropriate contraception, see Section 4.3.1.5).

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

1.2.5. Emerging, Preliminary, Draft Data from Healthy Subjects in Parts 1, 2 and/or 3

1.2.5.1. Safety Data

The clinical experience with PF-06817024 to date has consisted only of data emerging from the current study. As of 01 February, 2018 (the date of the last database cut-off), a total of 71 subjects have received blinded therapy (PF-06817024 or placebo) by IV or SC administration in the current, of which 49 are healthy subjects, 20 are subjects with CRSwNP and 2 are subjects with moderate-severe AD. Escalating doses of PF-06817024 tested in healthy subjects have included single doses of 10 mg, 30 mg, 100 mg, 300 mg and 1000 mg, a repeat dose of 100 mg all administered IV, and a single dose of 30 mg administered SC. Subjects with CRSwNP have been administered a single IV dose of 300 mg of PF-06817024 or placebo. Subjects with moderate-severe AD recruited as of the cut-off date have been administered the first IV dose of 600 mg of PF-06817024 or placebo. Subjects in the healthy and CRSwNP cohorts (Parts 1 and 2) have been followed for up to approximately 1-2 years.

As this study is currently ongoing and blinded, only summary, preliminary, blinded, unaudited safety, tolerability, PK, and immunogenicity data are available and presented below. Given the limited number of AD subjects recruited, the cumulative safety data to date primarily reflect the safety and tolerability in healthy subjects and subjects with CRSwNP (Parts 1 and 2). As of the above cutoff data, adverse effects (AEs) have been observed in 57 of 71 subjects (80.3%) receiving blinded therapy. The most commonly reported treatment-emergent adverse events (TEAEs) have fallen under the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOC) of Infections and Infestations (36.6%), Gastrointestinal Disorders (19.7%), Injury, Poisoning and Procedural Complications (16.9%), Musculoskeletal and Connective Tissue Disorders (15.5%), and Nervous System Disorders (15.5%). The most common (occurring in 3 or more subjects) AEs by Preferred Term were: upper respiratory tract infection (10 subjects, 14.1%); sinusitis, pain in extremity, nasal congestion, ecchymosis (5 subjects, 7.0%, each); and oral herpes, nausea, back pain, and dizziness (3 subjects, 4.2%, each). The safety profile has been generally similar across the healthy and CRSwNP subjects. Adverse effects in the System Organ Class of Respiratory, Thoracic, and Mediastinal Disorders appeared to be more frequent in the subjects with CRSwNP than in healthy subjects, likely reflective of their underlying disease. A variety of mild transfusion-related reactions were noted in the early cohorts of Part 1 of Study C0341001 in healthy subjects, but these were mitigated when the infusion time was increased from 60 to 90 minutes. In general, ongoing review of the preliminary data has revealed the AEs to be generally mild-moderate in severity and self-limited.

As of the date of the last database cut-off, there have been no deaths, or suspected unexpected serious adverse reactions (SUSARs) associated with the administration of blinded treatment. There have been 3 serious adverse effects (SAEs). One SAE was due to a motor vehicle accident in a healthy subject who had received a single dose of PF-06817024, 1000 mg IV, or placebo. The other two SAEs were due to 2 separate events (approximately 9 months apart) of respiratory tract infection in a single subject with CRSwNP and comorbid asthma who received a single dose of 300 mg PF-06817024 or placebo IV. Since all of the SAEs were in subjects participating in single dose cohorts, there were no discontinuations due to the SAEs; both subjects with SAEs have remained in the study for follow-up (between 1-2 years). One subject was lost to follow-up as subject did not want to return for extended follow up visits after completion of Day 211 visit. Additional details may be found in the current version of the Investigator's Brochure, the SRSD for PF-06817024.

1.2.5.2. PK Data

Based on a preliminary, draft dataset obtained in January 2018 and including interim data from subjects in the first two parts of the study, a non-compartmental PK analysis was performed and the derived PF-06817024 PK parameters are summarized descriptively in Table 1.

Following single IV doses in healthy subjects, the median time for occurrence of maximal concentration (T_{max}) ranged between 1.76 and 3 hours, while the median T_{max} after SC administration (30 mg) was 338 hours (≈14 days). PF-06817024 had a prolonged half-life ($t_{1/2}$) with mean values ranging from 79 to 94 days across all single dose healthy volunteer cohorts. Both maximal plasma concentration (C_{max}) and area under the concentration-time curve from time 0 to infinity (AUC_{inf}) appeared to be approximately dose proportional in healthy subjects across the 10-1000 mg IV range (see Table 1), indicating that PF-06817024 exhibits linear kinetics in humans within this dose range. Clearance (CL) values (geometric mean) ranged from 0.00206 L/h to 0.00259 L/h across all single IV dose healthy volunteer cohorts. Using the calculated geometric means of AUC_{inf} after single IV infusion and SC administration of the same dose (30 mg) in healthy subjects (8579/14590, see Table 1), the bioavailability (F) after SC administration is approximately 59% relative to IV infusion.

Multiple dose PK data were available only for 4 healthy subjects from the 100 mg IV cohort who received an additional 100 mg IV dose. The (geometric) mean C_{max} after the second dose was 42.47 µg/mL (geometric CV of 11%) across these 4 subjects and the associated median T_{max} was 1.54 hours. The (geometric) mean area under the concentration-time curve from the time of the second dose until 720 hours post-dose (AUC_{τ}) and until infinity (AUC_{inf}) was 16540 (geometric CV of 13%) and 73400 µg•hr/mL (geometric CV of 23%) respectively. Finally, the mean calculated $t_{1/2}$ after the second dose was 108 days (standard deviation (SD) of 10).

Following 300 mg IV administration in CRSwNP patients the median T_{max} was 2 hours and the associated (geometric) mean C_{max} was 89.79 µg/ml. These values are very similar to those observed in healthy subjects at the same dose (T_{max} at 2 hours and C_{max} of 97.49 µg/mL). Since the available data from the ongoing CRSwNP cohort were relatively limited, some PK parameters (eg, $t_{1/2}$, AUC_{inf}) were not calculated for the majority of the subjects. However, from currently available data, PF-06817024 concentration-time profiles in CRSwNP patients are not expected to be different compared to healthy subjects.

Table 1. Summary of Serum PF-06817024 Pharmacokinetic Parameter Values Following Intravenous (IV) Infusion and Subcutaneous (SC) Administration, Study C0341001 (Preliminary Data)

	10 mg IV SD (HV)	30 mg IV SD (HV)	100 mg IV SD (HV)	300 mg IV SD (HV)	1000 mg IV SD (HV)	30 mg SC SD (HV)	300 mg IV SD (CRSwNP)
N, n^1, n^2	6, 6, 5	6, 6, 6	7, 7, 3[a]	6, 6, 6	6, 6, 5	6, 6, 6	11, 11, 1[b]
AUC_{inf} (µg·hr/mL)	4377 (28)	14590 (28)	44510 (22)	116000 (22)	421000 (11)	8579 (37)	122000
AUC_{inf} (dn) (µg·hr/mL/mg)	437.7 (28)	486.8 (28)	445.1 (22)	386.6 (22)	421 (11)	285.5 (37)	407
C_{max} (µg/mL)	2.395 (51)	12.26 (20)	35.44 (12)	97.49 (7.5)	313.2 (17)	2.471 (43)	89.79 (41)
C_{max} (dn) (µg/mL/mg)	0.2395 (51)	0.4091(20)	0.3544 (12)	0.3249 (7.5)	0.3132 (17)	0.0823 (43)	0.2994 (41)
T_{max} (hr)	3.00 (1.15-4.05)	1.76 (1.02-2.33)	2.00 (1.03-8.03)	2.00 (1.53-8.00)	1.78 (1.53-4.00)	338 (338-1080)	2.00 (1.00-170)
CL, CL/F (L/hr)	0.002283 (28)	0.002055 (28)	0.00225 (22)	0.002587 (22)	0.002375 (11)	0.003498 (37)	0.00246
$t_{1/2}$ (Days)	89.9 ±16.14	87.85 ±16.95	81.77 ±33.74	78.73 ±16.75	89.14 ±8.524	93.58 ±13.82	105

Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± standard deviation for $t_{½}$.
N = number of subjects in the treatment group; n^1 = number of subjects contributing to the summary statistics; n^2 = number of subjects with reportable $t_{½}$, AUC_{inf}, AUC_{inf} (dn) and CL (or CL/F); SD = single dose; HV = healthy volunteers; CRSwNP = chronic rhinosinusitis with nasal polyps patients; IV = intravenous; SC = subcutaneous; CL = Dose/AUC_{inf} for SD IV treatments; CL/F = Dose/AUC_{inf} for SD SC treatments.
[a] n^2 = 3 for subjects remained in the SD period.
[b] Individual subject values reported.

Preliminary data from this ongoing Phase 1 study show that the incidence of anti-drug antibodies (ADAs) in PF-06817024 treated subjects is low (approximately 10%), with no apparent dose dependency. Data from neutralizing antibody (NAb) assays are not currently available.

1.3. Rationale

1.3.1. Study Rationale

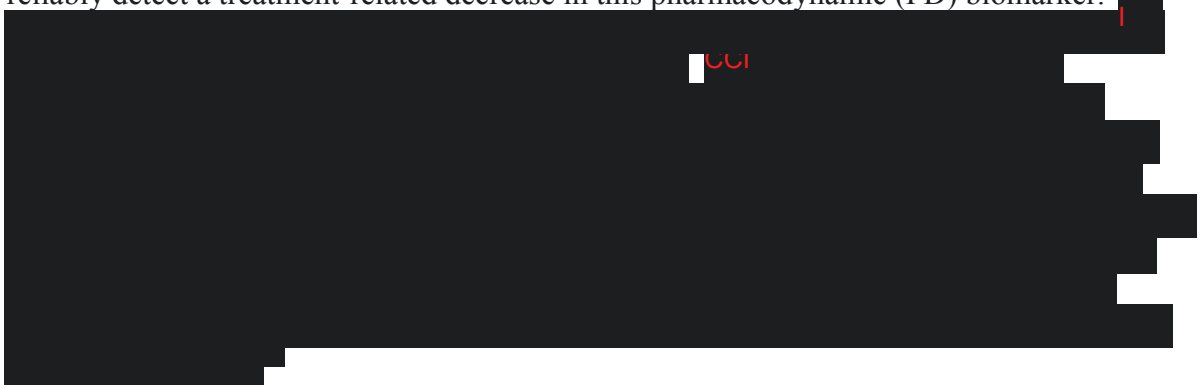
1.3.1.1. Parts 1 and 2

This is a first-in-human, placebo-controlled, double blind (pharmacist and sponsor open), single and multiple IV and SC dose study that will be conducted in two parts. Part 1 is a first-in-human, placebo-controlled, double blind, dose escalation study conducted in healthy subjects who may be mildly atopic. In Part 2, single doses of PF-06817024 will be given to one or more cohorts of patients with CRSwNP to enable initial evaluation of safety and tolerability in this patient population.

In all cohorts, the duration of the follow-up is selected to be 7 months after the last dose, which is ≥5 times the projected half-life of 41 days. If the emerging data project that half-life is longer than 41 days, the subjects will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit to cover approximately ≥5 times the observed half-life CCI [redacted] OR of sufficient duration to have projected exposures decrease below ADA drug tolerance levels CCI [redacted]

Part 1

Part 1 is a first-in-human, placebo-controlled, double blind (pharmacist and sponsor open), dose escalation study in healthy subjects who may be mildly atopic (see Section 3.1 for detailed study overview and Figure 1 for a schematic of the study design). As the current study is the first to dose PF-06817024 to humans, an escalating dose design is proposed with careful assessment and ongoing review of safety and analysis of pharmacokinetics of PF-06817024. The population selected for Part 1 of the study is healthy subjects who may be mildly atopic. For Part 1 Cohorts 1-4, subjects are required to be Phadiatop positive and have an IgE ≥50 kU/L (see Section 4.1 for inclusion/exclusion criteria). ImmunoCAP Phadiatop is a blood test designed to differentiate between atopic and non-atopic subjects. This test demonstrates the presence of specific IgE antibodies to common inhalant allergens. Total IgE levels ≥50 kU/L was selected as a threshold to provide adequate levels of IgE to reliably detect a treatment-related decrease in this pharmacodynamic (PD) biomarker. CC



The study design consists of single ascending doses (SAD) with selected cohorts rolling into a multiple dose component to receive a second dose at a minimum of 4 weeks (maximum of 12 weeks) after the first dose (see Section 3.1). The design is chosen to optimize the efficiency of the study, relative to the traditional design of a separate sequential multiple ascending dose study, without compromising subjects' safety. In general, single dose escalation will be conducted with IV administration. Subjects from the selected cohorts will receive a single IV dose of PF-06817024. After safety and PK at this dose and the next higher dose level have been confirmed, and sufficient exposure coverage for the second dose has been predicted, the same subjects will receive a second dose at the same dose level as the first dose (at a minimum of 4 weeks after the first dose) to evaluate the safety and PK of multiple doses of PF-06817024. A single cohort will receive one or more SC dose levels (at a minimum of four weeks apart) to allow evaluation of the safety and PK with SC administration. This cohort will similarly not be given a second dose until PK and safety of the first SC dose have been established, and sufficient exposure coverage for the second dose at a different dose level (based on safety and PK from an IV cohort) have been predicted. Please refer to Section 3.3 for details of dose escalation rules and criteria for administration of the second dose for multiple dose cohorts.

Part 2

Part 2 is a placebo-controlled, double blind (pharmacist and sponsor open) evaluation of single IV doses in one or more cohorts of patients with CRSwNP to assess the safety, tolerability, PK, CCI of PF-06817024 in this population. Part 2 dosing will start after the safety, tolerability and PK at the same or higher dose has been established in Part 1. Two cohorts of subjects with CRSwNP are planned. A decision on the number (1 or 2) of cohorts will be made in light of emerging safety, tolerability, PK, CCI of PF-06817024. Subjects in each cohort will be randomized in either a 1: 1 or 2: 1 (PF-06817024 : placebo) ratio, depending on the number of cohorts and the emerging data. Up to approximately 10 active (per dose) and approximately 15 placebo (overall) subjects will be enrolled in Part 2 for a planned total of up to approximately 35 subjects. CCI

CCI As the same or higher dose of PF-06817024 will have already been administrated to subjects in Part 1, and safety, tolerability, and PK thereby established prior to the start of Part 2, the reduction in the duration of clinical confinement and the reduction in the number of follow-up visits (but not the duration of follow-up) for this cohort is justified. CCI

CCI Overall, inclusion of patient cohorts in the first in human (FIH) study will provide key data in a timely manner to inform future clinical development.

1.3.1.2. Part 3

Part 3 is a placebo-controlled, double blind, pharmacist and sponsor open, cohort to evaluate safety, tolerability, PK, immunogenicity, CCI of repeat doses of PF-06817024 administered to subjects with moderate to severe AD. Approximately 20 subjects are planned to be enrolled in this cohort. Subjects will be randomized to receive PF-06817024 or placebo in a 3: 1 ratio (PF-06817024: placebo). Additional subjects up to a total of approximately 32 may be enrolled in a 3: 1 ratio (PF-06817024: placebo) CCI . Subjects randomized to PF-06817024 will receive a loading dose of 600 mg IV on Day 1, followed by 3 doses of 300 mg IV every 4 weeks (last dose being on Week 12). Placebo subjects will receive 4 IV doses of matching placebo every 4 weeks. This dosing regimen is expected to decrease the time to steady state

exposure and provide nearly complete target coverage CCI [redacted] based on currently available in vitro and clinical data.

CCI [redacted]

1.3.1.3. Parts 1, 2, and 3

The duration of the follow-up is selected to be at least 1 year after the last dose of study drug (at Week 12 for Part 3), which is ≥3 times the preliminary estimated half-life of approximately 90 days and >80% exposure (AUC) based on emerging data for the earlier cohorts of healthy subjects, which is adequate to estimate the elimination half-life. If the emerging data project that pharmacologically relevant exposure will extend significantly longer than 1 year, the subjects will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last planned regular visit until one of the following criteria has been met:

- The follow up period from the last dose of study drug is approximately ≥5 times the observed half-life; OR
- CCI [redacted]
- The period since the last dose of study drug is of sufficient duration to have projected exposures decrease below ADA drug tolerance levels; OR
- CCI [redacted]

CCI [redacted]

The Sponsor will inform the sites when subjects may be discharged from the study based on review of emerging data indicating that one or more of the above criteria are met. Current guidance is that subjects will be in the study for 5 half-lives ie, about 450 days from the last dose.

1.3.2. Dose Rationale

1.3.2.1. Part 1

The approach for dose selection for the 1st part of this study was based on all relevant information obtained in non-clinical pharmacology and toxicity studies and in absence of any clinical data. Considering that chronic exposure is more relevant for the mechanism of action of PF-06817024, and the dosing interval for the multiple dose component of this study (a minimum of 4 weeks and maximum of 12 weeks apart) will be different from that in the Good Laboratory Practices (GLP) monkey toxicity study (every 3 weeks), average concentration over dosing interval (C_{av}) is chosen to be the PK exposure limit. In addition, since the no observed adverse effect level (NOAEL) is the maximum dose evaluated in the 13 weeks GLP toxicity study in monkeys, the PK exposure limit will be set to be C_{av} of 442.5 µg/mL (calculated as AUC_{504} divided by 504 hours), which is 1/10th of the mean C_{av} at the NOAEL dose.

Linear PK is assumed in human PK projection. Projected C_{max}, AUC_{inf}, C_{av} and the safety margin relative to the PK stopping limit are listed in Table 2 for the planned dose levels, including single and multiple dose administration.

