Protocol C4461001

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

Statistical Analysis Plan
(SAP)

Version: 2

Date: 30 Oct 2022

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 30 NOV 2020	Original 30 Sep 2020	N/A	N/A
2 01 Sep 2022	Protocol Amendment 2 10 Jul 2021	To be consistent with Protocol Amendment 2	1. Section 6.2.2. Added details of NRS endpoint analysis. 2. Section 6.2.5. Removed the summary of dosing compliance according study team agreement. 3. Section 6.3. Added details of immune-based AEs. 4. Section 6.3.4. Modified the language of vital signs analysis. 5. Appendix 3. Visit window was updated and added window definition for NRS endpoints. 6. Appendix 6. Modified the SAS code for Estimand 1 to be consistent with Section 6.2.

2. INTRODUCTION

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

This is the first time PF-07242813 will be given to humans. The purpose of the study is to evaluate the safety, tolerability, and pharmacokinetics of escalating single and repeat doses of PF-07242813 in healthy participants and in participants with moderate to severe atopic dermatitis. An additional goal is to assess the pharmacodynamics of PF-07242813 in participants with moderate to severe AD, including potential effects on clinical signs and symptoms.

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

currently approved drugs that increase the proportion of patients achieving complete resolution of skin inflammation and / or are effective in patients who do not respond or become refractory to dupilumab.

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

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

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4461001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Objectives and Endpoints Part 1 (Healthy Adult Participants)

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

Objectives	***Endpoints***	***Estimands***
Primary:	***Primary:***	***Primary:***
To evaluate the safety and tolerability of PF-07242813 versus placebo, in participants with moderate to severe AD.	*Incidence of treatment-emergent adverse events (AEs and SAEs); vital signs, safety laboratory tests, and ECG.*	*There is no defined estimand for these endpoints; they will be analyzed using CaPS as applicable.*
Secondary:	***Secondary:***	***Secondary:***
To compare the efficacy of PF-07242813 versus placebo on percent change from baseline in Eczema Area and Severity Index (EASI) in participants with moderate to severe atopic dermatitis (AD).	*Percent change from baseline in EASI total score at Week 6.*	*Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the study intervention on a continuous endpoint; without prohibited medications during treatment.* *Study Intervention: PF-07242813 or placebo.* *Population: Participants with moderate to severe AD as defined by the inclusion and exclusion criteria.* *Variable: Percent change from baseline in EASI total score at Week 6.* *Intercurrent Events:* *a. Prohibited medications – all scores in participants who receive prohibited medication post randomization to Week 6 will be omitted from the analysis and treated as missing scores.*

Objectives	***Endpoints***	***Estimands***
		Missing scores will be imputed based on the assumption that participants do not benefit from the study intervention. *b. Inadequate compliance – participants data will be used as recorded.* *Events a and b are stated with precedence in descending order.* *Population level summary:* *The percent change from baseline mean difference between PF-07242813 and placebo in EASI score.*
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Objectives	*Endpoints*	*Estimands*
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CCI [redacted]	[redacted]	[redacted]
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Objectives	*Endpoints*	*Estimands*
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[redacted]	[redacted]	[redacted]

2.1.1. Primary Estimand(s): Healthy Adult Participants

There is no defined estimand; the data will be analyzed using CaPS as applicable.

2.1.2. Secondary Estimand(s): Atopic Dermatitis Participants

Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the study intervention on a continuous endpoint; without prohibited medications during treatment. For example:

- Study Intervention: PF-07242813 or placebo.
- Population: Participants with moderate to severe AD as defined by the inclusion and exclusion criteria.
- Variable: Percent change from baseline in EASI total score at Week 6.
- Intercurrent Events:

  a. Prohibited medications – all scores in participants who receive prohibited medication post randomization to Week 6 will be omitted from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the study intervention.

  b. Inadequate compliance – participants data will be used as recorded.

  Events a and b are stated with precedence in descending order.

- Population level summary: The percent change from baseline mean difference between PF-07242813 and placebo in EASI score.

[redacted]