Table 2. Predicted Human Exposure and Safety Margins Relative to Exposure Limits at Planned Dose Levels for Part 1

Regimen and Route of administration	Proposed Human Dose[a] (mg)	Predicted Human PK			Safety Margin[e]
		C_{max} (µg/mL)	AUC[c] (µg•hr/mL)	C_{av}[d] (µg/mL)	C_{av}
SD IV	10	4.7	2925	1.8	247.2
SD IV	30	14.2	8774	5.4	82.7
SD IV	100	47.2	29247	17.9	24.8
SD IV	300	141.5	87741	53.5	8.3
SD IV	1000	471.7	292470	178.4	2.5
SD IV	2000	943.4	584940	356.7	1.2
MD[b] IV	100	58.9	19445	27.0	16.4
MD[b] IV	300	176.7	58316	81.0	5.5
MD[b] IV	1000	588.9	194430	270.0	1.6
1st dose SC[f]	100	14.5	22813	12.0	36.9
2nd dose SC[f]	300[d]	52.3	31604	43.9	10.1

IV = Intravenous; MD = multiple dose; ND = not determined; SD = single dose.

a. Depending on the safety and PK data available, dose escalation may be adjusted to doses other than those outlined and will follow dose escalation and stopping rules (Section 3.2).

b. Total of 2 doses are given 30 days apart in human PK simulation (τ=720 hr), PK parameters are derived from concentration time profile after the second dose.

c. AUC_{inf} for single or 1st dose and AUC_{0-720} for the 2nd dose.

d. Human C_{av} is calculated as $AUC_{0-720}/720$.

e. Based on PK stopping limit of C_{av}= 442.5 µg/mL.

f. The SC cohort receives 100 mg as the first dose and 300 mg as the second dose.

CCI [redacted] With single IV dosing, the 10 mg proposed starting dose is estimated to provide an exposure margin of 247.2-fold for C_{av}. Analysis using the human equivalent dose (HED) approach indicates that the margin for proposed starting dose of 10 mg is 726-fold for a 75 kg individual relative to NOAEL of 300 mg/kg/dose (IV) in cynomolgus monkeys. The highest proposed IV infusion dose of 2000 mg is estimated to provide an exposure margin of 1.2-fold for C_{av}.

The multiple dose range planned is 100 mg to 1000 mg IV at a minimum of 4 weeks apart for a total of 2 doses. The starting dose of 100 mg IV for the multiple dose period is predicted to have a safety margin for C_{av} of 16.4-fold (Table 2). At the highest proposed dose of 1000 mg IV the safety margin for C_{av} is 1.6-fold.

Intermediate or lower doses may be evaluated instead of or in addition to the planned dose level(s). Dose escalation may be stopped at any time. Cohorts and/or additional subjects may be added if unplanned intermediate doses are to be evaluated for safety, PK, or CC [redacted] reasons. For any dose administered, the predicted exposure will not exceed the PK stopping limit.

1.3.2.2. Part 2

Single IV doses of PF-06817024 in one or two cohorts of patients with CRSwNP will be studied in Part 2. The need for a second dose and the doses selected for each cohort will be based on the emerging data from the study and will not exceed the highest dose tested in Part 1 that is found to be safe and well-tolerated.

1.3.2.3. Part 3

The dose rationale for Part 3 was based on emerging preliminary clinical data from the other parts of this study. The proposed dosing regimen of PF-06817024 for Part 3 consists of a single 600 mg IV loading dose followed by 3 doses of 300 mg IV every 4 weeks.

As discussed in Section 1.2.5.2 and presented in Table 1, the emerging clinical data from cohorts in Part 1 show that the half-life of PF-06817024 is approximately 79-94 days. Preliminary modeling using interim PK CCI [redacted] data available at the time of Protocol Amendment 4 from the healthy subject cohorts suggested that monthly dosing of PF-06817024 may be required for continuous, high level, suppression of IL-33 levels, despite the long half-life of PF-06817024. In order to shorten the onset of suppression of IL-33 levels CCI [redacted], a 600 mg loading dose of PF-06817024 is proposed in this study. The proposed dose of PF-06817024, the number doses, and/or the dosing interval may be modified in light of emerging safety, tolerability, PK, CCI [redacted] data in this population.

Assuming that PF-06817024 PK is similar between healthy subjects and AD patients, the average concentration (C_{av}) during the first and the last dosing interval of the proposed dosing regimen was predicted to be 84.1 μg/mL and 132.5 μg/mL respectively. Thus, the proposed dosing paradigm will provide safety margins of approximately 5.3-fold and 3.3-fold relative to the 600 mg loading dose and the third dose of 300 mg (due to accumulation the margin for 300 mg is less than the 600 mg), respectively, with respect to the toxicokinetic stopping limit of C_{av}=442.5 μg/mL.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

Part 1

- For the SAD component, the objective is to determine the safety and tolerability of single IV infusions and single SC doses of PF-06817024 in healthy subjects who may be mildly atopic.

- For the multiple dose component, the objective is to determine the safety and tolerability following administration of multiple IV and, potentially, repeat SC doses of PF-06817024 in healthy subjects who may be mildly atopic.

Part 2

- To determine the safety and tolerability of single IV infusions of PF-06817024 in patients with chronic rhinosinusitis with nasal polyps.

Part 3

- To determine the safety and tolerability of repeat IV doses of PF-06817024 in subjects with moderate to severe AD.

2.1.2. Secondary Objectives

Part 1

- To characterize the PK profile of PF-06817024 following single IV infusions and single SC doses of PF-06817024 in healthy subjects who may be mildly atopic.

- To characterize the PK profile of PF-06817024 following multiple IV and, potentially, SC doses of PF-06817024 in healthy subjects who may be mildly atopic.

- To evaluate immunogenicity of PF-06817024 in healthy subjects who may be mildly atopic.

Part 2

- To characterize the PK profile of PF-06817024 following single IV infusions of PF-06817024 in patients with chronic rhinosinusitis with nasal polyps.
- To evaluate immunogenicity of PF-06817024 in patients with chronic rhinosinusitis with nasal polyps.

Part 3

- To characterize the PK profile of PF-06817024 following repeat IV doses in subjects with moderate to severe AD.
- To evaluate immunogenicity of PF-06817024 in subjects with moderate to severe AD.

CCI

2.2. Endpoints

2.2.1. Primary Endpoints

Parts 1 and 2

- Incidence, severity and causal relationship of treatment emergent adverse events (TEAEs) and withdrawals due to TEAEs through the end of the study.

- Incidence and causal relationship of treatment emergent serious adverse events (SAEs) through the end of the study.

- Incidence and magnitude of abnormal chemistry, hematology, and urinalysis laboratory findings through the end of the study.

- Abnormal and clinically relevant changes in vital sign parameters through the end of the study.

- Abnormal and clinically relevant changes in electrocardiogram (ECG) parameters through the end of the study.

Part 3

- Incidence, severity and causal relationship of treatment emergent adverse events (TEAEs) and withdrawals due to TEAEs through the end of the study.

- Incidence and causal relationship of treatment emergent serious adverse events (SAEs) through the end of the study.

- Incidence and magnitude of abnormal chemistry, hematology, and urinalysis laboratory findings through the end of the study.

- Abnormal and clinically relevant changes in vital sign parameters through the end of the study.

- Abnormal and clinically relevant changes in electrocardiogram (ECG) parameters through the end of the study.

2.2.2. Secondary Endpoints

Parts 1 and 2

- PK parameters derived from serum PF-06817024 concentrations after single dose or multiple doses of PF-06817024, through the end of the study as data permits:

- Cohorts receiving single dose (IV infusions and SC doses): C_{max}, dose normalized $C_{max}(C_{max}(dn))$, time to reach maximum concentration (T_{max}), area under the concentration-time profile from time zero to infinity (AUC_{inf}), area under the concentration-time profile from time zero to the time of the last quantifiable concentration (AUC_{last}), area under the concentration-time curve within dosing interval (AUC_{tau}), $AUC_{tau}(dn)$, C_{av} , $t_{½}$, mean residence time (MRT), apparent volume of distribution (Vz/F) (SC only), apparent clearance (CL/F) (SC only),V_{ss} (IV only), and clearance (CL) (IV only).

- Cohorts receiving multiple doses (Part 1 only):
  - First Dose: C_{max}, T_{max}, AUC_{tau}, C_{av}, $C_{max}(dn)$ and $AUC_{tau}(dn)$.
  - Last (ie, second) Dose: C_{max}, $C_{max}(dn)$, T_{max}, AUC_{tau}, $AUC_{tau}(dn)$, C_{av}, $t_{½}$, MRT, Vz/F (SC only), V_{ss} (IV only), CL/F (SC only), CL (IV only), C_{min}, observed accumulation ratio for C_{max} ($R_{ac}(C_{max})$), and $R_{ac}(AUC_{tau})$.
- Incidence of ADA immune response through the end of the study.

Part 3

- PF-06817024 plasma concentrations in subjects with moderate to severe AD.
- Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) in subjects with moderate to severe AD.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI

CCI

3. STUDY DESIGN

3.1. Study Overview

The study was originally designed to be a two-part Phase 1, randomized, double-blind (sponsor and pharmacist unblinded), placebo-controlled, dose escalating clinical study with single and multiple doses of PF-06817024 in healthy subjects who may be mildly atopic (Part 1: Cohorts 1-7) and of one or two single doses of PF-06817024 in patients with chronic rhinosinusitis with nasal polyps (Part 2: Cohorts 8 and 9).

Amendment 4 adds Part 3, consisting of a single cohort (Cohort 13) of subjects with moderate – severe AD. Cohort 13 is a randomized, double-blind (sponsor and pharmacist unblinded), placebo-controlled, multiple dose evaluation of PF-06817024, as indicated in Figure 2.

Figure 1. Study Design Schematic

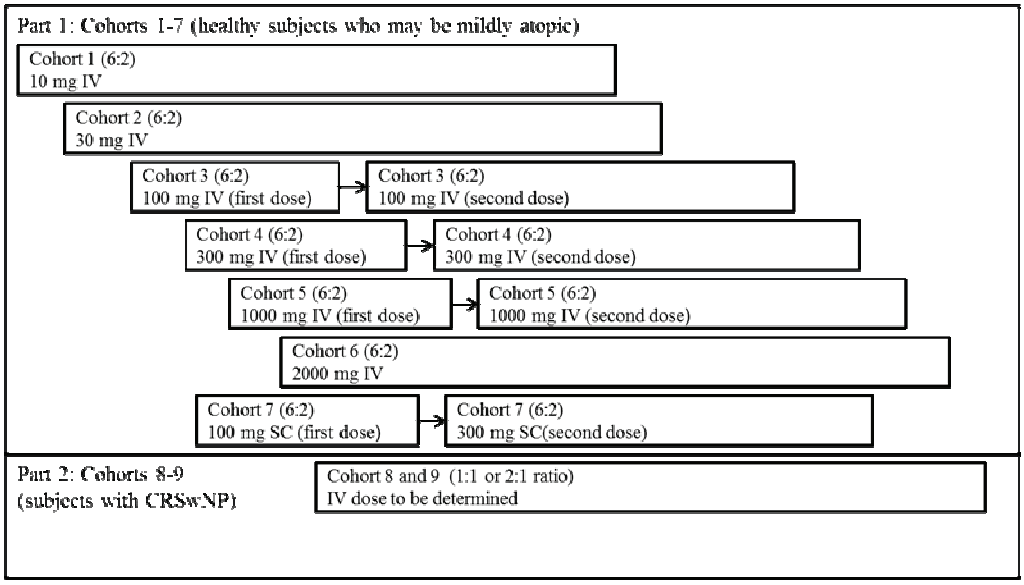
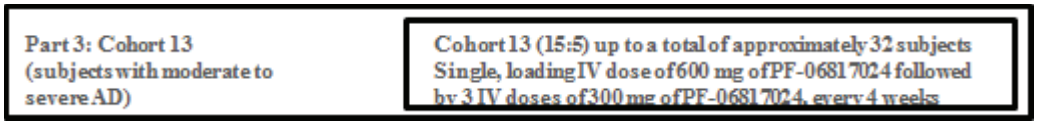


Figure 2. Study Design Schematic for Part 3



Cohorts 3-5 and Cohort 7: second dose occurs at a minimum of 4 weeks and maximum of 12 weeks after the first dose. Second dose is only administered if protocol safety criteria are met (see Section 3.3).

Except for the starting dose, the actual doses for other cohorts may be changed but will follow dose escalation and stopping rules (Section 3.2).

3.1.1. Part 1:

Approximately 56 healthy subjects who may be mildly atopic will be enrolled into the proposed cohorts listed below. This study starts with a single ascending dose (SAD) escalation design, with selected cohorts rolling into a multiple dose component. Up to approximately 80 healthy subjects who may be mildly atopic will be enrolled if separate multiple dose cohort(s) are required. Subjects may only participate in 1 cohort.

The study will be conducted at one or more clinical research centers. The above schematic (Figure 1) demonstrates the study design with the select SAD cohorts rolling over into the multiple dose component. Depending on the safety, CCI and pharmacokinetic data available, dose escalation may be adjusted to doses other than those planned in the study. Intermediate doses can be evaluated instead of or in addition to the planned dose levels.

A possible dosing scenario is included in the schematic.

Subjects will be sequentially randomized into IV cohorts (Cohorts 1 through 6) with Cohort 7 dosing occurring based on the criteria described in Section 3.2 (see Figure 1) as follows:

- Cohort 1 (n=8): 10 mg active (n=6) or placebo (n=2), IV.
- Cohort 2 (n=8): 30 mg active (n=6) or placebo (n=2), IV.
- Cohort 3 (n=8): 100 mg active (n=6) or placebo (n=2), IV x 2 doses.
- Cohort 4 (n=8): 300 mg active (n=6) or placebo (n=2), IV x 2 doses.
- Cohort 5 (n=8): 1000 mg active (n=6) or placebo (n=2), IV x 2 doses.
- Cohort 6 (n=8): 2000 mg active (n=6) or placebo (n=2), IV.
- Cohort 7 (n=8): 100 mg (first dose) followed by 300 mg (second dose) active (n=6) or placebo (n=2), SC.

Within 28 days of successful completion of the screening process, eligible subjects for the SAD period of the study will be enrolled and randomized to receive a single IV infusion of PF-06817024 or placebo. In order to mitigate any unanticipated acute safety risks within the SAD portion of the study (Cohorts 1 through 6), the first two subjects will be dosed (one receiving PF-06817024 and one receiving placebo). After a safety pause of at least 24 hours in duration, the remaining subjects within the cohort may be dosed. Cohorts 1 through 6 will be enrolled sequentially in a dose escalating fashion starting from the lowest dose proposed (10 mg). Subjects will be admitted into the clinic approximately 1 day prior to dosing and are required to remain in the clinic through completion of Day 5 evaluations. Subjects in the single dose cohorts will return for outpatient follow-up visits per Schedule of Activity Table B (SoA Table B).

The multiple dosing component of the study will consist of those subjects who received a single dose of PF-06817024 or placebo in Cohorts 3, 4, 5 and 7. Following the review of sufficient safety and PK data from a higher SAD dose, these subjects will be rolled over to receive a second dose of PF-06817024 or placebo at a minimum of 4 weeks and a maximum of 12 weeks after the first dose is received. If Cohorts 3, 4, or 5 are not able to be rolled over to receive a second dose between 4 and 12 weeks, separate IV multiple dose cohort(s) may be implemented (Cohorts 10 through 12, see below). Cohort 7 is planned to receive a SC administration of a lower dose of PF-06817024 followed by a second SC administration of a higher dose of PF-06817024 at a minimum of 4 weeks and maximum of 12 weeks after the first dose. Refer to Section 3.3 for additional information.

Subjects in the multiple dose cohorts (Cohorts 3 through 5 and Cohort 7) will be confined to the clinic from the day prior to dosing and through completion of Day 5 evaluations (minimum of 96 hours post first dose administration), and 48 hours after the second dose administration. Subjects will return for outpatient follow-up visits per the Schedule of Activities (SoA) Table C.

Throughout the study, adverse events (AEs) will be solicited, with specific attention to infusion and injection site reactions (ISR) and those linked to immune reactions. ADA responses will be monitored from samples collected at baseline and at the additional times post-dose as specified in the SoA. Samples found to be positive in the ADA assay will be further evaluated for neutralizing antibody (NAb) activity. Subjects having an unresolved adverse event that is possibly related to an ADA immune response will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit for up to 12 months after last drug administration or until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and Sponsor concurs with the investigator's assessment (see SoA). Subjects in any cohort may be confined beyond the period defined in the schedule of activities at the discretion of the investigator to accommodate the frequency of required follow-up. Subjects who are withdrawn from study for reasons other than safety may be replaced at the discretion of the sponsor.

If operational logistics or safety analysis prohibits any of the pre-specified cohorts from receiving their second dose (eg, required safety or PK data are not available in time for the second dose) as planned for Cohorts 3-5 or Cohort 7, or the Sponsor determines not to proceed with all multiple dose cohorts based upon the review of emerging data, the affected cohort(s) will return for outpatient follow-up visits per the SoA Table B. Additional subjects may be randomized into the following cohorts (Cohorts 10-12) as needed to complete the multiple dose portion of the study. The additional multiple dose cohorts would not be randomized until the dosing criteria for multiple dose cohorts (see Section 3.3) were completed:

- Cohort 10 (n=8): 100 mg active (n=6) or placebo (n=2), IV x 2 doses.
- Cohort 11 (n=8): 300 mg active (n=6) or placebo (n=2), IV x 2 doses.
- Cohort 12 (n=8): 1000 mg active (n=6) or placebo (n=2), IV x 2 doses.

The additional multiple dose cohorts would follow the SoA Tables A and C.

3.1.2. Part 2:

One or more cohorts of CRSwNP patients will receive a single dose of PF-06817024. Randomization will occur after safety data from Day 8 and PK data through at least Day 5 of the same or higher dose in Part 1 of the study has been reviewed and deemed safe.