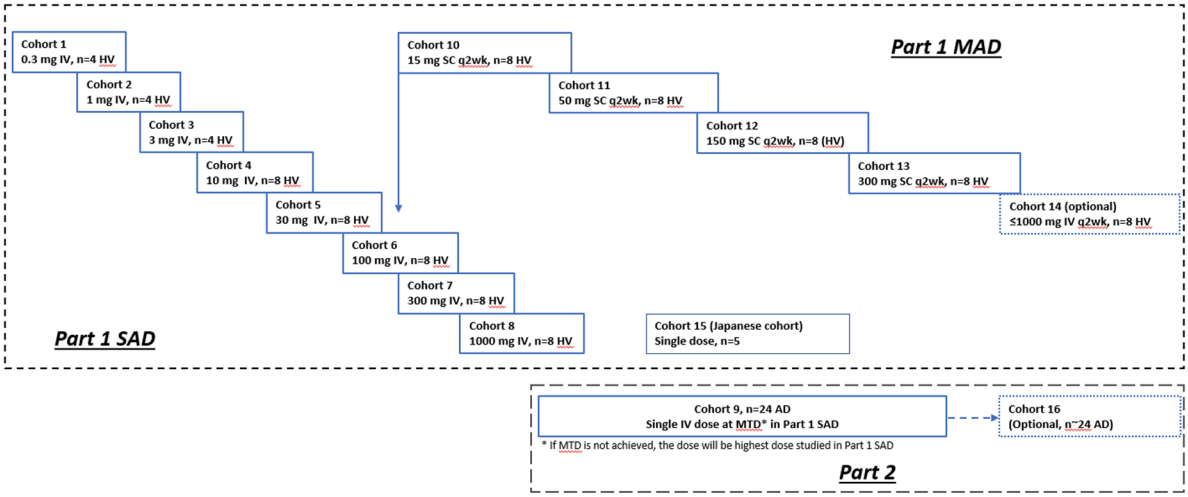
2.2. Study Design

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

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

Part 2 is a randomized, participant- and investigator-blind, sponsor-open, placebo-controlled investigation of the safety, tolerability, PK, and pharmacodynamics (including clinical effects) of PF-07242813 in participants with moderate to severe atopic dermatitis (AD). The first cohort in Part 2 (Cohort 9) will enroll 24 participants for the assessment of the clinical effects of PF-07242813 in AD and exploratory evaluations of pharmacodynamic activity. The number of participants enrolled in Cohort 9 will provide the total sample size (N=24) for statistical evaluation of the primary efficacy endpoint (placebo-corrected percent change from baseline in continuous EASI). Participants in Cohort 9 will receive the MTD defined in Part 1.

Figure 1. C4461001 Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

For the SAD/MAD and atopic dermatitis cohorts, baseline is defined as the last pre-dose measurement.

3.1. Endpoint(s): Part 1 - Healthy Adult Participants

3.1.1. Primary Endpoint(s)

- *Incidence of treatment-emergent adverse events (AEs and SAEs); vital signs, safety laboratory tests, cardiac telemetry (SAD only), and ECG.*

3.1.2. Secondary Endpoint(s)

- *PF-07242813 serum exposure as data permit: AUC_{last}, AUC_{inf}, C_{max}, T_{max} and $t_{1/2}$ after single doses; AUC_{τ}, C_{max}, and T_{max} after each repeated dose; and $t_{1/2}$ after the last repeated dose.*

3.1.3. Other Endpoint(s): Tertiary/Exploratory

- *PF-07242813 PK parameters, as data permit:* AUC_{last}*, dose normalized (dn),* AUC_{inf}*(dn),* C_{max}*(dn), CL and* V_z*/F/Vss after single doses;* AUC_{inf}*(dn),* C_{max} *(dn) after each repeated dose; CL/F, CL,* V_z*/F, accumulation ratio, peak to trough ratio (PTR) after the last repeated dose. F for SC administration.*

- *Incidence of the development of ADA and, if appropriate, NAb against PF-07242813 following single and multiple doses.*

- *Change from baseline in select anterior pituitary hormones levels and hormones regulated by them in blood that may include (but may not be limited to): HGH, IGF-1, TSH, T4 and Cortisol.*

- *Change from baseline in blood cytokine levels that may include, but not be limited to, TNFα, IL-6 and IFNγ if performed in concordance with clinical symptoms of cytokine release.*

3.2. Endpoint(s): Part 2 - Atopic Dermatitis Participants

3.2.1. Primary Endpoint(s)

- *Incidence of treatment-emergent adverse events (AEs and SAEs)*

- *Vital signs (blood pressure, pulse rate, respiratory rate, and temperature).*

- *Safety laboratory tests: Incidence and magnitude of clinical laboratory abnormalities including* hematology blood chemistry, and urinalysis*.*

- *ECG.*

3.2.2. Secondary Endpoint(s)

- *Percent change from baseline in EASI total score at Week 6.*

3.2.3. Other Endpoint(s): Tertiary/Exploratory

- *Serum PF-07242813 concentrations after administration will be determined by a validated assay.*

- *Proportion of participants achieving IGA score of clear (0) or almost clear (1) (on a 5 point scale) and a reduction from baseline of ≥2 points at Week 6 and other time points specified in the SoA.*

- *Percent change from baseline in EASI total score at time points in the SoA.*

- *Proportion of participants with moderate to severe AD achieving EASI-50/EASI-75/ EASI-90/EASI-100 (respectively 50%, 75%, 90%, and 100% improvement from baseline), at Week 6 and other time points specified in SOA.*

- *Incidence of development of antidrug antibodies (ADAs) and if appropriate, neutralizing antibodies (NAbs).*

- *Change from baseline in select anterior pituitary hormones levels and hormones regulated by them in blood that may include (but may not be limited to): HGH, IGF-1, TSH, T4 and Cortisol.*

- *Change from baseline in blood cytokine levels that may include, but not be limited to, TNFα, IL-6 and IFNγ if performed in concordance with clinical symptoms of cytokine release.*

- *Change from baseline in circulating biomarkers which may include Total IgE, TARC (CCL17), IL-31, IL-17A, eosinophils and lymphocyte subsets.*

- *Change from baseline in gene expression and/or histological endpoints may be measured from skin biopsies.*

- *Change from baseline in Patient-Oriented Eczema Measure (POEM) at Week 6 and at all other time points specified in the SoA.*

- *Change from baseline in Dermatology Life Quality Index (DLQI) at Week 6 and at all other time points specified in the SoA.*

- *Change from baseline in pruritus severity and frequency in Pruritus Numeric Rating Scale) at Week 6 and at all other time points specified in the SoA.*

3.3. Baseline Variables

In general, for all analyses, baseline will be defined based on observations collected prior to first dose. Baseline values for demographics, medical and other history, atopic dermatitis history will be based on measures collected at Visit 1/Screening visit. Study Day 1 is defined as the day the subject receives first dose of study drug. For purposes of all other analyses including analyses for change from baseline, the baseline value will be defined as measured on Day 1 predose. If a value is missing on Day 1, then the last available observation before Day 1 will be used.

3.4. Safety Endpoints

Safety will be assessed by the spontaneous reporting of AEs, physical examinations, and clinical laboratory results in all subjects who receive at least one dose of the investigational product. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns. Endpoints will be assessed as:

- Incidence of treatment emergent adverse events.
- Incidence of SAEs and AEs leading to discontinuation.
- Incidence of clinical abnormalities and change from baseline in selected clinical laboratory values, ECG measurements, and vital signs.

The safety endpoints will be defined in accordance with Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS).

3.4.1. Adverse Events

An adverse event will be considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (see Section 6.3.1).

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

Tier 2 events: These are events that are not tier 1 but are "common." A Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) is defined as a Tier 2 event if there are at least 4 in any treatment group.

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

3.4.2. Laboratory Data

Below is a list of hematology and serum chemistry test parameters.

- Hematology: hemoglobin, hematocrit, red blood cell count, reticulocyte count, platelet count, white blood cell count with differential, total neutrophils, eosinophils, monocytes, basophils, lymphocytes, coagulation panel.
- Serum chemistry: blood urea nitrogen, creatinine, creatine phosphokinase, glucose, sodium, potassium, chloride, calcium, total bicarbonate, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, bilirubin, alkaline phosphatase, lactate dehydrogenase, uric acid, albumin, total protein, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, cystatin C.

3.4.3. Vital Signs, including Height and Weight

Vital sign measurements are oral, temporal or tympanic temperature, provided the same method is used consistently throughout the study, respiratory rate, pulse rate, and blood pressures.

Weights are collected at the baseline.

3.4.4. Physical Examinations

A full physical examination includes head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance including skin (specific attention to infusion and injection site reactions), the respiratory, gastrointestinal, and cardiovascular systems, as well as towards participant reported symptoms.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description
Modified Intention to Treat (mITT)	*All participants randomly assigned to study intervention and who apply at least 1 dose of study intervention.*
PK concentration set	*All enrolled participants who applied at least one dose of PF-07242813 and in whom at least once concentration value is reported.*
PK parameters	The PK parameter analysis population will be defined as all randomized participants who received at least 1 dose of study intervention and who have at least 1 of the PK parameters of interest calculated.
Safety Analysis Set	*All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.*

4.1. Treatment Misallocation

All analyses will be performed on an “as-treated” basis and will not include data from participants who are randomized but not treated.

If a participant takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, PK and pharmacodynamic analyses, where applicable.

4.2. Protocol Deviations

Participants who experience events that may affect their PK profile may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis of atopic dermatitis cohort will be performed when all randomized subjects have either completed their 6-week study participation period or withdrawn early or should the study be stopped prematurely due to any reason, and the database is released.

5.1. Hypotheses and Decision Rules

5.1.1. Part 1 - Healthy Adult Participants

5.1.1.1. Statistical Hypotheses

No classical hypothesis testing will be performed.

5.1.1.2. Statistical Decision Rules

Not applicable.