- Cohorts 8 and 9: Subjects in each cohort will be randomized in either a 1 : 1 or 2 : 1 (PF-06817024: placebo) ratio, depending on the number of cohorts and the emerging data. Up to approximately 10 active (per dose) and approximately 15 placebo (overall) subjects will be enrolled in Part 2 for a planned total of up to approximately 35 subjects.

- Within 28 days of successful completion of the screening process, eligible CRSwNP patients will be admitted into the clinic approximately 1 day prior to dosing and are required to remain in the clinic through completion of Day 2 evaluations. Patients will return for outpatient follow-up visits per SoA Table D.

3.1.3. Part 3

- Part 3 will consist of a single cohort of subjects with moderate to severe AD (Cohort 13). Approximately 20 subjects in this cohort will be randomized to receive PF-06817024 or placebo in a 3: 1 ratio (PF-06817024: placebo). Additional subjects up to a total of approximately 32 may be enrolled in a 3: 1 ratio (PF-06817024: placebo) CCI [redacted] Subjects in this cohort randomized to PF-06817024 will receive a planned dosing regimen consisting of a 600 mg IV loading dose followed by 3 doses of 300 mg IV every 4 weeks.

- Within 42 days of successful completion of the screening process, eligible subjects will have baseline assessments performed, be randomized into the study, and receive the first dose of study drug. Subjects will return for follow-up visits as indicated in the SoA Table E. Due to the expected duration of the visits at which investigational product is administered, namely at Week 0 (Day 1), Week 4 (Day 29), Week 8 (Day 57), and Week 12 (Day 85), at the discretion of the Investigator, pre-dose activities (as specified in SOA Table E footnote "b" and Section 6.2) on Day 1, Day 29, Day 57, Day 85 may be performed on the preceding day (ie, on Day 0, Day 28, Day 56, Day 84) as inpatient in clinical site or outpatient.

3.2. Dose Escalation and Stopping Rules (Part 1)

During the SAD period, escalation to subsequent dose levels will occur following the sponsor's review of the available safety data from at least 4 subjects receiving active treatment and 1 receiving placebo through at least study Day 8 and PK data through at least Day 5 from the current cohort. The first dose of Cohort 7 (the SC cohort) can be administered after safety/tolerability data from at least 4 subjects receiving active treatment and 1 receiving placebo through Day 8 and PK data through Day 5 of a same or higher IV dose that has been reviewed and considered to be safe. The cumulative safety, PK and immunogenicity data available from previous cohorts will also be reviewed. There will be a minimum of 10 days between cohorts for dose escalation. Dose escalation stopping rules will be used to determine whether the maximum 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 investigators' decision to stop dose escalation. If dose escalation is stopped due to any of the criteria noted below, additional cohorts may receive the same or lower doses of the investigational compound.

Criteria for terminating dose escalation:

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

- Dosing will be paused for any treatment emergent serious adverse event (SAE) that occurs in a subject receiving active treatment until causality is fully assessed by the principal investigator (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, dosing will either cease, or the SAE will be evaluated by the sponsor's protocol review committee (or similar group of reviewers) 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 subjects 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 for the treatment group reaches or exceeds the PK stopping limit of C_{av} of 442.5 μg/mL.

- If, based on the observed data, the group average C_{av} of the next planned dose is projected to exceed 442.5 μg/mL, the PK stopping limit, 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 previous doses were well tolerated and after satisfactory review of the available safety and pharmacokinetic data.

3.3. Dosing Criteria for Multiple Dose Cohorts (Part 1)

Initiation of the multiple dose safety/tolerability and PK evaluation is planned to begin at the 100 mg IV dose level in Cohort 3 (Day 32, second dose). The Sponsor and PI will review criteria in Table 3 prior to progression to the second dose within Cohorts 3-5, 7 and 10-12 if implemented.

Table 3. Second Dose Prerequisites

Study Cohort	Second Dose Prerequisites
1	N/A (single dose cohort)
2	N/A (single dose cohort)
3 (10 if implemented)	Day 8 safety and Day 5 PK data from first dose in Cohort 4* Cumulative safety and PK from Cohorts 1-3
4 (11 if implemented)	Day 8 safety and Day 5 PK data from first dose in Cohort 5* Cumulative safety and PK data from Cohorts 1-4 Available safety through at least 7 days following second dose of Cohort 3 (Cohort 10 if implemented)*
5 (12 if implemented)	Day 8 safety and Day 5 PK data from first dose in Cohort 6* Cumulative safety and PK data from Cohorts 1-5 Available safety through at least 7 days following second dose of Cohort 4 (Cohort 11 if implemented)*
6	N/A (single dose cohort)
7	First SC dose has been reviewed and considered safe Day 8 safety and Day 5 PK data from the same or higher IV dose *
8	N/A (single dose cohort)
9	N/A (single dose cohort)

*at least 4 subjects receiving active treatment and 1 receiving placebo

4. SUBJECT SELECTION

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

4.1. Inclusion and Exclusion Criteria

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

4.1.1. Inclusion Criteria (Parts 1 and 2)

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

1. ***Part 1***: Healthy female subjects of non-childbearing potential and/or male subjects who, at the time of screening, are between the ages of 18 and 55 years, inclusive. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG or clinical laboratory tests.

   Part 2: Female subjects of non-childbearing potential, female subjects of childbearing potential who have a documented bilateral tubal ligation or bilateral salpingectomy and/or male subjects, who at the time of screening, are between the ages of 18 and 65 years, inclusive.

   Parts 1 and 2: Female subjects of non-childbearing potential must meet at least one of the following criteria:

a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

b. Have undergone a documented hysterectomy and/or bilateral oophorectomy.

c. Have medically confirmed ovarian failure to be reviewed with the Sponsor.

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

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

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

4. Quantiferon- Tuberculosis (TB) test and chest X-ray with no evidence of current, active TB or previous inactive TB, general infections, heart failure, malignancy, or other clinically significant abnormalities taken at Screening or within 3 months prior to Screening. Chest X-ray to be read by a qualified radiologist.

5. ***Part 1 (Cohorts 1 through 4 only)***: Subjects who are Phadiatop positive (historical positive test results with appropriate documentation are acceptable). (Note: any replacement subjects for Cohorts 1 through 4 are exempt from this inclusion criteria).

6. ***Part 1 (Cohorts 1 through 4 only)***: Subjects with at least one test result of IgE ≥50 kU/L (≥120 ng/mL) within the past 6 months. (Note: any replacement subjects for Cohorts 1 through 4 are exempt from this inclusion criteria).

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

   Part 2: Body Mass Index (BMI) of 17.5 to 35 kg/m^2; and a total body weight >50 kg (110 lbs).

8. ***Part 2 only***: A minimum bilateral Nasal Polyp Score (NPS) of 5 out of a maximum score of 8 (with a unilateral score of at least 2 for each nostril) from the screening endoscopy (see Appendix 3).

9. ***Part 2 only***: Presence of at least two of the following symptoms prior to screening: nasal blockade/obstruction/congestion; nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell.

4.1.1.1. Inclusion Criteria for Part 3 only

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

2. Male or female subjects, who at the time of screening, are between the ages of 18 and 75 years, inclusive. Subjects above 70 years need to be discussed with the sponsor.

   Female subjects of non-childbearing potential must meet at least one of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy.

   c. Have medically confirmed ovarian failure to be reviewed with the sponsor.

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

3. All female subjects of child bearing potential and male subjects who, in the opinion of the investigator, are able to father children and are sexually active and whose partners are at risk for pregnancy must agree to use at least one highly effective method of contraception consistently and correctly for the duration of the active treatment period (date of first dose) through the end of the study (until discharged from the study). Additionally, males must use a condom to prevent possible transmission of study drug to a partner. See Section 4.3.2.4.

4. Negative Quantiferon TB (QFT-TB) Gold at time of screening.

5. Chest X-ray with no evidence of general infections (including evidence of active TB), heart failure, malignancy, or other clinically significant abnormalities taken at Screening or within 3 months prior to Screening. Chest X-ray to be read by a qualified radiologist.

6. Body Mass Index (BMI) of 17.5 to 40 kg/m^2; and a total body weight >50 kg (110 lbs).

7. Must have the following atopic dermatitis criteria:

   a. Have a clinical diagnosis of chronic atopic dermatitis (also known as atopic eczema) for at least 1 year prior to Day 1 and have the diagnosis of AD confirmed (Hanifin and Rajka criteria of AD[52] refer to Appendix 16) at the Screening visit.

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 otherwise have been medically inadvisable (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 the screening and baseline visits).

8. Must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps, or other ultraviolet light sources during the study.

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

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

4.1.2. Exclusion Criteria (Parts 1 and 2)

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

1. ***Part 1***: Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, autoimmune, or neurologic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

   Part 2: Evidence or history of clinically significant hematological, renal, endocrine, gastrointestinal, cardiovascular, hepatic, psychiatric, autoimmune, or neurologic disease.

2. Subjects with a history of or current positive results for any of the following serological tests:

   - ***Part 1 (Cohorts 1 through 4 only)***: Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb).

   - ***Part 1 and Part 2:*** anti-Hepatitis C antibody (HCV Ab) or human immunodeficiency virus (HIV).

   - ***Part 1 (Cohorts 5 and later) and Part 2***: Subjects will be screened for Hepatitis B virus infection and will be excluded if positive for Hepatitis B surface antigen (HBsAg). Subjects with HBsAg negative testing but who test positive for hepatitis B core antibody (HBcAb) must have further testing for hepatitis B

surface antibody (HBsAb). If HBsAb is negative, the subject will be excluded from the study.

3. Subjects with a history of anaphylaxis. ***Part 2 only***: subjects with only sensitivity and/or anaphylaxis to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may be enrolled, if in the opinion of the investigator, the subject is aware of the hypersensitivity and avoids aspirin/NSAIDs.

4. History of recent active infections within 28 days prior to the screening visit. ***Part 2 only***: subjects with a history of sinus infections that have not required antibiotic treatment within 28 days prior to the screening visit are permitted to enter the study. Note: patients may be rescreened after infection resolves.

5. Subjects with a fever within 7 days prior to dosing.

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

7. 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).

8. Part 1 and Part 2: Pregnant female subjects, breastfeeding female subjects, male subjects with partners currently pregnant, or male or female subjects pursuing artificial reproductive technologies including but not limited to sperm/egg donation.

   Part 1: Female subjects of childbearing potential, male subjects able to father children who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study (see Section 4.3.1.5, Lifestyle Guidelines).

   Part 2: Female subjects of childbearing potential unless they have a documented bilateral tubal ligation or bilateral salpingectomy, male subjects able to father children who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study (see Section 4.3.1.5, Lifestyle Guidelines).

9. A positive urine drug screen (see Section 7.1.1.1).

10. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males; (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor) within 6 months of Screening.

11. ***Part 1***: Screening supine blood pressure ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If blood pressure (BP) is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.

Part 2: Screening supine blood pressure ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic), following at least 5 minutes of supine rest. If blood pressure (BP) is ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.

12. Screening supine 12-lead ECG demonstrating QTc >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc or QRS values should be used to determine the subject's eligibility.

13. ***Part 1 only***: Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study treatment. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

    Herbal supplements and hormone replacement therapy must be discontinued at least 28 days prior to the first dose of study treatment.

14. ***Part 1 only***: Subjects with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:

    - Aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT) **or** alanine transaminase (ALT)/serum glutamic pyruvic transaminase (SGPT) ≥1.5x upper limit of normal (ULN);

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

15. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to dosing.

16. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

17. Severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

The following additional exclusion criteria for ***Part 2 only***:

18. Subjects with a history of allergic reaction to topical lidocaine or topical oxymetazoline.

19. Subjects taking topical oxymetazoline (outside of study procedures: nasal endoscopy).

20. Subjects treated with anti-immunoglobulin E (IgE) therapy (omalizumab) or anti-IL-5 (mepolizumab) within 130 days prior to Screening.

21. Subjects receiving systemic corticosteroids within 6 weeks before screening or scheduled to receive systemic corticosteroids during the study period for another condition. Subjects 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. See Exclusion Criteria 28 for additional asthma exacerbation corticosteroid restrictions.

22. Subjects taking leukotriene antagonists/modifiers unless subject has been taking such an agent continuously for at least 28 days prior to Screening.

23. Subjects taking monoclonal antibody (mAB) and/or immunosuppressive treatment, excluding specific agents discussed above.

24. Subjects with a history of helminthic infestation or resident/recent travel from an endemic area within 90 days prior to Screening.

25. Subjects with a sino-nasal outcome test (SNOT-22) <7.

26. Subjects who have undergone any nasal surgery (including polypectomy) within 6 months before screening or have had more than 5 sinonasal surgeries in the past 10 years of which no more than 2 were surgeries with major changes to the lateral wall structure of the nose.

27. Subjects with a history of prior radiation exposure for research purposes within the past year where participation in this study would place them over the FDA limits for annual radiation exposure. This guideline is an effective dose of 5 rem received per year.

28. Subjects with a history of asthma having **any** of the following:

- Forced Expiratory Volume (FEV_1) <60% predicted as documented via spirometry (acceptable from up to 3 months prior to screening).

- An asthma exacerbation requiring systemic (oral and/or parenteral) steroid treatment within 2 months prior to screening or requiring hospitalization for >24 hours for treatment of asthma within 3 months prior to screening.

- Are on a dose of greater than 1000 μg fluticasone, or an equivalent inhaled corticosteroid, per day.
- A supplemental oxygen requirement.
- A diagnosis of allergic fungal sinusitis/allergic fungal rhinosinusitis.

4.1.2.1. Exclusion Critieria Part 3 only

1. Pregnant female subjects, breastfeeding female subjects, male subjects with partners currently pregnant, or male or female subjects pursuing artificial reproductive technologies including but not limited to sperm/egg donation (see Section 4.3.2.4, Lifestyle Guidelines).

   Female subjects of childbearing potential, male subjects able to father children who are unwilling or unable to use at least one highly effective method of contraception as outlined in this protocol for the duration of the study (see Section 4.3.2.4, Lifestyle Guidelines).

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

3. 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.

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

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

6. Have evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, lupus) at the time of Day 1 that would interfere with evaluation of atopic dermatitis or response to treatment.

7. Have a history of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1 (for exception regarding latent Tuberculosis (TB) infection see Inclusion Criterion 4 and 5 in Section 4.1.1.1 or skin infections that lead to hospitalizations see Exclusion Criterion 8).

8. Have active chronic or acute skin infection (except latent TB infection see Inclusion Criterion 4 and 5 in Section 4.1.1.1) 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 subjects may be rescreened after infection resolves.

9. Subjects with a history of helminthic infestation or resident/recent travel from an endemic area within 90 days prior to Screening

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

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

12. Subjects will be screened for Hepatitis B virus infection and will be excluded if positive for Hepatitis B surface antigen (HBsAg). Subjects with HBsAg negative testing but who test positive for hepatitis B core antibody (HBcAb) must have further testing for hepatitis B surface antibody (HBsAb). If HBsAb is negative, the subject will be excluded from the study

13. Subjects positive for HCVAb are to be excluded unless known to have been treated with a known curative therapy and negative for HCV [redacted].

14. Human immunodeficiency virus (HIV) positive subjects will be excluded.

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

16. Subjects with a history of anaphylaxis with the following exceptions: subjects 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 subject is aware of the hypersensitivity and avoids -the problematic allergen. Subjects must carry appropriate treatment for anaphylaxis and must know how to manage the anaphylactic reactions.

17. Subjects with a fever within 7 days prior to dosing.

18. A positive urine drug screen except marijuana where use is permitted by local law and regulations (see Section 7.1.1.1).

19. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males; (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor) within 6 months of Screening.

20. Screening supine blood pressure ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic), following at least 5 minutes of supine rest. If blood pressure (BP) is ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility.

21. Screening supine 12-lead ECG demonstrating corrected QT (QTc) >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three QTc or QRS values should be used to determine the subject's eligibility.

22. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 56 days prior to dosing.

23. 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).

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

24. Have received any of the following treatment regiments with the specified timeframes outlined below:

    - Systemic Corticosteroids:

      - Subjects receiving systemic corticosteroids within 4 weeks prior to first dose of study drug or scheduled to receive systemic corticosteroids during the study period for another condition. Subjects 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. See Exclusion Criteria 28 for additional asthma exacerbation corticosteroid restrictions.

    - Leukotriene antagonists/modifiers:

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

- Any prior or current use of Anti-IL-33 targeted therapies is exclusionary.
- Within 6 months of first dose of study drug:
  - Anti-IL-4 and/or IL-13 targeted therapies (eg, lebrkizumab, tralokinumab) except for dupilumab (within 4 months of first dose of study drug).
  - mepolizumab, reslizumab.
- Within 12 months of first dose of study drug:
  - Benralizumab.
- Within 6 months of first dose of study drug:
  - Any cell-depleting agents including but not limited to rituximab: within 6 months of first dose of study drug or 5 half-lives (if known), whichever is longer, or until lymphocyte count returns to normal, whichever is longer.
- Within 12 weeks of first dose of study drug:
  - Any Janus Kinase (JAK) inhibitors, including any clinical studies in which a JAK inhibitor was a possible study treatment.
  - Other biologics: within 12 weeks of first dose of study drug or 5 half-lives (if known), whichever is longer.
- Within 6 weeks of first dose of study drug:
  - Have been vaccinated with live or attenuated live vaccine.
- Within 4 weeks of first dose of study drug:
  - Use of oral immune suppressants (eg, cyclosporine A [CsA], azathioprine, MTX, Celcept, 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.
  - Oral or topical phosphodiesterase (PDE) 3 or PDE4 anatgonists (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.

- Within 1 week of first dose of study drug:
  - Topical treatments that could affect atopic dermatitis (eg, corticosteroids, calcineurin inhibitors, tars, antibiotic creams, topical antihistamines).

    Note: Corticosteroid inhalers at allowed doses (see Exclusion criteria 28) and intranasal sprays are allowed for stable asthma and allergic rhinitis subjects respectively.