5.1.2. Part 2 - Atopic Dermatitis Participants

Statistical inference will be made on the secondary endpoint: (percentage change from baseline in EASI score at Week 6). The null hypothesis is that there is no difference between the treatment group and the placebo group. The alternative hypothesis is that the treatment group (PF-07242813 arm) is superior to the placebo group at Week 6. The study will be considered positive, if this null hypothesis is rejected.

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

Cohort 9 will enroll 24 participants with moderate to severe AD at the MTD.

5.2. General Methods

5.2.1. Statistical Method: Part 1 - Healthy Participants Single and Multiple Ascending Dose

Given the exploratory nature, descriptive statistics and graphic visualization will be provided for these segments. No formal statistical hypothesis testing is planned.

5.2.2. Analyses for Binary Endpoints: Part 2 – Atopic Dermatitis Participants

Landmark (cross-sectional) analyses of key binary endpoints will calculate and test for risk differences using the method of Chan and Zhang (1999).[2] Risk differences, 90% confidence interval and 1-sided p-value will be presented.

For all binary endpoints, a summary based on the mITT Observed Efficacy Set of the number of subjects in each category based on observed cases in each treatment arm at each time point will be produced and the response rate will also be plotted against time, by treatment group.

Exploratory categorical analyses that include or assess the effects of covariates may be done on an exploratory basis. Exploratory longitudinal analyses may also be performed

5.2.3. Analyses for Continuous Endpoints: Part 2 - Atopic Dermatitis Participants

Landmark (cross-sectional) analysis of key continuous endpoints will use analysis of covariance (ANCOVA). The ANCOVA model will include terms for treatment arm and baseline score of the dependent variable. Least-squares means at the mean overall baseline score will be presented along with 90% confidence intervals.

Mixed model repeated measures (MMRM) models will be used. The fixed effects of treatment, visit (Weeks 1, 2, 3, 4, and 6), and treatment-by-visit interaction will be included. Visit will be modeled as a categorical covariate. Unstructured covariance matrix will be assumed for the model errors. Compound symmetry covariance matrix will be used if the model with unstructured covariance doesn’t converge.

When modeling the percentage change from baseline values, the variable for visit will start with the first post-baseline visit, and the actual baseline value will be included as a covariate. At each visit, estimates of least square mean (LSM) values and the LSM differences between the PF-07242813 and the placebo arm will be derived from the model. The corresponding p-values and 90% confidence intervals will also be derived from the model.

Unless stated otherwise, descriptive summary statistics for all continuous variables will be presented on mITT observed data by treatment group and will include the following:
n, mean, median, standard deviation, minimum and maximum.

5.2.4. Analyses for Categorical Endpoints: Part 2 - Atopic Dermatitis Participants

NA.

5.2.5. Analyses for Time-to-Event Endpoints: Part 2 – Atopic Dermatitis Participants

NA.

5.3. Methods to Manage Missing Data

5.3.1. PK Data

5.3.1.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ",where LLQ will be replaced with the value for the lower limit of quantification).

5.3.1.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if any of the following cases is true:

- A concentration has been collected as ND (ie, not done) or NS (ie, no sample);
- A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

5.3.1.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters. If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose level with ≥3 evaluable measurements.

If an individual participant has a known biased estimate of a PK parameter (due for example to an unexpected event), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Efficacy Data

The following patient level data descriptions are also required for defining the pre-specified analyses:

Defined Analysis Data set (at the data level) – endpoint specific	Description
Primary Estimand Continuous Endpoint Set	This set will include all patients in the mITT population. All data for a subject after the initiation of prohibited medications will be set to missing. Note the primary estimand requires multiple imputation which will be performed on this dataset, the multiple imputations themselves will not be saved in the database, however, the SAS specifications and random number seed will be.
Secondary Estimand Categorical Endpoint Set	This set will include all patients in the mITT population. All data for a subject after the initiation of prohibited medications, withdrawal of either study drug or the study itself will be set to a failure. Any other additional missing data will be recorded as a failure. Subjects will have either a success or failure in the dataset for all scheduled visits.
Observed Efficacy Set	This set will include all patients in the mITT population and all observed data and includes all data recorded from the CRF pages. No data will be set to missing or modified from the original CRF record.

The primary analysis will use the primary estimand continuous endpoint set. For each landmark analysis (eg, Cross sectional analysis by week) missing data will imputed using a control-based imputation method. PROC MI will first be called at the visit and a control-based method (implemented with the missing not at random (MNAR) option) will impute missing vehicle observations under the assumption data are missing at random (MAR) and impute missing treatment observations assuming they are similar to corresponding vehicle patients. Imputation will use the full conditional specification (FCS) method, the imputed data for the treatment and placebo arms will be combined for the analysis.

Summaries of continuous data will use the observed data only and no additional considerations are needed.