  - Herbal medications with known anti-inflammatory effects or otherwise taken for AD.

25. Require treatment with prohibited concomitant medication(s) (Section 5.9.2) or have received a prohibited concomitant medication within the specified time prior to Day 1.

26. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

27. 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 subject will not be included in the study

28. Subjects with a history of inadequately controlled or uncontrolled asthma having **any** of the following:

- Forced Expiratory Volume (FEV_1) <60% predicted as documented via spirometry (acceptable from up to 3 months prior to screening).
- An asthma exacerbation requiring systemic (oral and/or parenteral) steroid treatment within 2 months prior to screening or requiring hospitalization for >24 hours for treatment of asthma within 3 months prior to screening.
- Are on an inhaled dose of greater than 1000 µg fluticasone, or an equivalent inhaled corticosteroid, per day.
- A supplemental oxygen requirement.
- A diagnosis of allergic fungal sinusitis/allergic fungal rhinosinusitis.

4.2. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria.

Part 1

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria. Subjects will be randomized within each cohort to receive either PF-06817024 (PF) or placebo (Pbo) as described in Section 3.1. The randomization ratio in the study will be 6:2 (PF:Pbo) for Cohorts 1 through 7. If additional Cohorts 10 through 12 are required, the randomization ratio in these cohorts will also be 6:2 (PF:Pbo).

Part 2

Subjects in Cohorts 8 and 9 will be randomized in either a 1: 1 or 2 : 1 (PF-06817024: placebo) ratio, depending on the number of cohorts and the emerging data. Up to approximately 10 active (per dose) and approximately 15 placebo (overall) subjects will be enrolled in Part 2.

Part 3

Subjects will be randomized in an approximately 3: 1 (PF-06817024: placebo) ratio. Approximately 20 subjects are planned to be enrolled into a single cohort in Part 3. Additional subjects up to a total of approximately 32 may be enrolled in a 3: 1 ratio (PF-06817024: placebo) based on analysis of emerging safety, PK, CCI [redacted] data.

4.3. Lifestyle Guidelines

4.3.1. Parts 1 and 2

The following guidelines are provided:

4.3.1.1. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the pre-dose pharmacokinetic sample. Water is permitted without restriction.
- Non-caffeinated drinks may be consumed with meals and the evening snack during confinement at the clinical research unit (CRU).
- Lunch will be provided as early as 2 hours after the start of infusion or SC injections.
- Dinner will be provided approximately 7 to 8 hours after the start of infusion or SC injections.
- An evening snack may be permitted.

- While confined, the total daily nutritional composition should be approximately 55% carbohydrate, 30% fat and 15% protein. The daily caloric intake per subject should not exceed approximately 3200 kcal.

4.3.1.2. Alcohol, Caffeine and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol during clinical confinement at the CRU. All subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Subjects will abstain from caffeine-containing products for 24 hours prior to the start of dosing and during clinical confinement at the CRU and 2 hours prior to follow-up visits.

- Subjects will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the research unit.

4.3.1.3. Activity

- Subjects will be confined to the procedure room for the first 4 hours after dosing during continuous cardiac monitoring, except to use the bathroom or for meals. After this, if the equipment setup allows, subjects 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 study site to facilitate continuous monitoring (eg, bedside urinals should be provided to accommodate subjects' excretory needs).

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

4.3.1.4. Travel

- Subjects should be informed that travel to areas with endemic helminthes (including but not limited to Southeast and Southwest Asia, South America, and Africa) must not be planned for at least 6 months after the last dose of PF-06817024.

4.3.1.5. Contraception

All male subjects who, in the opinion of the investigator, are able to father children and are sexually active and whose partners are at risk for pregnancy (Part 1 and Part 2) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period (date of first dose) through the end of the study (until discharged from the study). The investigator or his or her designee, in consultation with the subject, will select/confirm an appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for the

correct use of at least 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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

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

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

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

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

6. Female partner who meets the criteria for non-childbearing potential must meet at least one of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy.

   c. Have medically confirmed ovarian failure.

NOTE: Women of childbearing potential are excluded from Part 1 of this study. For Part 2 of this study, female subjects may be of childbearing potential provided that they have undergone a documented bilateral tubal ligation or bilateral salpingectomy.

4.3.2. Part 3

4.3.2.1. Meals and Dietary Restrictions

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

4.3.2.2. Alcohol, Caffeine and Tobacco

- Non-caffeinated drinks may be consumed with meals.

- Subjects will abstain from alcohol for 24 hours prior to all clinic vists. All subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Subjects will abstain from caffeine-containing products for 24 hours prior to all visits till the completion of infusion of the IP and necessary activities such as ECG, vitals, respiratory rate (RR). Moderate consumption (eg, 1 cup (8 oz) of coffee/tea, 12 oz of caffeinated soda, but not including highly caffeinated beverages such as "Red Bull") may be allowed after the completion of these activities until the end of the visit.

- Subjects will abstain from the use of tobacco- or nicotine-containing products for 6 hours prior to all clinic visits and till the completion of the blood draws.

4.3.2.3. Activity

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

4.3.2.4. Contraception

All fertile male subjects and female subjects who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use at least one highly effective method of contraception consistently and correctly for the duration of the active treatment period (date of first dose) through the end of the study (until discharged from the study). The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use at least one highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

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

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

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

3. Male sterilization with absence of sperm in the postvasectomy ejaculate.

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

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

   Any consideration of using sexual abstinence as a contraception method must be discussed with the sponsor and will be decided on a case-by-case basis.

   In addition to the use of at least one highly effective method of contraception by the male subject or his partner, male subjects must use a condom to prevent possible transfer of study drug in seminal fluid.

   For all subjects required to use contraception per protocol, the PI needs to document in the case report form (CRF), what form of contraception the subject (and/or partner) has agreed to use during the study. The selected and approved contraception method must be used for a long enough period prior to dosing to ensure that the selected contraception method is effective at the time of the first dose of study drug.

   At each subsequent study visit, a contraception check will be performed prior to the dosing of study drug (on dosing visits) to confirm that appropriate contraception has been used since the last study visit and to confirm what method will be used until the next study visit. The type of contraception used will be documented in the CRF for every visit.

   Pregnancy testing of female subjects of childbearing potential will be done at every visit and results from the testing will also be documented in the CRF. In addition, pregnancy testing will also be done at home when the interval between study visits is greater than 1 month.

4.3.2.5. Travel

- Subjects should be informed that travel to areas with endemic helminthes (including but not limited to Southeast and Southwest Asia, South America, and Africa) should not be planned for at least 6 months after the last dose of PF-06817024. Subjects traveling to such areas should take appropriate precautions (eg, avoiding walking barefooted, using protective clothing, etc) to the extent possible.

4.3.2.6. Other

- On study visit days, showering or bathing is permitted prior to attending the study visit, but subjects should not apply emollients.

C

C

4.3.3. Rater Qualifications (Part 3)

Clinical evaluations of AD will be performed by an experienced and qualified dermatologist (board certified or equivalent). An experienced and qualified non-dermatologist physician or experienced medical professional with experience in the conduct of AD clinical trials may be permitted to perform the clinical evaluations of atopic dermatitis when designated by primary site Investigator and agreed by Pfizer sponsor team. CCI

4.4. 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 team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational

staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

The investigator will assign subject numbers to the subjects as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number.

5.2. Breaking the Blind

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or an electronic process. Blinding codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should consult with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF)/data collection tool (DCT). A data blinding plan will be created prior to randomization and will be maintained throughout the course of the study.

Blood specimens will be obtained from all subjects for pharmacokinetic analysis to maintain the study blind at the investigator site. Only the investigator site(s) staff and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to subject treatments in order to permit real-time interpretation of the safety and pharmacokinetic data; and provide information necessary to potentially alter the dose escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from subjects randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

5.3. Subject Compliance

Study treatment will be administered under the supervision of investigator site personnel.

5.4. Investigational Product Supplies

5.4.1. Dosage Form and Packaging

Investigational drug product, PF-06817024 Solution for Injection, 100 mg/mL**,** will be supplied by Pfizer in a sterile, single-use glass vial with an aluminum flip off seal for both intravenous and subcutaneous administration.

Placebo is supplied by Pfizer as a liquid solution in a glass vial with an aluminum flip off seal for intravenous or subcutaneous administration.

5.4.2. Preparation and Dispensing

See the Investigational Product Manual (IP Manual) for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

PF-06817024 and placebo will be prepared by qualified unblinded site personnel according to the IP Manual. The investigational product will be administered in a blinded fashion to the subject.

5.4.3. Administration

PF-06817024 and placebo are administered intravenously and subcutaneously.

Following an overnight fast of least 10 hours (except for Part 3 as specified in the IP Manual), subjects will receive study treatment at approximately 08:00 hours (plus or minus 4 hours). Study treatment will be administered as approximately 60-90 minute intravenous infusion (Parts 1 and 2), approximately 90 minute intravenous infusion for Part 3, as specified in the IP manual, using a calibrated infusion pump for subjects receiving IV administration (this may be modified up to 120 minutes by the Sponsor study team and the PI). Study drug must not be administered as an IV push or bolus. The start and stop time of the infusion will be recorded. Time 0 is the time when the study drug infusion begins. The infusion rate and amount of volume infused will be recorded. For SC administration, study treatment will be injected subcutaneously. Each injection should occur at a different site on the abdomen or thigh, approximately 1 cm apart. Administer study treatment according to the IP Manual.

5.5. Injection/Infusion Discontinuation

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

- If a subject experiences symptoms typical of infusion reactions (eg, lightheadedness, nausea, chills, fever), the study drug 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 drug 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. Subjects will receive appropriate treatment at the discretion of the investigator.

5.6. Investigational Product Storage

The investigator or an approved representative (eg, pharmacist) will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. Unused (unopened) investigational product or placebo vials stored at room temperature can be returned to 2°C to 8°C (36°F to 46°F) storage within 8 hours. Unused vials must not be left at room temperature for more than 8 hours.

From a microbiological point of view, the prepared products (active and placebo) must be used within 24 hours starting from the start of dose preparation. If the prepared investigational product is left at room temperature for more than 8 hours, contact the Study Manager, or equivalent. See the IP Manual for additional information.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All study drugs will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

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

5.8. Concomitant Treatment(s)

5.8.1. Part 1

Subjects will abstain from all concomitant treatments, except for the treatment of adverse events, as described in the Exclusion Criteria sections of this protocol. Limited use of non-prescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

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.

5.8.2. Parts 1 and 2

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects 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.

5.8.3. Part 3

Subjects will be queried about concomitant medication (including topical medications and treatments, over-the-counter and prescription medications and treatments, and vaccinations) at each study visit. 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 42 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 (see Exclusion criteria 28) and intranasal sprays are allowed for stable asthma and allergic rhinitis subjects respectively.
- Non-medicated emollient and sunscreen are the only topical products permitted to be used on atopic dermatitis skin during the study. Subjects are recommended not to switch the emollient or sunscreen during the study.

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

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

Acetaminophen may be used intermittently (not to exceed 2.4 g/day). Vitamin and mineral supplements of standard potency are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis).

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

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

5.9. Prohibited Treatments and Medications during the Study

5.9.1. Part 2

- Systemic corticosteroids.
- Topical oxymetazoline (outside of study procedures: nasal endoscopy).
- Monoclonal antibody (mAB) or immunosuppressive treatment.
- Anti-immunoglobulin E (IgE) therapy (omalizumab).
- Anti-IL-5 (eg, mepolizumab) therapy.
- Leukotriene antagonists/modifiers unless patient is on a continuous treatment for at least 28 days prior to Screening.

Patients with CRSwNP and asthma randomized into the study will be on standard of care treatment for their disease at time of randomization as prescribed by their physician that will not include prohibited concomitant medications as noted in Section 5.9.1. Subjects that are randomized into the study will continue on their baseline treatment regimen during the study. Subjects randomized into the study will additionally have access to standard of care therapy, that may include the prohibited treatments and medications defined in Section 5.9.1, if such additional therapy is deemed necessary to treat their underlying disease. A protocol deviation is to be completed for any patient that takes a prohibited treatment or medication during the study and the Sponsor is to be notified. The patient may be replaced at the discretion of the principal investigator and/or the Sponsor.

5.9.2. Part 3

Subjects are required to discontinue and avoid using certain medications and treatments (per inclusion and exclusion criteria in Section 4.1.1.1 and 4.1.2.1). Subjects should be instructed at each visit to contact the study site investigator promptly if there are any intended changes or additions to concomitant medications. These include:

- Systemic and parenteral corticosteroids.
- Leukotriene antagonists/modifiers unless patient is on a stable dose.
- Anti-IL-33 targeted therapies.
- Anti-IL-4 and/or IL-13 targeted therapies (eg, dupilumab, lebrkizumab, tralokinumab).
- Mepolizumab, reslizumab.
- Benralizumab.

- Any cell-depleting agents including but not limited to rituximab.
- Any JAK inhibitors.
- Other biologics.
- Investigational drugs.
- Live or attenuated vaccines.
- Oral immune suppressants (eg, cyclosporine A [CsA], azathioprine, MTX, Celcept, mycophenolate-mofetil, IFN-γ).
- Oral or topical phosphodiesterase (PDE) 3 or PDE4 anatgonists (eg, apremilast, crisaborole).
- Oral/topical histamine H4 antagonists.
- Phototherapy (NB-UVB) or broad band phototherapy.
- Regular use (more than 2 visits per week) of a tanning booth/parlor.
- Topical treatments that could affect atopic dermatitis (eg, corticosteroids, calcineurin inhibitors, tars, antibiotic creams, topical antihistamines).
- An inhaled dose of greater than 1000 μg fluticasone, or an equivalent inhaled corticosteroid, per day.
- Herbal medications with known anti-inflammatory effects or otherwise taken for AD.

A protocol deviation is to be completed for any subject that takes a prohibited treatment or medication during the study and the sponsor is to be notified. The subject may be replaced at the discretion of the sponsor if prohibited treatments have been taken prior to Week 16.

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, subjects must also avoid prolonged exposure to the sun and avoid the use of tanning booths, sun lamps or other ultraviolet light sources during the study.

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

Herbals supplements are only allowed on a case by case basis; please contact the Pfizer staff. Herbal medications with 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 investigational product.

Restrictions on certain vaccinations are described in Section 5.9.2.2.

5.9.2.1. Rescue Medications

Subjects 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 5.9.2) and the concomitant drugs and doses are maintained unchanged throughout the first 16 weeks of the study. Although no specific rescue treatment is recommended, subjects randomized into the study may have access to standard of care therapy, that may include prohibited treatments and medications defined in Section 5.9.2, if deemed necessary by the investigator to treat their underlying disease. CCI [redacted]

5.9.2.2. Vaccinations

Vaccination with live virus, attenuated live virus, or any live viral components is prohibited within 42 days of Day 1 dosing during the study, and for 6 weeks after the last dose of investigational product. Similarly, current routine household contact with individuals who have been vaccinated with live vaccine components should be avoided during treatment and for 6 weeks following completion of treatment.

Such vaccines include: FluMist® (intranasal influenza vaccine), attenuated rotavirus vaccine, varicella (chickenpox) vaccine, attenuated typhoid fever vaccine, oral polio vaccine, MMR (measles, mumps, rubella) vaccine and vaccinia (smallpox) vaccine. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted.

6. STUDY PROCEDURES

6.1. Part 1/Part 2

6.1.1. Screening

In Part 1 and Part 2, subjects will be screened within 28 days prior to administration of the study treatment to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section. If the time between Screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then subjects do not require re-screening if the Day 0 laboratory results meet the eligibility criteria.

In Part 1 only, a subject who qualified for this protocol (or who was excluded from Cohort 1-4 for IgE or Phadiatop results but otherwise qualified for this protocol) but did not enroll from an earlier cohort may be used in a subsequent cohort without re-screening provided the Day 0 laboratory results meet the eligibility criteria for this study. A subject who qualified for this protocol, completed Day 0 procedures and assessments, and was not dosed as one of the first two subjects in a cohort may be dosed after the study required minimum 24 hour pause (see Section 3.1) without repeating Day 0 procedures and assessments as long as no more than 48 hours separate Day 0 and Day 1. CCI [redacted]

The following procedures will be completed for both *Part 1 and Part 2*:

- Obtain written informed consent.
- Review Inclusion and Exclusion criteria.
- Collect demography.
- Collect height and weight.
- Obtain medical history including:
  - History of illegal drug, alcohol and tobacco use.
  - Complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose.
- Obtain supine blood pressure (BP), pulse rate (PR) and oral temperature.
- Conduct full physical examination.

  Note: A full physical examination may be done at screening or may be deferred to Day 0 at the discretion of the principal investigator (PI).
- Collect single 12-lead electrocardiogram (ECG).
- Chest X-ray.

  Note: Chest X-ray results within 3 months of the screening visit otherwise a chest x-ray must be performed and results obtained prior to randomization.
- Collect blood and urine specimens for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).

- Serum FSH concentration for any female who has been amenorrheic for at least 12 consecutive months.

- HIV, HBsAg, HBcAb, HCVAb (HBsAb test if screening results for HBsAg are negative and HBcAb are positive starting for Part 1 (Cohort 5 and later) and Part 2-see Section 4.1.2) tests.

- QuantiFERON – Tuberculosis (TB) Gold Test.

- Part 1 only: Phadiatop test (historical positive test result with appropriate documentation is acceptable Cohorts 1-4 only). Starting with Cohort 5 and later, Phadiatop is to be collected prior to dosing.

- Serum IgE or test results within 6 months of screening visit (*Part 1 Cohorts 1-4 only)*. CCI [redacted]

- Pregnancy test for female subjects of childbearing potential who have a documented bilateral tubal ligation or bilateral salpingectomy (*Part 2 only).*

- Urine Drug Test and Alcohol Breath Test.

  Note: Subjects may undergo a urine drug test at the discretion of the investigator at any time during the study. An alcohol breath test is not mandatory but may be given at Screening or any other time during the study at the discretion of the investigator.

- Spirometry: results acceptable within 3 months of screening visit otherwise a spirometry must be performed and results obtained prior to randomization (*Part 2 subjects with a history of asthma only*).

- C CCI [redacted]

- Obtain information regarding the use of prior treatment and the occurrence of adverse events.

- Contraception Check.

- Nasal Endoscopy and NPS (*Part 2 only*).

Note: The screening nasal endoscopy including NPS is to be completed after all other screening criteria have been verified. If a subject is eligible for the study, they will undergo nasal endoscopy including assessment of NPS, CCI [redacted], ideally on Day 0. However, the baseline NPS CCI [redacted] may be determined up to 5 days prior to Day 0. Thus, if a subject is screened and found eligible for the study based on NPS no more than 5 days prior to Day 0, the NPS from screening may be

used as the Day 0 NPS. CCI [redacted]

To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines and Concomitant Treatment(s) sections of the protocol.

6.1.2. Study Period

In Part 1 and Part 2, for the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible:

- ECGs: obtain prior to vital signs and as close as possible to scheduled time, but prior to blood specimen collection.
- Blood pressure/pulse rate: obtain as close as possible to scheduled time, but prior to blood specimen collection.
- Pharmacokinetic blood specimens: obtain at scheduled time.
- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

When an intravenous catheter is utilized for blood sample collections, pre-dose ECGs and vital signs (pulse rate [PR], BP, RR and Oral Temperature) assessments may be collected prior to IV insertion of the catheter or at least 2 hours after IV insertion of the catheter.

6.1.2.1. Part 1 and Part 2: Day 0

Part 1 and Part 2: Subjects will be admitted to the Clinical Research Unit on Day 0. Part 2 only: Day 0 may be an outpatient visit (at the discretion of the investigator). If Day 0 is an outpatient visit, the subject should be carefully instructed about fasting, avoidance of dietary/alcohol indiscretions, and avoidance of strenuous exercise. Additional baseline safety laboratory samples will need to be collected at Day 1 (-2 hours to -5 minutes). The following procedures will be completed following admission to the CRU:

- Review Inclusion and Exclusion criteria (updated since screening).
- Review changes in the subject's medical history since screening, including history of illegal drug, alcohol and tobacco use (updated since screening).
- Conduct full physical examination, if deferred from the screening visit. If a full physical examination was conducted at screening, perform a limited physical examination at Day 0.
- Collect weight.
- Obtain oral temperature.

- Collect blood and urine samples for the following:

  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast). The results must have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed on Day 1.

  C CCI [redacted]

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

  - Pregnancy test for female subjects of childbearing potential who have a documented bilateral tubal ligation or bilateral salpingectomy (*Part 2 only).*

  - Urine Drug Test and Alcohol Breath Test at the discretion of the investigator.

    Note: Subjects may undergo a urine drug test at the discretion of the investigator at any time during the study. An alcohol breath test is not mandatory but may be given at Screening or any other time during the study at the discretion of the investigator.

C CCI [redacted]

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

If a subject is eligible for the study, they will undergo nasal endoscopy including assessment of NPS, CCI [redacted] to assess the CCI [redacted], ideally on Day 0. However, the baseline NPS CCI [redacted] may be determined up to 5 days prior to Day 0. Thus, if a subject is screened and found eligible for the study based on NPS no more than 5 days prior to Day 0, the NPS from screening may be used as the Day 0 NPS. CCI [redacted].

- C CCI [redacted]

- Contraception Check.

- Obtain information regarding the use of prior treatment and the occurrence of adverse events.

Subjects will begin fasting at least 10 hours prior to the collection of the pre-dose PK sample on Day 1.

6.1.2.2. Part 1 and Part 2: Day 1

Prior to dosing, the following procedures will be completed:

- Initiate continuous cardiac monitoring at least 2 hours prior to dosing. This continuous cardiac monitoring may also be performed any time after admission, but prior to dosing.

  Note: To establish a baseline, telemetry should be recorded for at least 2 hours before dosing. This may be done 2-hours 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 subject is awake. Continuous cardiac monitoring will be conducted approximately -5 minutes pre-dose through the 8 hour post-dose period.

- Obtain supine blood pressure (BP), pulse rate (PR), respiratory rate (RR) and & oral temperature. Pre-dose vitals may be collected prior to IV insertion of the catheter or at least 2 hours after IV insertion of the catheter.

- Collect triplicate 12-lead ECG measurements (*Part 1 only.)*

  Note: ECGs will be collected in triplicate at approximately 2-4 minutes.

- Collect single 12-lead ECG measurements (*Part 2 only)*.

- Pre-dose ECGs may be collected prior to IV insertion of the catheter or at least 2 hours after IV insertion of the catheter.

- Insert IV catheter for blood collection.

  Note: Site may insert IV catheter for blood sample collection up to 24 hours prior to study drug administration. IV catheter should be inserted in the extremity contra lateral to that into which test article will be administered. Heparin is not to be utilized.

- Collect blood samples for the following:
  - Pharmacokinetic analysis (following at least a 10-hour fast).

  - Immunogenicity (ADA, NAb) blood sampling.
- Obtain information regarding the use of prior treatment and the occurrence of adverse events.
- After all pre-dose procedures have been completed, insert IV catheter for study drug infusion (IV cohorts only) and administer the study treatment (see STUDY TREATMENTS and Administration Sections).

After dosing, the following procedures will be completed at the time(s) indicated in the SoA:

Note: The 1 hour post-dose procedures are to be implemented for all cohorts (IV and subcutaneous [SC]) as close to 1 hour as possible. For the IV Cohorts, procedures are to occur after investigational product infusion is completed (see Dosage and Administration Instructions (DAI). ECG and vital sign procedures may be collected up to 10 minutes prior to investigational product infusion completion. If any intravenous infusion time exceeds 100 minutes, the post-dose time points for Day 1 (through 24 hours) will shift out relative to the end of infusion.

- Maintain continuous cardiac monitoring for 8 hours (or longer if considered clinically necessary by the investigator) following dose administration.
- Vital Signs (supine BP, PR, RR and oral temperature).
- Collect triplicate 12-lead ECG measurements (*Part 1 only*).

  Note: ECGs will be collected in triplicate at approximately 2-4 minutes.
- Collect single 12-lead ECG measurements (*Part 2 only*).
- Collect blood samples for the following:

- Pharmacokinetic analysis.

- [redacted]

- Assess infusion/injection site reaction.

  Note: Subjects will be continuously monitored for infusion site reactions (for IV administration) from start of drug administration until the end of infusion. Injection site reactions (for SC administrations) should be monitored continuously for the first 30 minutes and then at time points indicated in the SoA.

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

- Obtain information regarding the use of concomitant treatment.

6.1.2.3. Part 1 and Part 2: Days 2, 3 and 4

The following procedures will be completed as indicated in the SoA. Day 2 will occur for *Part 1* and *Part 2*, Days 3 and 4 for *Part 1 only*.

- Conduct limited physical examination (*Part 2 only*).

- Collect weight (*Part 2 only*).

- Vital Signs (supine BP, PR, RR and oral temperature).

- Collect triplicate 12-lead ECG measurements (*Part 1 only*).

  Note: ECGs will be collected in triplicate at approximately 2-4 minutes.

- Collect single 12-lead ECG measurements (*Part 2 only*).

- Collect blood and urine samples for the following:

  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).

  - Pharmacokinetic analysis.

  - [redacted]

  - Pregnancy test for female subjects of childbearing potential who have a documented bilateral tubal ligation or bilateral salpingectomy (*Part 2 only).*

- Assess infusion/injection site reaction.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Obtain information regarding the use of concomitant treatment.
- Contraception check (*Part 2 only*).
- Discharge from Clinical Research Unit confinement (*Part 2 only*).

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the Clinical Research Unit and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.1.2.4. Part 1 and Part 2: Day 5

The following procedures will be completed:

- Conduct limited physical examination.
- Collect weight.
- Vital Signs (supine BP, PR, RR and oral temperature).
- Collect triplicate 12-lead ECG measurements (*Part 1 only*).

  Note: ECGs will be collected in triplicate at approximately 2-4 minutes.
- Collect single 12-lead ECG measurements (*Part 2 only*).
- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).
  - Pharmacokinetic analysis.

[redacted]

[redacted]

- Pregnancy test for female subjects of childbearing potential who have a documented bilateral tubal ligation or bilateral salpingectomy (*Part 2 only).*

- Assess infusion/injection site reaction.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Obtain information regarding the use of concomitant treatment.
- Contraception check.
- Discharge from Clinical Research Unit confinement (*Part 1 only*).

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Clinical Research Unit until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the Clinical Research Unit and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.1.2.5. Part 1 and Part 2: Days 8 and 15

Part 1 and *Part 2*: Subjects will return to the Clinical Research Unit on Days 8 and 15 following the IV infusion/SC injection for outpatient visits. The visit window noted in the SoA is to be followed for all visits, which is relative to Day 1 dose administration. At this visit, the following procedures will be completed as indicated in the SoA.

- Conduct limited physical examination.
- Collect weight.
- Vital Signs (supine BP, PR, RR and oral temperature).
- Collect blood and urine samples for the following:

- Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).
- Pharmacokinetic analysis.
- [redacted]
- Immunogenicity (ADA, NAb) blood sampling (Day 15 only).
- [redacted]
- Pregnancy test for female subjects of childbearing potential who have a documented bilateral tubal ligation or bilateral salpingectomy (*Part 2 only).*

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Contraception check.
- Obtain information regarding the use of concomitant treatment and the occurrence of adverse events.

6.1.2.6. Part 1 SAD and Part 2 Days 32 through Day 211

Part 1: Subjects who do not roll over into the multiple dose component of the study will return to the Clinical Research Unit on Days 32, 46, 61, 91, 121, 151, 181, and 211.

Part 2: Patients will return on Days 32, 61, 91, 121, 181, and 211 following the IV infusion for outpatient visits.

The visit window noted in the SoA is to be followed for all visits, which is relative to Day 1 dose administration. At these visits, the following procedures will be completed as indicated in the SoA.

- Conduct limited physical examination, except at final study visit when a full physical examination is required.

  Note: A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

- Collect weight.

- Vital Signs (supine BP, PR, RR and oral temperature).
- Collect single 12-lead ECG measurement (except Day 46 for *Part 1*).
- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry and Urinalysis (following at least a 4-hour fast).
  - Pharmacokinetic analysis.
  - Immunogenicity (ADA, NAb) blood sampling.
  - Pregnancy test for female subjects of childbearing potential who have a documented bilateral tubal ligation or bilateral salpingectomy (*Part 2 only).*
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Contraception check.
- Obtain information regarding the use of concomitant treatment.

Part 1: SAD Cohorts 1, 2 and 6 will be discharged from the study at approximately Day 211. SAD Cohorts 3-5 will also be discharged from the study at approximately Day 211 if NOT rolled over into multiple dose component of study.

Part 2: Cohorts 8 and 9 will be discharged from the study at approximately Day 211.

6.1.2.7. Part 1: Multiple Dose Cohorts Day 31

Subjects will be admitted to the Clinical Research Unit on approximately Day 31. If subjects are not admitted into the clinic for the second dose by Day 35 (Day 32 +3 days), subjects should follow SoA Table B Day 32 follow-up visit; if subjects are not admitted into the clinic for the second dose by Day 51 (Day 46+5 days), subjects should follow SoA Table B Day 32 and Day 46 follow-up visits; if subjects are not admitted into the clinic for the second dose by Day 66 (Day 61+5 days), subjects should follow SoA Table B Day 32, Day 46, and Day 61 follow-up visits. SoA Table C visits would then shift out accordingly (by days of delay for each cohort/subject affected) ensuring 7 months of follow-up after the second dose. If a subject cannot receive a second dose within the allotted time due to unexpected circumstances (eg, scheduling), they should follow SoA Table B through the end of the study. The following procedures will be completed following admission to the CRU.

- Conduct limited physical examination.

  Note: A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

- Collect weight.
- Vital Signs (supine BP, PR, RR and oral temperature).
- Urine Drug Test and Alcohol Breath Test at the discretion of the investigator.
- Collect blood and urine specimens for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).
  - [redacted]
- Contraception check.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Obtain information regarding the use of concomitant treatment.

Subjects will begin fasting at least 10 hours prior to dosing on Day 32.

6.1.2.8. Part 1: Multiple Dose Cohorts Day 32

Prior to dosing, the following procedures will be completed:

- Initiate continuous cardiac monitoring at least 2 hours prior to dosing. This continuous cardiac monitoring may also be performed any time after admission, but prior to dosing.

  Note: Telemetry may be collected after study team and investigator review safety data required prior to initiating multiple dosing per protocol Section 3.1.

- Obtain supine blood pressure (BP), pulse rate (PR), respiratory rate (RR) and & oral temperature. Pre-dose vitals may be collected prior to IV insertion of the catheter or at least 2 hours after IV insertion of the catheter.

  Note: Vital signs include BP, PR, RR, and oral temperature. RR is to be collected at Day 32 prior to dosing (up to 2 hours prior), daily during confinement, and at all follow-up visits.

- Collect triplicate 12-lead ECG measurements. Pre-dose ECGs may be collected prior to IV insertion of the catheter or at least 2 hours after IV insertion of the catheter.

  Note: ECGs will be collected in triplicate approximately 2-4 minutes apart.

- Insert IV catheter for blood collection.

  Note: Site may insert IV catheter for blood sample collection up to 24 hours prior to study drug administration. IV catheter should be inserted in the extremity contra lateral to that into which test article will be administered. Heparin is not to be utilized.

- Collect blood samples for the following:

  - Pharmacokinetic analysis (following at least a 10 hour fast).

- Immunogenicity (ADA, NAb) blood sampling.

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

- Obtain information regarding the use of concomitant treatment.

- After all pre-dose procedures have been completed, insert IV catheter for study drug infusion (IV cohorts only) and administer the study treatment (see STUDY TREATMENTS and Administration Sections).

After dosing, the following procedures will be completed at the time(s) indicated in the SoA:

Note: The 1 hour post-dose procedures are to be implemented for all cohorts (IV and subcutaneous [SC]) as close to 1 hour as possible. For the IV Cohorts, procedures are to occur after investigational product infusion is completed (see Dosage and Administration Instructions (DAI). ECG and vital sign procedures may be collected up to 10 minutes prior to investigational product infusion completion. If any intravenous infusion time exceeds 100 minutes, the post-dose time points for Day 32 (through 24 hours) will shift out relative to the end of infusion.

- Maintain continuous cardiac monitoring for 8 hours (or longer if considered clinically necessary by the investigator) following dose administration.

- Vital Signs (supine BP, PR, RR and oral temperature).

- Obtain triplicate 12-lead ECG measurements.

- Collect blood samples for the following:

  - Pharmacokinetic analysis.

  - [redacted]

- Assess infusion/injection site reaction.

  Note: Subjects will be continuously monitored for infusion site reactions (for IV administration) from start of drug administration until the end of infusion. Injection site reactions (for SC administrations) should be monitored continuously for the first 30 minutes and then at time points indicated in the SoA.

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

- Obtain information regarding the use of concomitant treatment.

6.1.2.9. Part 1: Multiple Dose Cohorts Days 33 and 34

The following procedures will be completed:

- Conduct limited physical examination (Day 34 only).

  Note: A Full physical examinations is required at final study visit. A limited physical examination will be completed at all other times specified in the SoA. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

- Collect weight (Day 34 only).
- Vital Signs (supine BP, PR, RR and oral temperature).
- Obtain single 12-lead ECG measurements.
- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).
  - Pharmacokinetic analysis.

- Obtain information regarding the use of concomitant treatment and the occurrence of adverse events.
- Assess infusion/injection site reaction.
- Discharge from Clinical Research Unit confinement (Day 34).

6.1.2.10. Part 1 Multiple Dose Cohorts Days 46 through Day 241

Subjects will return to the Clinical Research Unit on Days 46, 61, 91, 121, 151, 181, 211 and 241 following the IV infusion/SC injection for outpatient visits. The visit window noted in the SoA is to be followed for all visits, which is relative to the day of administration for the second dose (a minimum of 4 weeks after the first dose). At these visits, the following procedures will be completed as indicated in the SoA.

- Conduct limited physical examination.

  Note: Full physical examination is required at the final study visit. A limited physical examination will be completed at all other times specified in the SoA. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

- Collect weight.

- Obtain single 12-lead ECG measurement at all visits except Day 46.

- Vital Signs (supine BP, PR, RR and oral temperature).

- Collect blood and urine samples for the following:

  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).

  - Pharmacokinetic analysis.

  - Immunogenicity (ADA, NAb) blood sampling.

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”

- Contraception check.
- Obtain information regarding the use of concomitant treatment.
- Cohorts 3-5 and 7 if rolled into the multiple dose component of the study /Cohorts 10-12 (if implemented) discharge from the study at approximately Day 241.

6.1.2.11. Extended Follow-up (Part 1 and Part 2)

Subjects having an unresolved adverse event that is possibly related to an ADA immune response will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit for up to 12 months after last drug administration or until the adverse event or its sequelae resolve or stabilize at a level acceptable to the investigator and Sponsor concurs with the investigator's assessment. If the emerging data project that half-life is longer than 41 days, subjects will be asked to return for extended follow-up visit(s) at up to 3 month intervals beyond the last follow-up visit to cover approximately ≥5 times the observed half-life CCI CCI [redacted] OR of sufficient duration to have projected exposures decrease below ADA drug tolerance levels CCI [redacted] At these visits, the following procedures will be completed as indicated in the SoA.

- Conduct limited physical examination.