Analysis of binary data will use the Secondary Estimand Categorical Endpoint Set. This dataset by definition has no missing data since all missing values will have been set to a failure. Summaries will use the Observed Efficacy Set and will report results on an observed case (OC) basis.

6. ANALYSES AND SUMMARIES

6.1. Part 1: Healthy Adult Participants

6.1.1. Primary Endpoint(s)

6.1.1.1. Safety Summaries and Analyses

All safety analyses will be performed on the safety population.

All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Change from baseline on laboratory data and vital signs will be additionally summarized. Participant listings will also be produced for these safety endpoints.

6.1.1.1.1. Adverse Events

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date. Events that occur in a non-treatment period (follow-up or washout period) will be counted as treatment emergent and attributed to the previous treatment taken.

6.1.1.1.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol. To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter. Baseline of safety laboratory tests will be the last pre-dose measurement.

6.1.1.1.3. Vital Signs

Single supine blood pressure (both diastolic and systolic), pulse rate, respiratory rate and/or temperature will be collected at times specified in the Schedule of Activities in the protocol.

The following vital signs endpoints will be determined and summarized for each treatment group.

- Actual values, change from baseline in supine blood pressure, pulse rate, respiratory rate and temperature over all measurements taken postdose;
- The maximum decrease and increase from baseline over all measurements taken postdose for supine blood pressure.

Baseline will be defined as the last pre-dose recording. The increase from baseline will be calculated by subtracting the baseline value from each post-dose measurement to give the change from baseline for each participant. The maximum of these values over the duration of dosing will be reported as maximum increase from baseline, except where a participant does not show an increase. In such an instance, the minimum decrease will be reported.

Similarly, decrease from baseline will be calculated by subtracting each post-dose measurement from individual participant's baseline value. Maximum decrease from baseline will be reported as the minimum value of the changes from baseline. In cases where a participant does not show a decrease, the minimum increase will be reported.

Maximum absolute values and changes from baseline for vital signs will also be tabulated by treatment using categories as defined in Appendix 1.

6.1.1.1.4. Electrocardiograms

The QT, QTc, PR, heart rate (HR) and QRS complex will be recorded at each assessment time, as specified in the Schedule of Activities.

If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

$$\text{QTcF} = \frac{\text{QT}}{(\text{RR})^{1/3}} \qquad \text{where RR} = 60/\text{HR(if not provided)}.$$

The average of the triplicate ECG measurements collected before dose administration on Day 1 of each cohort will serve as each participant's baseline value.

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

Changes from baseline will be defined as the change between postdose ECG parameter values and the baseline. If triplicate postdose measurements are collected, the average of the values will be used in the analysis.

The maximum absolute value (post-dose) and the maximum increase from baseline for QTcF, QT, heart rate, PR and QRS, will be determined over all measurements taken post-dose and reported.

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

Safety QTc Assessment

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

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

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

In addition, an attempt will be made to explore and characterize the relationship between serum concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

In addition, PR and QRS maximum values and maximum increases from baseline will also be tabulated by treatment using categories as defined in Appendix 1.

6.1.2. Pharmacokenetic Endpoints

All PK analysis will be performed on the PK analysis set (see Section 4).

Plasma samples will be collected as specified in the SoA of the protocol and analysed for PF-07242813.

The PK parameters detailed in the Table 2 will be calculated for PF-07242813 (if possible) from the concentration-time values using standard non-compartmental methods:

Table 2. Serum PK Parameters (Part 1)

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

Parameter	*Definition*	*Method of Determination*
$t_{1/2}$[a]	*Terminal elimination half-life*	$Log_e(2)/k_{el}$, *where kel is the terminal phase rate constant calculated by a linear regression of the loglinear -concentration time- curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression*
CCI [redacted]	[redacted]	[redacted]
[redacted]		
[redacted]		τ [redacted]

a. If data permit.

The PK parameters in Table 2 will be listed and summarized for participants in the PK parameter analysis set. Missing values will be handled as detailed in Section 5.3.1. Each PK parameter will be summarized by dose and will include the set of summary statistics as specified in the table below.

Table 3. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last} , AUC_{inf}, $AUC\tau$, AUC(dn), C_{max}, C_{max}(dn), CCI [redacted]	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

There will be two summary tables presenting all PK parameters for SAD and MAD separately. They will include data from all cohorts and will be presented by dose. For the derivation of PK parameters, actual PK sampling times will be used.

To assess the relationship between the PK parameters and dose, dose normalized AUC_{inf}, AUC_{last} and C_{max} will be plotted against dose and SC or IV (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented and that data from all cohorts are presented on the plot but SAD, MAD SC and MAD IV will be identified with different symbols. The SAD and MAD groups will have corresponding placebo groups throughout, if applicable. The PK data from Japanese cohort will be summarized separately.

Supporting data from the estimation of $t_{½}$ will be listed where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. These data may be included in the clinical study report.

Presentations for PF- 07242813 concentrations will include:

- A listing of all concentrations sorted by subject ID, cohort (SAD or MAD), dose and nominal time postdose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- A summary of concentrations by cohort, dose and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- Median concentrations time plots (on both linear and semi-log scales) against nominal time postdose by cohort and dose (all treatments on the same plot per scale, based on the summary of concentrations by cohort, dose and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by cohort and dose (all treatments on the same plot per scale, based on the summary of concentrations by cohort, dose and time postdose).

- Individual concentration time plots by cohort and dose (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each dose per scale).

- Individual concentration time plots by subject (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each subject (containing all doses) per scale].

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-07242813 concentration is quantifiable in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

CCI [redacted]

[redacted]

- CCI [redacted]

[redacted]

[redacted]

6.2. Part 2: Atopic Dermatitis Participants

6.2.1. Secondary Endpoint (s): Percentage Change from Baseline in EASI Score at Week 6

6.2.1.1. Main Analysis

- Estimand strategy: Estimand E1 (Section 3.1.2). This estimand is intended to provide an estimate of the treatment effect in the absence of prohibited medication use in a population that may or may not be fully compliant with the treatment.

- Analysis set: mITT (Section 4) using data prepared in the description of the Primary Estimand Continuous Endpoint Set.

- Analysis methodology: Percent change from baseline will be analyzed using an ANCOVA with the observed (or imputed) Week 6 percentage change from baseline EASI score as the dependent variable with treatment arm and baseline EASI score as the independent variables.

- Intercurrent events and missing data: Data after study drug discontinuation and prohibited medication will be excluded and set to missing. Missing data which will be multiply imputed using a control-based strategy as described in (Section 5.3.2). Hundred (100) imputed datasets will be used in the analysis and results combined using PROC MIANALYZE.

- The least-squares (LS) means, the 90% confidence interval for the LS means, the difference between the LS means for each pair of treatment groups, and the corresponding 90% confidence interval will be presented for percent change from baseline in EASI score.

CCI

CCI

[redacted]

6.2.4. Study Conduct and Participant Disposition

Subjects' evaluation, disposition and discontinuation will be summarized according to CaPS.

6.2.5. Study Treatment Exposure

The exposure to study drug will be summarized by the total number of days of dosing, mean/median number of days and number and percent of subjects in exposure duration categories.

6.2.6. Concomitant Medications and Nondrug Treatments

Prior drug and non-drug treatment, concomitant drug and non-drug treatment will be summarized according to CaPS.

6.2.7. Subset Analyses

No subset analyses are planned; however the impact of different baseline subgroups on the primary and key secondary endpoints may be explored on ad-hoc basis, and will not be reported in Clinical Study Report.

6.3. Safety Summaries and Analyses

The analysis population for safety is described in Section 4. Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs) and laboratory tests. A complete list of laboratory parameters can be obtained in Section 8.2.2.5 of the protocol.

All the tables, listings and graphs for adverse events, lab parameters and vital sign and ECG will follow Pfizer standards. The binary safety endpoints including the incidences of on-treatment AEs, withdrawals due to AEs and serious AEs will be analyzed using the exact test described in Section 5.2.2. A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers.

6.3.1. Adverse Events

All the tables, listings and graphs for adverse events, lab parameters and vital sign and ECG will follow Pfizer standards. The binary safety endpoints including the incidences of on-treatment AEs, withdrawals due to AEs and serious AEs will be analyzed using the exact test described in Section 5.2.2. A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers.

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan. There are no Tier 1 events for this study. Tier 1 displays will not be created.

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

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

For tier-2 events, the proportion of AEs observed in each treatment groups will be presented along with the point estimates and associated 95% confidence intervals of the risk difference for each active treatment compared with placebo using the exact methods described in Section 5. AEs will be arranged in the output sorted in descending point estimate of the risk difference within system organ class. Footnotes in the outputs will include the methods used to derive any p-values and confidence intervals as per Pfizer standards.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

6.3.2. Immune-based AEs

Immune-based adverse events will be summarized by visits. If ADA results are available, immune-based adverse events may be summarized by categories of ADA results (for example, by ADA positive, negative, and not-tested categories). Immune-based adverse events will include infusion and injection site reaction, and clinically evaluated results of anaphylaxis based on the Sampson's Criteria, and AEs based on the Anaphylactic Reaction Standardised MedDRA Query (SMQ), Angioedema SMQ, Hypersensitivity SMQ, cytokine storm, and delayed immune response.

6.3.3. Laboratory Data

Laboratory data will be listed and summarized in accordance with the CaPS reporting standards. Summaries of subjects meeting pre-specified monitoring and discontinuation criteria will be created using methods for categorical data.