  Note: Full physical examination is required at the final study visit. A limited physical examination will be completed at all other times specified in the SoA. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

- Collect blood samples for the following:
  - Pharmacokinetic analysis.
  - CCI [redacted]
  - Immunogenicity (ADA, NAb) blood sampling.
  - CCI [redacted]
  - Safety labs for extended follow-up visits may be done at the discretion of the PI for cohorts currently in the study.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Contraception check.
- Obtain information regarding the use of concomitant treatment.

6.1.2.12. Subject Withdrawal (Part 1 and Part 2)

Withdrawal of consent: Subjects who request to discontinue receipt of study treatment 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 subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF/Data Clarification Form (DCF) page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up: All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site. The early termination visit only applies to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or site staff should attempt to contact the subject twice. After two attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the

subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the following assessments:

- Full physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit.
- Vital Signs (supine BP, PR, RR and oral temperature).
- Collect triplicate 12-lead ECG measurements (*Part 1 only)*.
- Collect single 12-lead ECG measurements (*Part 2 only).*
- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).
  - Pregnancy test for female subjects of childbearing potential who have a documented bilateral tubal ligation or bilateral salpingectomy (*Part 2 only).*
  - Pharmacokinetic analysis.
  - [redacted]
  - Immunogenicity (ADA, NAb) blood sampling.
- [redacted]

CCI [redacted]

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

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

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor (provided the nature of the safety event does not preclude dose escalation and exposure stopping limits are observed).

6.2. Part 3

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to

CCI [redacted]

- Pre-dose vitals may be collected prior to IV insertion of the catheter or at least 2 hours after IV insertion of the catheter and must be done as close to the dosing time as possible. Pre-dose vitals will be recorded as 0 hr measurements.

- Pre-dose ECGs may be collected prior to IV insertion of the catheter or at least 2 hours after IV insertion of the catheter and must be done as close to the dosing time as possible. Pre-dose ECG measurements will be recorded as 0 hr measurements.

- Pre-dose activities on Day 1, Day 29, Day 57, Day 85 may be performed, at the discretion of the investigator, on the day preceding each dose (ie, on Day 0, Day 28, Day 56, Day 84) as inpatient in clinical site or outpatient. Inpatient subjects will be admitted to the clinic day prior to the dosing visits (Day 1, Day 29, Day 57, Day 85). The pre-dose activities include medical history, atopic dermatitis history including atopic disease history, history of illegal drug, alcohol and tobacco use, inclusion/exclusion criteria, physical examination, weight, urine drug test and alcohol breath test, pregnancy test, safety laboratory (hematology, chemistry, urinanalysis), CCI [redacted] clinical assessments (Fitzpatrick skin type, CCI [redacted] Pre-dose safety labs for the purposes of Inclusion/Exclusion criteria may be done 2 days prior to dosing on Day 1. Pre-dose samples collected for PK, Immunogenicity, CCI [redacted] and CCI [redacted] will be recorded as 0 hr samples.

- CCI [redacted] CCI
  CCI [redacted]

- Physical examination must be conducted prior to dosing on the dosing visit days.

- For dosing visits performed as outpatient visits, the subject should be carefully instructed about fasting, avoidance of dietary/alcohol indiscretions, and avoidance of strenuous exercise. See Section 4.3.2.

6.2.1. Screening

Subjects will be screened within 42 days prior to administration of the study treatment to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section. If the time between Screening and dosing exceeds 42 days as a result of unexpected delays (eg, delayed drug shipment), then subjects do not require re-screening if the Day 0 laboratory results meet the eligibility criteria.

Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results; the last value will be used to determine eligibility. If results return to normal within the 6-week screening period, the subject may enter the study. Sites will be permitted to re-screen subjects (with a new screening number) who initially do not meet eligibility criteria once. If some screening laboratory tests are missing, but the subject has met all the remaining Inclusion/Exclusion criteria, then these missing laboratory tests must be performed at an unplanned visit during the screening window. Alternatively, the tests may be performed prior to randomization or on Day 1 provided the results are available to determine eligibility prior to randomization.

The following procedures will be completed as applicable and stipulated in the Schedule of Activities:

- Obtain written informed consent.
- Perform AD assessments : EASI, IGA.
- Columbia Suicide Severity Rating Scale (C-SSRS) assessment.
- Review Inclusion and Exclusion criteria.
- Collect demography.
- Obtain medical history including:
  - History of illegal drug, alcohol, and tobacco use.

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

- AD history, including other atopic diseases.

- Collect height and weight.

- Obtain supine blood pressure (BP), pulse rate (PR) and temperature.

- Conduct full physical examination.

  Note: A full physical examination may be done at screening or may be deferred to Day 1 at the discretion of the principal investigator (PI).

- Collect single 12-lead electrocardiogram (ECG).

- Chest X-ray.

  Note: Chest X-ray results within 3 months of the screening visit otherwise a chest x-ray (standard posterior-anterior and lateral views) must be performed and results obtained prior to randomization.

- Collect blood and urine specimens for the following:

  - Safety laboratory tests: includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).

  - Serum FSH concentration for any female who has been amenorrheic for at least 12 consecutive months.

  - HIV, HBsAg, HBcAb, HCVAb (HBsAb test if screening results for HBsAg are negative and HBcAb are positive).

  - QuantiFERON – Tuberculosis (TB) Gold Test.

  - Pregnancy test for female subjects of childbearing potential.

  - Urine Drug Test and Alcohol Breath Test.

    Note: Subjects may undergo a urine drug test at the discretion of the investigator at any time during the study. An alcohol breath test is not mandatory but may be given at Screening or any other time during the study at the discretion of the investigator.

- Spirometry: results acceptable within 3 months of screening visit otherwise a spirometry must be performed and results obtained prior to randomization (for subjects with a history of asthma, only).

- Obtain information regarding the occurrence of adverse events.

- Contraception Check.

  To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines (Section 4.3.2) and Concomitant Treatment(s) sections of the protocol.

6.2.2. Part 3 (Day 1, Day 29, Day 57, Day 85) – Dosing visits

Prior to dosing, the following procedures will be completed:

C
C
I

- Review Inclusion and Exclusion criteria (updated since screening) (Day 1 only).

- Review changes in the subject's medical history since screening, including history of illegal drug, alcohol and tobacco use, atopic dermatitis history including other atopic diseases, medication history (updated since screening) (Day 1 only).

- Obtain supine blood pressure (BP), pulse rate (PR), respiratory rate (RR) and & temperature. Pre-dose vitals may be collected prior to IV insertion of the catheter or at least 2 hours after IV insertion of the catheter.

- Perform a limited physical examination. Full physical examination maybe done on Day 1 if a limited physical examination is performed at screening.

- Pre-dose single ECGs may be collected prior to IV insertion of the catheter or at least 2 hours after IV insertion of the catheter and must be done on the day of dosing.

- Weight.

- Insert IV catheter for blood collection.

Note: Site may insert IV catheter for blood sample collection up to 24 hours prior to study drug administration only for subject who will be admitted to the clinical site a day prior to dosing. IV catheter for blood sampling may be replaced with phlebotomy procedures at the investigator's discretion. All blood samples for laboratory testing must be drawn from the extremity contralateral to that into which test article will be administered. If an indwelling catheter is used, heparin is not to be utilized to maintain patency.

- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory tests include Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast). The available results must have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed. Results for most laboratory tests collected on the visit day likely will not be available on the same day for review before dosing, in which case the available laboratory tests will only consist of those from the previous visit. All such laboratory results must be reviewed prior to dosing. Pregnancy testing MUST have been performed within the permitted window and the result MUST be negative for female subjects of childbearing potential prior to dosing.
  - Urine Drug Test and Alcohol Breath Test (Day 1).
  - Pharmacokinetic analysis.
  - CCI [redacted]
  - Immunogenicity (ADA, NAb) blood sampling.
  - Pregnancy test for female subjects of childbearing potential.
  - Urine Drug Test and Alcohol Breath Test (Day 1 only).
- Perform AD assessments: Fitzpatrick skin type assessment (Day 1 only), CCI [redacted].
- Obtain information regarding the use of prior treatment and the occurrence of adverse events.
- Contraception check.
- CCI [redacted]

- After all pre-dose procedures have been completed, insert IV catheter for study drug infusion (IV cohorts only) and administer the study treatment (see STUDY TREATMENTS and Administration Sections).

After dosing, the following procedures will be completed at the time(s) indicated in the SoA:

Note: The 1.5 hour post-dose procedures are to be implemented for as close to 1.5 hour as possible. Procedures are to occur after investigational product infusion is completed (see Dosage and Administration Instructions (DAI). PK draws need to be done after the completion of infusion. ECG and vital sign procedures may be collected up to 10 minutes prior to investigational product infusion completion. If any intravenous infusion time exceeds 1.5 hrs, the post-dose time points for Day 1 will shift out relative to the end of infusion. The actual times need to be documented in the CRF. In the event the infusion is interrupted and restarted, the start and end times for the infusion prior and post interruption must be collected.

- Vital Signs (supine BP, PR, RR and temperature).
- Collect single 12-lead ECG measurements.
- Collect blood samples for the following:
  - Pharmacokinetic analysis (1.5 and 4 hours).
- Remove IV catheter(s).
- Assess infusion/injection site reaction.

  Note: Subjects will be frequently monitored for infusion site reactions from start of drug administration until the end of infusion.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”
- Obtain information regarding the use of concomitant treatment.
- Discharge from the clinical site if the subject has been admitted.

6.2.3. Part 3 (Day 8)

- Conduct limited physical examination.
- Vital Signs (supine BP, PR and temperature).

- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).
  - Pharmacokinetic analysis.
  - Immunogenicity (ADA, NAb) blood sampling.
  - [redacted]
  - Pregnancy test for female subjects of childbearing potential.
- [redacted]
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Contraception check.
- Obtain information regarding the use of concomitant treatment and the occurrence of adverse events.

6.2.4. Part 3 (Day 113, Day 141, Day 169, Day 253, Day 337)

- [redacted]
- Collect weight.
- Obtain supine blood pressure (BP), pulse rate (PR) and temperature.
- Conduct limited physical examination.

  Note: Full physical examinations are required at the final study visit and early termination visit. A limited physical examination will be completed at all other times specified in the SoA. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.
- Collect single 12-lead ECG measurements (Day 113, Day 141 and Day 253).
- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast) (Day 113, Day 253 and Day 337).

- Pharmacokinetic analysis (Day 113, Day 253 and Day 337).

[redacted]

- Immunogenicity (ADA, NAb) blood sampling (Day 113, Day 253 and Day 337).
- Pregnancy test for female subjects of childbearing potential.

[redacted]

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Contraception check.
- Obtain information regarding the use of concomitant treatment.

6.2.5. Extended Follow-up

At these visits, the following procedures will be completed as indicated in the SoA.

[redacted]

- Obtain supine blood pressure (BP), pulse rate (PR) and temperature.
- Collect weight.
- Conduct limited physical examination.

  Note: Full physical examination is required at the final study visit. A limited physical examination will be completed at all other times specified in the SoA. A full physical examination may also be performed at the discretion of the investigator at a follow-up visit if there is a new or open AE.

- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).
  - Pharmacokinetic analysis.

[redacted]

- Immunogenicity (ADA, NAb) blood sampling.
- Pregnancy test for female subjects of childbearing potential.

[redacted]

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Contraception check.
- Obtain information regarding the use of concomitant treatment.

6.2.6. Subject Withdrawal

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

Lost to follow-up: All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site. The early termination visit only applies to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or site staff should attempt to contact the subject twice. After two attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events (AEs).

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the following assessments:

[redacted]

- Full physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit.
- Vital Signs (supine BP, PR and temperature) at the discretion of the Investigator.
- Collect weight.
- Collect single 12-lead ECG measurements (if subject withdraws before Day 113).
- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).
  - Pregnancy test for female subjects of childbearing potential.
  - Pharmacokinetic analysis.

[redacted]

  - Immunogenicity (ADA, NAb) blood sampling.

[redacted]

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?”
- Contraception check.
- Obtain information regarding the use of concomitant treatment.

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

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

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor (provided the nature of the safety event does not preclude dose escalation and exposure stopping limits are observed).

6.2.7. End of Study (EOS)

Subjects will be discharged either by phone or may need to return for one final visit. See Section 1.3.1.3 for criteria for discharge.

The following procedures will be done at the discharge visit if required.

[redacted]

- Full physical examination.
- Vital Signs (supine BP, PR and temperature) at the discretion of the Investigator.
- Collect blood and urine samples for the following:
  - Safety laboratory tests: Safety laboratory includes Hematology, Chemistry, and Urinalysis (following at least a 4-hour fast).
  - Pregnancy test for female subjects of childbearing potential.
  - Pharmacokinetic analysis.

- Immunogenicity (ADA, NAb) blood sampling.

[redacted]

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Contraception check.
- Obtain information regarding the use of concomitant treatment.
- Discharge from study.

7. ASSESSMENTS

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 subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventative 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.

7.1. Part 1 and 2

7.1.1. Safety

7.1.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the STUDY PROCEDURES 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 labs may be obtained at any time during the study to assess any perceived safety concerns.

Table 4. Laboratory Tests

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/urea 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]	FSH[b] HCG[c] Urine drug screening[d] HIV, HBsAg, HBcAb, and HCVAb[e] HBsAb[f] Phadiatop[e] QuantiFERON-TB Gold Test[e]
	Additional Tests (Needed for Hy's law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. At Screening only, in females who are amenorrheic for at least 12 consecutive months.
c. HCG (human chorionic gonadotropin) for female subjects of childbearing potential who have a documented bilateral tubal ligation or bilateral salpingectomy (Part 2 only)
d. At Screening, Day 0, and Day 31 (screening and Day 0 only for SAD cohorts).
e. At screening only. Phadiatop collection for Part 1 only; starting with Cohort 5 and later, Phadiatop is to be collected prior to dosing.
f. HBsAb test if screening results for HBsAg are negative and HBcAb are positive (for Part 1 (Cohort 5 and later) and Part 2.

- *Part 1*: Minimum requirement for drug screening includes: cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.

- *Part 2*: Minimum requirement for drug screening includes: cocaine, opiates/opioids, benzodiazepines and amphetamines.

- Subjects may undergo random urine drug screening at the discretion of the investigator. Drug screening conducted prior to dosing must be negative for subjects to receive study medication.

[redacted]

7.1.1.2. Pregnancy Testing (Part 2)

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at Screening, admission or Day 1 of all study periods, and follow-up visits. Results will be obtained prior to dosing during each period.

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

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

7.1.1.3. 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 subject reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects 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.

7.1.1.4. Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in STUDY PROCEDURES section of this protocol. 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 subject'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. Subjects should be instructed not to speak during measurements.

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.

7.1.1.5. Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes rest in supine position by observing and counting the respirations of the subject 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.

7.1.1.6. Temperature

Temperature will be measured orally. No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

7.1.1.7. Electrocardiogram

Electrocardiograms (ECGs) should be collected at times specified in the STUDY PROCEDURES section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2-4 minutes apart during clinical confinement at times specified in the SoA. Single ECGs will be collected at all other designated visits per SoA. The average of the triplicate ECG measurements collected pre-dose on Day 1 will serve as each subject'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 subjects, 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.

For triplicate ECGs, if the average of QTc values from the triplicate measurements 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 subject 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 are 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 physician's interpretation determines that the QTc values are in the acceptable range.

7.1.1.8. Continuous Cardiac Monitoring by Telemetry

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 study site, or verifiable arrhythmia quantification is required. 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 subject 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.

7.1.1.9. Infusion and Injection Site Reaction Assessment

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

Subject enrolled in to the SC single dose cohort will be monitored for signs of injection site reactions included but not limited to erythema, swelling, skin ulceration, pain or pruritus.

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.

7.1.2. Pharmacokinetic, Immunogenicity, [redacted] Samples

All samples will be collected according to the times outlined in the SoA. Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the study. Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures for PK, Anti-PF-06817024 ADA and NAb analysis; [redacted].

The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (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. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

As part of understanding the pharmacokinetics, [redacted] and immunogenicity of the study drug, samples may be used for further characterization and/or evaluation of the bioanalytical method. [redacted]

PK and immunogenicity samples from subjects receiving placebo will not be routinely analyzed. [redacted]

7.1.3. Pharmacokinetics (PK) for PF-06817024

Blood samples (4 mL) to provide a minimum of 1.5 mL serum for pharmacokinetic analysis will be collected into appropriately labeled tubes containing no anticoagulant or gel serum separator at times specified in the SoA section of the protocol.

The actual times for sample collection may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT).

7.1.4. Immunogenicity

Blood samples (4 mL) to provide a minimum of 1.5 mL serum for ADA and NAb analysis will be collected into appropriately labeled tubes containing no anticoagulant or gel serum separator.

Samples will be analyzed using a validated analytical method in compliance with Pfizer/vendor standard operating procedures (SOPs). Samples determined to be positive for ADA may be further characterized for NAb.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]


CCI
CCI
CCI
CCI
CCI

CCI [redacted]

7.1.9. Blood Volume

The total blood sampling volume for individual subjects in Part 1 of this study is approximately 690.5 mL for those in the SAD portion (from Screening through Day 211) and approximately 835 mL for those in the multiple dose component (from Screening through Day 241). The total blood sampling volume for individual subjects in Part 2 of this study (from Screening through Day 211) is approximately 624 mL. Table 5 and Table 6 reflect approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days.

Table 5. Blood Volume for Part 1

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL) (SAD/multiple dose)
		Screening	Study Period (SAD/multiple dose)	Follow-Up Visits (SAD/multiple dose)	
Safety Labs (including hematology, serology, chemistry and FSH)	7	1	5/10	10/8	112/133
QuantiFERON TB Gold Test	3	1	0	0	3
Phadiatop	4	1	0	0	4
PK	4	0	10/20	10/8	80/112
CCI					
Immunogenicity (ADA, NAb)	4	0	1/3	9/8	40/44
CCI					
TOTAL					690.5/835

SAD = Single ascending dose; TB = Tuberculosis.

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters or extended follow-up visits, if applicable. Each extended follow-up visit will increase the Total Blood Volume by 11 mL per visit.

Table 6. Blood Volume for Part 2

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow-Up Visits	
Safety Labs (including hematology, serology, chemistry, HCG and FSH)	7	1	2	9	84
QuantiFERON TB Gold Test	3	1	0	0	3
PK	4	0	7	9	64
CCI					
Immunogenicity (ADA, NAb)	4	0	1	7	32
CCI					
TOTAL					624

TB = Tuberculosis.

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters or extended follow-up visits, if applicable. Each extended follow-up visit will increase the Total Blood Volume by 13 mL per visit.

7.1.9.1. Potential Cases of Acute Kidney Injury

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

An increase of ≥0.3 mg/dL (or ≥26.5 μmol/L) in serum creatinine relative to subjects' own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48-hours from awareness

If the second assessment (after the 1st observations of ≥0.3 mg/dL (or ≥26.5 μmol/L) in serum creatinine relative to subjects' own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 μmol/L), the subject should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury

Subjects should return to the investigational site and be evaluated as soon as possible, preferably within 48-hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include: serum

blood-urea-nitrogen, serum creatine kinase, serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute-kidney-injury, with no other cause(s) of laboratory abnormalities identified should be considered as potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 subjects in the same cohort are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 μmol/L), an assessment of whether the finding may be considered adverse drug reaction should be undertaken.

CCI

CCI

CCI

7.1.16. Endoscopy (Part 2 only)

A nasal endoscopy is to be completed during the screening period per SoA Table D. A qualified ear, nose, and throat (ENT) physician is to complete the nasal endoscopy and endoscopic nasal polyp score (NPS) to determine study eligibility.

7.1.16.1. Nasal Polyp Score (Part 2 only)

The NPS used to assess eligibility for inclusion in this study is a modified version of the staging system proposed by the Rhinosinusitis Initiative in 2006,[44] as used in studies of nasal steroids,[45] dupilumab,[46] omalizumab,[47] reslizumab,[48] and mepolizumab[49] in CRSwNP. The NPS is to be completed and calculated by an ENT physician (see Appendix 3).

7.2. Part 3

7.2.1. Safety

7.2.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the STUDY PROCEDURES 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 labs may be obtained at any time during the study to assess any perceived safety concerns. Abnormal safety labs maybe repeated at investigator's discretion. Safety labs maybe collected by standard phlebotomy or from the IV catheter.

Table 7. Laboratory Tests

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/urea 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]	FSH[b,f] HCG[c] Urine drug screening[f,g] HIV, HBsAg, HBcAb, and HCVAb[e,f] HBsAb[d] QuantiFERON-TB Gold Test[f]
	Additional Tests (Needed for Hy's law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. At Screening only, in females who are amenorrheic for at least 12 consecutive months.
c. Serum or Urine HCG (human chorionic gonadotropin) (sensitivity of ≤25 mIU/mL) for female subjects of childbearing potential.
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. At screening.
g. At Day 1.

- Minimum requirement for drug screening includes: cocaine, opiates/opioids, benzodiazepines and amphetamines.

- Subjects may undergo random urine drug screening at the discretion of the investigator. Drug screening conducted prior to dosing must be negative for subjects to receive study medication. If urine drug test result at baseline is not available, subject with a negative drug test result at screening may be dosed if the subject has no prior history of drug abuse.

- Any remaining serum/plasma from samples collected for clinical safety labs at baseline may be retained for at least 2 years from the time of collection or 1 year after the completion of the study (whichever comes first), after which they can be discarded. CCI [redacted]

7.2.1.2. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test with sensitivity of at least 25 mIU/mL, will be performed at Screening, all study periods (Week 0, Week 1, Week 4, Week 8, Week 12, Week 16), follow-up (Week 20, Week 24, Week 36, Week 48) and extended follow-up visits. Results will be obtained prior to dosing during each period. A negative pregnancy result is required before the subject may receive the investigational product. In addition, urine pregnancy tests must be done at home by female subjects of childbearing potential at the nominal visits corresponding to Week 28, Week 32, Week 40 and Week 44 and every month between the scheduled extended visit follow-up visits. PI must be informed immediately if pregnancy test is positive and must see the PI for retesting. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ ethics committees (ECs) or if required by local regulations.

Pregnancy testing MUST have been performed within the permitted window and the result MUST be negative for female subjects of childbearing potential prior to dosing. Pregnancy test results will be documented in the CRF.

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

7.2.1.3. 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 subject reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects 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.

7.2.1.4. Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in STUDY PROCEDURES section of this protocol. 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 subject'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. Subjects should be instructed not to speak during measurements.

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.

7.2.1.5. Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes rest in supine position by observing and counting the respirations of the subject 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.

7.2.1.6. Temperature

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.

7.2.1.7. Electrocardiogram

Electrocardiograms (ECGs) should be collected at times specified in the STUDY PROCEDURES section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

Single ECGs will be collected at all other designated visits per SoA. 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 subjects, 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 subject 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 are 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 physician's interpretation determines that the QTc values are in the acceptable range.

7.2.1.8. Infusion and Injection Site Reaction Assessment

Subjects will be monitored for signs of any infusion site reactions including but not limited to erythema, swelling, bruising, pain or pruritus as 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.

7.2.2. Pharmacokinetic, Immunogenicity, CCI [redacted] Samples

All samples will be collected according to the times outlined in the SoA. Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site prior to initiation of the study. Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures for PK, Anti-PF-06817024 ADA and NAb analysis; CCI [redacted]

The samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the processing steps (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. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

As part of understanding the pharmacokinetics (PK), CCI and immunogenicity of the study drug, samples may be used for further characterization and/or evaluation of the bioanalytical methods. CCI

PK and immunogenicity samples from subjects receiving placebo will not be routinely analyzed. CCI

7.2.2.1. Pharmacokinetics (PK) for PF-06817024

Blood samples (4 mL) to provide a minimum of 1.5 mL serum for pharmacokinetic analysis will be collected into appropriately labeled tubes containing no anticoagulant or gel serum separator at times specified in the SoA Table E of the protocol.

The actual times for sample collection may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT).

7.2.2.2. Immunogenicity

Blood samples (4 mL) to provide a minimum of 1.5 mL serum for ADA and NAb analysis will be collected into appropriately labeled tubes containing no anticoagulant or gel serum separator.

Samples will be analyzed using a validated analytical method in compliance with Pfizer/vendor standard operating procedures (SOPs). Samples determined to be positive for ADA may be further characterized for NAb.

CCI

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI

CCI

CCI

CCI

[redacted]

7.2.5. Blood Volume

The total blood sampling volume for individual subjects in Part 3 of this study (from Screening through Day 337) is approximately 368 mL (Table 8). The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days.

Table 8. Blood Volume for Part 3

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period (Day1/ Week 0-Day 113/ Week 16)	Follow-Up Visits (Day 141/ Week 20 – Day 337/ Week 48)	
Safety Labs (including hematology, serology, chemistry, HCG and FSH)	7	1	6	2	63
QuantiFERON TB Gold Test	3	1	0	0	3
PK	4	0	10	2	48
CCI					
Immunogenicity (ADA, NAb)	4	0	6	2	32
CCI					
TOTAL					368

ADA = antidrug antibody; CCI FSH = follicle-stimulating hormone; HCG = human chorionic gonadotropin; TB = Tuberculosis; CCI NAb = neutralizing antibody; PK = pharmacokinetic; CCI

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters or extended follow-up visits, if applicable. Each extended follow-up visit will increase the Total Blood Volume by 44 mL per visit.

7.2.5.1. Potential Cases of Acute Kidney Injury

See Section 7.1.9.1.

7.2.6. Atopic Dermatitis History

Atopic Dermatitis Disease History includes AD diagnosis, AD history including atopic disease history, duration of AD, the use of topical treatments, systemic treatments and other treatments for AD. Inclusion/exclusion criteria assessment includes diagnosis of chronic AD (per Eichenfield revised criteria of Hannifin and Rajka-Appendix 16, EASI (includes BSA) – Appendix 8 and IGA – Appendix 10) performed at the screening visit.

7.2.7. Spirometry (subjects with a history of asthma only)

Spirometry is to be completed during the screening period per SoA Table E. Post screening spirometry may be performed at investigator discretion to assess potential changes in lung function. Spirometry will be performed using standardized equipment. Spirometry will be performed in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force: standardization of lung function testing guidelines 2005.[38] Sufficient forced expiratory maneuvers (up to a maximum of 5) will be performed to produce at least 1 technically adequate tracing. The forced expiratory volume in one second (FEV_1) will be recorded as absolute volumes in liters and in terms of predicted values (Third National Health and Nutrition Examination Survey (NHANES III))[39] according to age, height, race and gender. The best (largest) FEV_1 measurement from the technically adequate tracings collected will be used to determine eligibility for the study.

7.2.8. Physician Assessments

7.2.8.1. Fitzpatrick Skin Type Assessment

As part of baseline characteristics, a skin type assessment will be done at the Day 1 visit using the Fitzpatrick Skin Phototype assessment (Appendix 7). This is used to classify a person's skin type by their response to sun exposure (ie, burning or tanning).

7.2.8.2. Eczema Area and Severity Index (EASI)[63]

The EASI quantifies the severity of a subject's atopic dermatitis based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring by the atopic dermatitis clinical evaluator of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body. See Appendix 8.

7.2.8.4. Investigator Global Assessment (IGA)[64]

The clinical evaluator of atopic dermatitis will perform an assessment of the overall severity of atopic dermatitis and assign an IGA score and category as described in Appendix 10. The assessment will be a static evaluation without regard to the score at a previous visit.

7.2.8.5. Columbia Suicide Severity Rating Scale (C-SSRS)[66]

Columbia suicide severity rating scale is a validated tool to evaluate suicidal ideation and behavior (Appendix 15).

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 subject will not be included in the study.

CCI

CCI

CCI

CCI

CCI

CCI

CCI

[redacted]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the Sponsor as a SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through the end of the study. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

AEs (serious and nonserious) should be recorded on the CRF/DCT from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings.
- Clinically significant symptoms and signs.
- Changes in physical examination findings.
- Hypersensitivity.
- Progression/worsening of underlying disease.
- Drug abuse.
- Drug dependency.

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

- Drug overdose.
- Drug withdrawal.
- Drug misuse.
- Drug interactions.
- Extravasation.
- Exposure during pregnancy (EDP).

- Exposure via breastfeeding.
- Medication error.
- Occupational exposure.

8.4. Medication Errors

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

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

- Medication errors involving subject exposure to the investigational product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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

8.5. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death.
- Is life-threatening (immediate risk of death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions).
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

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

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 x ULN, or ≥8 x ULN (whichever is smaller).

Concurrent with:

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

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

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

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities.

- Hospice facilities.

- Respite care (eg, caregiver relief).
- Skilled nursing facilities.
- Nursing homes.
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pre-treatment laboratory abnormality).
- Social admission (eg, subject has no place to sleep).
- Administrative admission (eg, for yearly physical examination).
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol).
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs/DCTs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF/DCT, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF/DCT, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

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

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

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

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

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation

or spillage) using the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

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

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

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

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

8.11. Occupational Exposure

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

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

8.12. Withdrawal Due to Adverse Events (see also the section on Subject Withdrawal)

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

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

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

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

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

8.14.2. Nonserious Adverse Event Reporting Requirements

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

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study are outlined here and further detailed in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. The Statistical Analysis Plan 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.

CCI [redacted]

The study will be divided into two parts. Part 1 is the healthy subject section while Part 2 will include the patient cohorts. Results of Parts 1 and 2 will be summarized and displayed in separate tables when appropriate. Results from the SAD and multiple dose portions of Part 1 may also be displayed in separate tables as appropriate.

An additional Part 3 with AD subjects is included as part of Protocol Amendment #4. Results will be summarized and displayed in separate tables when appropriate.

In addition, summarizations of unblinded preliminary safety, PK, CCI [redacted] may be performed for each part after Week 12 safety, PK, and CCI [redacted] have been obtained from a majority of subjects in that Part, as applicable, but prior to the end of the study and full safety follow-up. Further details will be defined in the SAP.

9.1. Sample Size Determination

For Parts 1 and 2, the sample size of approximately 56 healthy subjects (up to 80 if separate multiple dose cohorts are needed) and up to approximately 35 patients with CRSwNP, for a total of up to approximately 91 subjects (up to 115 with separate multiple dose cohorts), was based on the clinical considerations to provide safety, tolerability information and pharmacological considerations and on the desire to minimize exposure to healthy subjects at each dose level. Early withdrawals may be replaced to ensure sufficient subjects at each dose level to adequately assess safety and PK information and to provide a placebo group

comparison group. No formal statistical testing will be applied to the safety, PK [redacted] data.

For Part 3, the sample size of approximately 20 subjects with moderate to severe AD was based on the clinical considerations to provide safety, tolerability, and [redacted] information, and on the desire to minimize exposure to AD subjects before the safety and tolerability of PF-06817024 in subjects with AD is established. Additional subjects up to a total of approximately 32 will be [redacted] Early withdrawals may be replaced to ensure sufficient subjects at each dose level to assess safety, PK [redacted] information adequately and to provide a placebo group comparison group. No formal statistical testing will be applied to the safety, PK or [redacted].

9.2. Efficacy Analysis

Efficacy analysis is not applicable to this study.

9.3. Pharmacokinetic Analysis

The PK concentration population will be defined as all randomized subjects who received at least 1 dose of PF-06817024 and in whom at least 1 concentration value is reported. The PK parameter analysis population is defined as all enrolled subjects who received at least 1 dose of PF-06817024 and in whom at least one of the PK parameters of interest is calculated.

PK parameters for PF-06817024 following single and multiple dose administration will be derived from the concentration-time profiles by non-compartmental analysis. The PK parameters are defined in Table 9.

Table 9. Definition of PK Parameters in Study C0341001

Parameter	Definition	Period†	Method of Determination
C_{max}	Maximum serum concentration	SD/MD	Observed directly from data
C_{max}(dn)	Dose normalized C_{max}	SD/MD	C_{max}/Dose
C_{min}	Trough serum concentration	MD	Observed directly from data
T_{max}	Time for C_{max}	SD/MD	Observed directly from data as time of first occurrence
AUC_{last}	Area under the plasma concentration-time profile over the dosing interval τ	SD	Linear/Log trapezoidal method
AUC_{inf}*	Area under the plasma concentration-time profile from zero to infinity	SD	Linear/Log trapezoidal method
AUC_{tau}	Area under curve within dosing interval, τ = 720 hr for single dose cohort	MD	Linear/Log Trapezoidal method

Table 9. Definition of PK Parameters in Study C0341001

Parameter	Definition	Period†	Method of Determination
AUC_{tau}(dn)	Dose normalized AUC_{tau}	MD	AUC_{tau}/Dose
C_{av}	Average concentration over dosing interval	MD	AUC_{tau} /tau
CL* (IV only)	Clearance	SD	Dose / AUC_{inf}
Vss* (IV only)	Volume of distribution at steady state	SD	$AUMC_{inf}/AUC_{inf}$*CL
CL/F* (SC only)	Apparent clearance	SD	Dose/AUC_{inf}
Vz/F* (SC only)	Apparent volume of distribution	SD	Dose/(AUC_{inf}·k_{el})
$t_{1/2}$*	Terminal elimination half-life	SD/MD	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.
$R_{ac,}$ AUCtau	Accumulation ratio for AUC_{tau}	MD	AUC_{tau} last dose/AUC_{tau} first dose
$R_{ac,}$ C_{max}	Accumulation ratio for C_{max}	MD	C_{max} last dose/C_{max} first dose

† Period column defines whether a parameter should be calculated after single dosing (SD), multiple dosing (MD), or both (SD/MD).
*As data permits.

The concentration of PF-06817024 will be descriptively summarized and plotted by PK sampling time and treatment group. PK parameters will be descriptively summarized by treatment group.

Dose normalized AUC_{tau}, and C_{max} will be plotted against dose (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.

CCI

[redacted]

[redacted]

CCI

CCI

CCI

9.6. Safety Analysis

TEAEs, withdrawals due to TEAEs, treatment emergent SAEs, ECGs, vital sign parameters, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, or vital sign abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Immunogenicity (ADA, NAb) results will be listed and summarized by cohorts and time points. Subject level immune response will also be summarized by cohorts. Effect of positive ADA and neutralizing immune response on safety, CCI and PK may be assessed, if appropriate.

Medical history, physical examination, continuous cardiac monitoring per SoA, and neurologic examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on continuous cardiac monitoring per SoA, physical and/or neurologic examinations conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that is used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be considered

source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at Screening will be reported.

Part 3 safety analyses will be done as described above.

9.6.1. Electrocardiogram (ECG) Analysis

Abnormal and clinical relevant changes for the ECG parameters QT interval, heart rate, QTc interval, PR interval and QRS interval will be summarized by treatment and time.

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

Safety QTc

	Borderline (msec)	Prolonged (msec)
Absolute Value	≥450 - <480	≥480
Absolute Change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

If more than one ECG is collected at a nominal time post dose (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 three individual ECG tracings has a QTc value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report 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 QTc post dose from the time-matched average baseline triplicates on Day 0, or the average of the pre-dose triplicate values on Day 1.

Part 3 ECG data analysis will be done as described above.

9.7. Interim Analysis

No formal interim analysis will be conducted for this study. However, 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 assessment, facilitating dose-escalation decisions, facilitating PK/[redacted] modeling, and/or to support clinical development. Unblinded results will be reviewed by a designated limited number of Sponsor colleagues within the study team. Refer to the study's Data Blinding Plan and/or Statistical Analysis Plan for specific details including delineation of study team members who will be involved in these unblinded reviews as well as steps to be instituted ahead of initiation of any unblinded review to ensure study integrity is maintained.