6.3.4. Vital Signs

Vital signs will be summarized at baseline and all visits specified in SoA.

6.3.5. Electrocardiograms

ECG parameters, if applicable, will be summarized at baseline and all visits specified in SoA.

6.3.6. Physical Examination

Physical examinations may be summarized at baseline and all-available post-baseline visits.

7. INTERIM ANALYSES

7.1. Introduction

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

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

7.2. Interim Analyses and Summaries

NA.

8. REFERENCES

1. Casella G. Refining binomial confidence intervals. Can J Statist 1986; 14: 113–129.4.

2. Chan ISF and Zhang Z. Test based exact confidence intervals for the difference of two binomial proportions. *Biometrics*, 1999, **55**:1201–1209.

3. Mosteller RD (1987) Simplified calculation of body surface area. N Engl J Med 317 (17): 1098 (letter).

9. APPENDICES

Appendix 1. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

Absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤60	>60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Measurements that fulfill these criteria are to be listed in report.

Appendix 2. Summary of Efficacy Analyses

Efficacy Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model/Method
Week 6 PCFBL in EASI	Primary Analysis	mITT	MI	ANCOVA
All Visits IGA Response	Secondary Analysis	mITT	NRI	Chan and Zhang (1999)[2]
All Visits CFBL PP-NRS Response	Secondary Analysis	mITT	OD	MMRM
All Visits EASI – 75 Response	Secondary Analysis	mITT	NRI	Chan and Zhang (1999)[2]
CCI	[redacted]	[redacted]	[redacted]	[redacted]
	Main analysis	mITT	All data collected will be included regardless of intercurrent events. Missing data will be imputed.	ANCOVA
	CCI	[redacted]	[redacted]	[redacted]

PCFBL= Percent change from baseline; CFBL= Change from baseline; ANCOVA = Analysis of Covariance; OD = Observed data.

Appendix 3. Data Derivation Details

Appendix 3.1. Definition and Use of Visit Windows in Reporting

Visit windows will be used for efficacy variables (except change from baseline in pruritus NRS severity and frequency), and for any safety data (except the laboratory data) that display or summarize by study visit. For other endpoints (eg, ECG, vital signs, Physical Exam, Skin tolerability etc.), visit windows will be applied for summary statistics by study visits if required.

Visit No.	Visit Label	Target Day	Visit Window
	Screening	N/A	-42 ≤ day ≤-1
1	Baseline*	1	day = 1
2	Week 1	8	2 ≤ day ≤ 11
3	Week 2	15	12 ≤ day ≤22
4	Week 4	29	23 ≤ day ≤36
5	Week 6	43	37 ≤ day ≤50
6	Week 8	57	51 ≤ day ≤71
7	Week 12	85	72 ≤ day ≤99
8	Week 16	113	day ≥100
* Baseline analysis visit window may be considered as day ≤1 in some analyses (eg, those involving change from baseline). That is, in case that Day 1 observation is missing, the last observation by the first dosing date may be considered as the baseline. The baseline measurements for demography, height, pre-study medical history and medications will be collected at the "Screening" visit.			

If two or more visits fall into the same window, keep the one closest to the Target Day. If two visits are equaled distant from the Target Day in absolute value, the later visit should be used.

Appendix 3.2. Definition and Use of Visit Windows in pruritus NRS

Visit Label	Target Day	Visit Window
Baseline*	1	day = 1
Day 2	2	day = 2
Day 3	3	day = 3
Day 4	4	day = 4
Day 5	5	day = 5

Day 6	6	day = 6
Day 7	7	day = 7
Day 8	8	day = 8
Day 9	9	day = 9
Day 10	10	day = 10
Day 11	11	day = 11
Day 12	12	day = 12
Day 13	13	day = 13
Day 14	14	day = 14
Week 2	15	15 ≤ day ≤ 22
Week 4	29	23 ≤ day ≤ 36
Week 6	43	37 ≤ day ≤ 50
Week 8	57	51 ≤ day ≤ 71
Week 12	85	72 ≤ day ≤ 99
Week 16	113	day ≥100
* Baseline analysis visit window may be considered as day ≤1 in some analyses (eg, those involving change from baseline). That is, in case that Day 1 observation is missing, the last observation by the first dosing date may be considered as the baseline. The baseline measurements for demography, height, pre-study medical history and medications will be collected at the "Screening" visit.		

If two or more visits fall into the same window (only for Weeks 2, 4, 6, 8, 12, 16), keep the one closest to the Target Day. If two visits are equaled distant from the Target Day in absolute value, the later visit will be used.

Appendix 4. Eczema Area and Severity Index (EASI)

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

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

Clinical Sign Severity Scoring Criteria for the 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.

%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 (see table below). When measuring, the handprint unit refers to the size of each individual subject's hand with fingers in a closed position.