9.8. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer study sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs/DCTs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

For studies conducted at non-Pfizer study sites, it is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

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

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs/DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs/DCTs must be signed by the investigator or by an authorized staff

member to attest that the data contained on the CRFs/DCTs is true. Any corrections to entries made in the CRFs/DCTs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs/DCTs must match those charts.

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

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs/DCTs and hospital records), all original signed informed consent documents, copies of all CRFs/DCTs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board / Ethics Committee

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

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

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

12.3. Subject Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

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

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

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

12.4. Subject Recruitment

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06817024 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs/DCTs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

16. REFERENCES

1. Cayrol C, Girard JP. IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy. Current Opin Immunol 2014; 31:31-7.

2. Molofsky AB, Savage AK, Locksley RM. Interleukin-33 in Tissue Homeostasis, Injury, and Inflammation. Immunity. 2015; 42(6):1005-19.

3. Martin NT, Martin MU. Interleukin 33 is a guardian of barriers and a local alarmin. Nat Immunol 2016; 17(2):122-31.

4. Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. J Allergy Clin Immunol 2015; 135(3):626-35.

5. Wynn TA. Type 2 cytokines: mechanisms and therapeutic strategies. Nat Rev Immunol 2015; 15(5):271-82.

6. Rivellese F, Suurmond J, de Paulis A, et al. IgE and IL-33-mediated triggering of human basophils inhibits TLR4-induced monocyte activation. Eur J Immunol 2014; 44(10):3045-55.

7. Suzukawa M, Iikura M, Koketsu R, et al. An IL-1 cytokine member, IL-33, induces human basophil activation via its ST2 receptor. J Immunol 2008; 181(9):5981-9.

8. Vocca L, Di Sano C, Uasuf CG, et al. IL-33/ST2 axis controls Th2/IL-31 and Th17 immune response in allergic airway diseases. Immunobiology 2015; 220(8):954-63.

9. Maier E, Werner D, Duschl A, et al. Human Th2 but not Th9 cells release IL-31 in a STAT6/NF-kappaB-dependent way. J Immunol 2014; 193(2):645-54.

10. Bachert C, Pawankar R, Zhang L, et al. ICON: chronic rhinosinusitis. The World Allergy Organization journal. 2014; 7(1):25.

11. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology 2012; 50(1):1-12.

12. Alobid I, Benitez P, Bernal-Sprekelsen M, et al. Nasal polyposis and its impact on quality of life: comparison between the effects of medical and surgical treatments. Allergy. 2005; 60(4):452-8.

13. Bhattacharyya N, Orlandi RR, Grebner J, et al. Cost burden of chronic rhinosinusitis: a claims-based study. Otolaryngol-Head Neck Surg 2011; 144(3):440-5.

14. Browne JP, Hopkins C, Slack R, et al. Health-related quality of life after polypectomy with and without additional surgery. Laryngoscope. 2006; 116(2):297-302.

15. Vlaminck S, Vauterin T, Hellings PW, et al. The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: a 3-year prospective observational study. Am J Rhinol Allergy 2014; 28(3):260-4.

16. Vento SI, Ertama LO, Hytonen ML, et al. Nasal polyposis: clinical course during 20 years. Ann Allergy Asthma Immunol 2000; 85(3):209-14.

17. Lam K, Schleimer R, Kern RC. The etiology and pathogenesis of chronic rhinosinusitis: a review of current hypotheses. Curr Allergy Asthma Rep 2015; 15(7):41.

18. Stevens WW, Lee RJ, Schleimer RP, et al. Chronic rhinosinusitis pathogenesis. The J Allergy Clin Immunol 2015; 136(6):1442-53.

19. Van Zele T, Claeys S, Gevaert P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy. 2006; 61(11):1280-9.

20. Scheckenbach K, Wagenmann M. Cytokine patterns and endotypes in acute and chronic rhinosinusitis. Current Allergy Asthma Rep 2016; 16(1)(Jan):3.

21. Bachert C, Holtappels G. Pathophysiology of chronic rhinosinusitis, pharmaceutical therapy options. GMS Curr Top Otorhinolaryngol Head Neck Surg 2015; 14:Doc09.

22. Hirota T, Takahashi A, Kubo M, et al. Genome-wide association study identifies eight new susceptibility loci for atopic dermatitis in the Japanese population. Nat Genet 2012; 44(11):1222-6.

23. Bonnelykke K, Matheson MC, Pers TH, et al. Meta-analysis of genome-wide association studies identifies ten loci influencing allergic sensitization. Nat Genet 2013; 45(8):902-6.

24. Savenije OE, Mahachie John JM, Granell R, et al. Association of IL33-IL-1 receptor-like 1 (IL1RL1) pathway polymorphisms with wheezing phenotypes and asthma in childhood. The Journal of allergy and clinical immunology. 2014; 134(1):170-7.

25. Li J, Zhang Y, Zhang L. Discovering susceptibility genes for allergic rhinitis and allergy using a genome-wide association study strategy. Curr Opin Allergy Clin Immunol 2015; 15(1):33-40.

26. Liao B, Cao PP, Zeng M, et al. Interaction of thymic stromal lymphopoietin, IL-33, and their receptors in epithelial cells in eosinophilic chronic rhinosinusitis with nasal polyps. Allergy 2015; 70(9):1169-80.

27. Cohen ES, Scott IC, Majithiya JB, et al. Oxidation of the alarmin IL-33 regulates ST2-dependent inflammation. Nat Commun 2015; 6:8327.

CCI

CCI

CCI

CCI

CCI [redacted]

44. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: developing guidance for clinical trials. Journal Allergy Clin Immunol 2006; 118(5 Suppl):S17-61.

45. Tuncer U, Soylu L, Aydogan B, et al. The effectiveness of steroid treatment in nasal polyposis. Auris Nasus Larynx. 2003; 30(3):263-8.

46. Bachert C, Mannent L, Naclerio RM, et al. Dupilumab in chronic sinusitis with nasal polyposis, with and without asthma. Allergy 2015; 70 (Suppl S101)107 (Abstr 1516).

47. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 2013; 131(1):110-6-e1.

48. Gevaert P, Lang-Loidolt D, Lackner A, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. J Allergy Clin Immunol 2006; 118(5):1133-41.

49. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. Journal Allergy Clin Immunol 2011; 128(5):989-95 e1-8.

50. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117(2):391-97.

CCI [redacted]

52. Eichenfield LF, Tom WI, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis. Journal of the American Academy of Dermatology 2014;71(3):338-51.

53. Beck, L. A., D. Thaci, J. D. Hamilton, N. M. Graham, T. Bieber, R. Rocklin, J. E. Ming, H. Ren, R. Kao, E. Simpson, M. Ardeleanu, S. P. Weinstein, G. Pirozzi, E. Guttman-Yassky, M. Suarez-Farinas, M. D. Hager, N. Stahl, G. D. Yancopoulos and A. R. Radin (2014). "Dupilumab treatment in adults with moderate-to-severe atopic dermatitis." N Engl J Med 371(2): 130-139.

54. Deckers, I. A., S. McLean, S. Linssen, M. Mommers, C. P. van Schayck and A. Sheikh (2012). "Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies." PLoS One 7(7): e39803.

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

56. Homey, B., M. Steinhoff, T. Ruzicka and D. Y. Leung (2006). "Cytokines and chemokines orchestrate atopic skin inflammation." J Allergy Clin Immunol 118(1): 178-189.

57. Cornelissen, C., J. Luscher-Firzlaff, J. M. Baron and B. Luscher (2012). "Signaling by IL-31 and functional consequences." Eur J Cell Biol 91(6-7): 552-566.

58. Auriemma, M., G. Vianale, P. Amerio and M. Reale (2013). "Cytokines and T cells in atopic dermatitis." Eur Cytokine Netw 24(1): 37-44.

59. Slater, N. A. and D. S. Morrell (2015). "Systemic therapy of childhood atopic dermatitis." Clin Dermatol 33(3): 289-299.

60. Leung, D. Y. and T. Bieber (2003). "Atopic dermatitis." Lancet 361(9352): 151-160.

61. Ring, J., A. Alomar, T. Bieber, M. Deleuran, A. Fink-Wagner, C. Gelmetti, U. Gieler, J. Lipozencic, T. Luger, A. P. Oranje, T. Schafer, T. Schwennesen, S. Seidenari, D. Simon, S. Stander, G. Stingl, S. Szalai, J. C. Szepietowski, A. Taieb, T. Werfel, A. Wollenberg, U. Darsow, F. European Dermatology, D. European Academy of, Venereology, A. European Federation of, D. European Task Force on Atopic, D. European Society of Pediatric, A. Global and N. Asthma European (2012). "Guidelines for treatment of atopic eczema (atopic dermatitis) part I." J Eur Acad Dermatol Venereol 26(8): 1045-1060.

CCI [redacted]

63. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, et al. (2001) The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol 10: 11–18.JM HanifinM. ThurstonM. OmotoR. CherillSJ Tofte2001The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group.Exp Dermatol101118.

64. Siegfried E, Korman N, Molina C, Kianifard F, Abrams K (2006) Safety and efficacy of early intervention with pimecrolimus cream 1% combined with corticosteroids for major flares in infants and children with atopic dermatitis. J Dermatolog Treat 17: 143-150.E. SiegfriedN. KormanC. MolinaF. KianifardK. Abrams2006Safety and efficacy of early intervention with pimecrolimus cream 1% combined with corticosteroids for major flares in infants and children with atopic dermatitis.J Dermatolog Treat17143150.

CCI [redacted]

66. Posner, K., M. A. Oquendo, M. Gould, B. Stanley and M. Davies (2007). "Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants." The American journal of psychiatry 164(7): 1035-1043.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted] CCI [redacted]

CCI [redacted]	[redacted]	[redacted]
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

[redacted]

Appendix 3. Nasal Polyp Score (NPS)[44]

Polyp Score	Polyp Size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior nasal cavity
Each side's Nasal Polyp Score (0-4) will be determined for each side (left, right). Bilateral NPS (0-8) = left NPS (0-4) + right NPS (0-4).	

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix 5. Abbreviations

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

Abbreviation	Term
CCI [redacted]	[redacted]
AD	Atopic Dermatitis
ADA	Anti drug antibody
AE	Adverse event
Abs	Absolute
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	Area under the curve
AUC24	Area under the concentration-time curve from time 0 to 24 hours
AUC504	Area under the concentration-time curve from time 0 to 504 hours
AUCinf	Area under the concentration-time profile from time zero to infinity
AUClast	Area under the concentration-time profile from time zero to the time of the last quantifiable concentration
AUCtau	Area under the concentration–time curve within dosing interval
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
BSA	Body Region Surface Area
BUN	Blood urea nitrogen
Cav	Average concentration over dosing interval
CCI [redacted]	[redacted]
CDRs	Complementarity-determining regions
CL	Clearance
CL/F	Apparent clearance
Cmax	Maximum observed concentration
CO2	Carbon dioxide (bicarbonate)
CRF	Case report form
CRS	Chronic rhinosinusitis
CRSwNP	Chronic rhinosinusitis with nasal polyps
CRU	Clinical Research Unit
CSA	Cyclosporine A
CSA	Clinical study agreement
CSR	Clinical study report
CSSR-S	Columbia Suicide Severity Rating Scale
CT	Computerized axial tomography
CV	Cardiovascular
DAI	Dosage and administration instructions

Abbreviation	Term
DCT	Data collection tool
CCI [redacted]	[redacted]
DCF	Data Clarification Form
dn	Dose normalized
DNA	Deoxyribonucleic acid
EASI	Eczema and Severity Index
EC	Ethics committee
ECG	Electrocardiogram
CCI [redacted]	[redacted]
EDP	Exposure during pregnancy
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
ENT	Ear, nose and throat
EudraCT	European Clinical Trials Database
EU	European Union
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
GM-CSF	Granulocyte-macrophage colony stimulating factor
CCI [redacted]	[redacted]
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV Ab	Anti-Hepatitis C antibody
HED	Human equivalent dose
HIV	Human immunodeficiency virus
Hs-CRP	High Sensitivity C-Reactive Protein
IFN-γ	Interferon-gamma
IGA	Investigator Global Assessment
IP	Investigational Product
IB	Investigator's brochure
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	Identification
IgE	Immunoglobulin E
IgG1	Immunoglobulin Gamma 1
IL	Interleukin
IL1RL1	Interleukin 1 Receptor-Like 1
ILCs	Innate lymphoid cells
IND	Investigational new drug

Abbreviation	Term
INR	International normalized ratio
IRB	Institutional review board
ISR	Injection site-reactions
IUD	Intrauterine device
IV	Intravenous
JAK	Janus Kinase
K2EDTA	Potassium salt ethylenediaminetetraacetic acid
LFT	Liver function test
LSLV	Last subject last visit
mAB	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MD	Multiple dose
MTX	Methotrexate
mm2	IL-33 amino acids 112-270 with 4 cysteines changed to serine
CCI	[redacted]
MRT	Mean residence time
NAb	Neutralizing antibody
N/A	Not applicable
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
CCI	[redacted]
NSAIDs	Nonsteroidal anti-inflammatory drugs
Pbo	Placebo
CCI	[redacted]
PDE	Phosphodiesterase
PF	PF-06817024
PI	Principal investigator
PK	Pharmacokinetics
pM	Picomolar
CCI	[redacted]
PR	Pulse rate
PRO	Patient Reported Outcome
PROM	Patient-reported outcome measure
PT	Prothrombin time
CCI	[redacted]

Abbreviation	Term
QTc	Corrected QT
Rac	Accumulation ratio
RBC	Red blood cell
CCI	[redacted]
RR	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Single dose
SCr	Serum creatinine
CCI	[redacted]
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SNOT	Sino-Nasal Outcome Test
SoA	Schedule of Activities
SOC	System Organ Classes
SOP	Standard Operating Procedure
SRSD	Single reference safety document
CCI	[redacted]
CCI	[redacted]
t½	Terminal half-life
Tmax	Time to reach maximum concentration
CCI	[redacted]
TB	Tuberculosis
TEAEs	Treatment emergent adverse events
Th2	T lymphocytes
THC	Tetrahydrocannabinol
TK	Toxicokinetics
ULN	Upper limit of normal
CCI	[redacted]
US	United States
UVA	Ultraviolet A
UVB	Ultraviolet B
Vss	Volume of distribution at steady state
Vz/F	Apparent volume of distribution
WBC	White blood cell
wt	Wild-type

Appendix 6. Clinical Criteria for Diagnosing Anaphylaxis Guidance[50]

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

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 likely allergen for that patient* (minutes to several hours):

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

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

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

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

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

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

   b. 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.

Appendix 7. Fitzpatrick Skin Type

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

Appendix 8. EASI

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

Lesion Severity by Clinical Signs: The basic characteristics of atopic dermatitis lesions - erythema, induration/papulation, excoriation, and lichenification - provide a means for assessing the severity of lesions. Assessment of these four main clinical signs is performed separately for four body regions: head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks). Average erythema, induration/papulation, excoriation, and lichenification are scored for each body region according to a 4 point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Morphologic descriptors for each clinical sign severity score are shown in Table 10.

Table 10. 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 11). When measuring, the handprint unit refers to the size of each individual subject's hand with fingers in a closed position.

Table 11. Handprint Determination of Body Region Surface Area (BSA)

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

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

The extent (%) to which each of the four body regions is involved with atopic dermatitis is categorized to a numerical Area Score using a non-linear scaling method according to the following BSA scoring criteria (Table 12).

Table 12. 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 13. 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 SoA Table E.

CCI [redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

CCI [redacted]

[redacted]

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

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 10. Investigator Global Assessment (IGA) Score

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

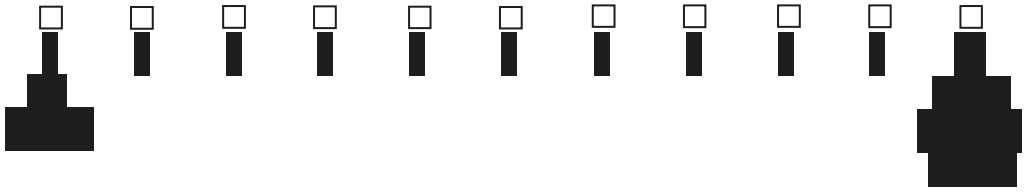
* The IGA will exclude scalp, palms, and soles from the assessment/scoring.

CCI

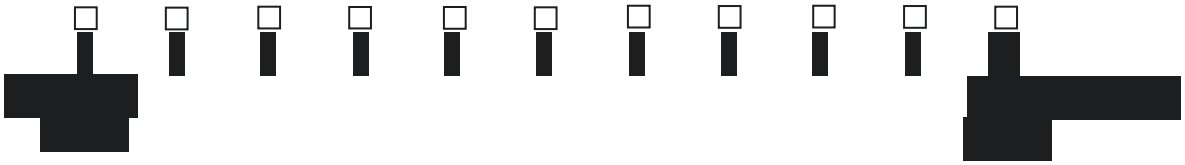
[redacted]

CCI

[redacted]



[redacted]



CCI [redacted]

[redacted]

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

CCI

CCI

[redacted]

[redacted]

Appendix 15. Columbia Suicide Severity Rating Scale (C-SSRS)

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* _____

Appendix 16. Diagnostic Criteria for Atopic Dermatitis

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

Hanifin and Rajka's Diagnostic Criteria for Atopic Dermatitis

Major Criteria (must have at least three)

Pruritus

Typical morphology and distribution:

- Adults: flexural lichenification or linearity
- Children and infants: involvement of facial and extensor surfaces

Chronic or relapsing dermatitis

Personal or family history of atopy

Minor Criteria (must have at least three)

Xerosis

Icthyosis/keratosis pilaris/palmer hyperlinearity

Immediate (type 1) skin test reactivity

Elevated serum IgE

Early age at onset

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

Hand/foot dermatitis

Nipple eczema

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

CCI

[redacted]