Handprint Determination of %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.

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 (see table below).

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 below.

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.

CCI

[redacted]

[redacted]

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

[redacted]

Appendix 5. Patient Reported Outcomes

Appendix 5.1. Peak Pruritis Numerical Severity Scale (PP-NRS)

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

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

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

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

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

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

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

[redacted]

CCI

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Total POEM Score (Maximum 28): _____

[redacted]

CCI

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

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

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

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

CCI [redacted]

```
libname c4461001  "/Volumes/app/…… /data_vai" ;


data ps;
        set c4461001.adps;
run;

data look;
        set ps;
        where param = "EASI02-Total Sum"  and viswin ne .;
        keep subjid param paramn avisit age sex trta viswin visit xviswin aval base chg pchg trtan;
run;

**example data for a single visit;
**created from systemic study ;
**ignore values, only used for illustration;

**data already has one record per subject per visit even if
**data is missing. Proc Mi needs missing values in order to impute;
data ex1;
        set look;
        where viswin = 9;
keep subjid dose  chg aval base;
run;


proc means data=ex1;
        class dose;
        var chg aval;
run;

proc sort data=ex1 out=ex2;
   *data must be sorted before using proc mi;
        by  dose;
run;

*imputing aval=observed so range of endpoint 0-72 can be included in;
*mi procedure;
proc mi data=ex2 seed=1022 nimpute=100 out=outimp max=72 min=0;
        class dose;
        monotone regpmm(aval= base/details k=5);

        mnar model( aval/modelobs = (dose="0"));
        var base   aval;
run;

proc univariate data=outimp;
var aval;
histogram ;
```

[redacted]

```
run;


data outimp1;
            set outimp;
            chg = aval - base;**calculate chg from baseline;
           pchg=(aval-base)/base*100; **calculate pchg from baseline;
run;
proc sort data = outimp1 out = outimp2;
   by _imputation_  dose subjid;
run;

proc mixed data=outimp2;
           by _imputation_;
           class dose(ref='0');
           model chg = base dose;
           lsmeans dose / diff alpha=.1;
           ods output diffs=diffs lsmeans=lsmeans;
run;

data diffsout;
            set diffs;
            **only keep within  contrasts vs placebo;
            where dose = 0;
run;

**now use mianalyze on lsmean differences;
**First sort by group,  and _dose (dose = 0 for all groups);
proc sort data=diffsout out=diffsout1;
           by  _dose _imputation_;
run;

**now mianalyze by  and _dose;
**NB mianalyze only uses estimates and standard errors not CI limits etc.;
proc mianalyze data=diffsout1  alpha=.1;  **specify alpha for 90% CIs here;
     by  _dose;
     modeleffects estimate;
     stderr stderr;
     ods output parameter
estimates=parameterestimates;
run;
```

CCI

[redacted]

CCI [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

Appendix 11. List of Abbreviations

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

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

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

Abbreviation	Term
IFN-α	Interferon alpha
CCI	[redacted]
IgE	immunoglobulin E
IgG	immunoglobulin G
IGRA	Interferon Gamma Release Assay
CCI	[redacted]
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IP-10	interferon-induced protein 10
IP manual	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWR	interactive Web-based response
LFT	liver function test
LLOQ	lower limit of quantification
JAK	Janus Kinase
LDL	low density lipoprotein
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
Mg	milligram
MMP12	Matrix metalloproteinase 12
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging
Msec	millisecond
MTX	methotrexate
N/A	not applicable
NOAEL	no-observed-adverse-effect level
NRS	Numerical Rating Scale
NTIS	Night time itch scale
CCI	[redacted]
PCD	primary completion date
PCP	primary care physician
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PG	polypropyle glycol

Abbreviation	Term
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PI	principal investigator
PK	pharmacokinetic(s)
CCI	[redacted]
PPD	Purified Protein Derivative
CCI	[redacted]
PR	pulse rate
PRO	Patient reported outcomes
CCI	[redacted]
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QFT-G	QuantiFERON-TB Gold Test
QFT-GIT	QuantiFERON-TB Gold In-tube Test
QT	Q wave interval
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
Qual	qualitative
QW	once a week
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
S Cystatin C	serum Cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SSID	subject study identification n
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TARC	thymus- and activation-regulated chemokine
TB	tuberculosis
TBili	total bilirubin
TdP	Torsade de Pointes
TEAE	treatment emergent adverse events
T_{max}	time taken to reach the maximum concentration
CCI	[redacted]
TYK2	Tyrosine Kinase 2

Abbreviation	Term
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
UVA	ultraviolet A light
CCI	[redacted]
UVB	ultraviolet B light
VZV	varicella zoster virus
WBC	white blood cell
WOCBP	woman of childbearing potential