Protocol C3941002

A PHASE 2A, RANDOMIZED, DOUBLE BLIND, VEHICLE CONTROLLED, PARALLEL GROUP STUDY TO ASSESS THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-07038124 OINTMENT FOR 6 WEEKS IN PARTICIPANTS WITH MILD TO MODERATE ATOPIC DERMATITIS OR PLAQUE PSORIASIS

Statistical Analysis Plan
(SAP)

Version: **2.0**

Date: 16 June2021

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APPENDICES

1. VERSION HISTORY

This SAP for Study C3941002 is based on the protocol dated 19 August 2020.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
Amendment	Section 3 Adding IGA/PGA response at other timepoints besides week 6 as secondary endpoint CCI [redacted]	Longitudinal profile of IGA/PGA response are of clinical importance CCI [redacted]
	Section 6.1.1 and 6.2.3.1 Data collected for subjects after early drug discontinuation will not be censored.	Estimand is irrespective of non-compliance.
	Section 6.1.1.1 and 6.2.3.1 Number of multiple imputation is changed from 100 to 1000	To increase the precision of variance estimate of the treatment effect based on multiple imputation
	Section 6.2.3 For ANCOVA analysis at week 6 for secondary endpoints, multiple imputation will be used for missing data.	To be consistent with primary endpoint analysis.

	Section 6.2.3 CCI [redacted]	

2. INTRODUCTION

PF-07038124 is a topical phosphodiesterase 4 (PDE4) inhibitor that is being investigated for the treatment of atopic dermatitis (AD) and plaque psoriasis (psoriasis).

The purpose of the study is to investigate the efficacy, safety, tolerability and pharmacokinetics of topical PF-07038124 in participants with mild to moderate AD or mild to moderate psoriasis. Participants will receive either PF-07038124 or a vehicle control for 6 weeks.

Phosphodiesterases (PDE) are a family of enzymes that breakdown the ubiquitous second messengers, cAMP and cyclic guanosine monophosphate (cGMP), that regulate various cellular processes. PDE4 is a subfamily that includes the four isozymes, each encoded by separate genes, PDE4 A, B, C and D. Inhibitors of the PDE4 family have been the focus of intense drug development over many years due to their broad potential in inflammatory diseases such as AD and psoriasis.

PF-07038124 is a potent and selective PDE4 inhibitor intended to be used for topical administration for the treatment of AD and psoriasis. PF-07038124 inhibits the enzymatic activity of the PDE4 isoforms that have been tested with a half maximal inhibitory concentration (IC_{50}) of 0.505 nM and 0.3 nM on PDE4B and PDE4D, respectively. PF-07038124 inhibits cytokine production and release from T cells and monocytes in peripheral blood mononuclear cells (PBMC) over a range of concentrations that is dependent on the cytokine that is being modulated. The IC_{50} for release of lipopolysaccharide (LPS) stimulated tumor necrosis factor (TNF) α is most sensitive with an IC_{50} of 0.15 nM. The IC_{50}'s for inhibition of interferon (IFN) γ, IL-4, and IL-13 from lectin stimulated PBMCs are 1, 4 and 135 nM, respectively. PF-07038124 exhibited greater inhibitory activity on IL-13 release than was seen with other PDE4 specific inhibitors, consistent with its inhibitory activity on additional PDEs, such as PDE3 at higher concentrations. PF-07038124 increased the level of cAMP in human PBMCs in a dose dependent manner, consistent with its primary mechanism of action as a PDE inhibitor.

An ex vivo human skin model of Th2 inflammation was used to measure the activity of PF-07038124 in its ointment formulation with topical application. This model has been used to test the activity of other topical therapeutic compounds, including topical [redacted]

corticosteroids, Janus kinase (JAK) inhibitors and the PDE4 inhibitor crisaborole (Eucrisa®). In this model system with a single dose application on excised human skin 20 hours prior to stimulation of the T cells in the skin tissue, PF-07038124 inhibited inflammatory cytokine gene expression at the dose strengths of 0.1, 0.06, 0.03 and 0.01%, with little to no activity at 0.001% strength relative to the vehicle (placebo) control.

Based on its cytokine inhibition profile, topical administration of PF-07038124 is anticipated to provide potential therapeutic benefit in the treatment of AD and psoriasis by targeting the T-helper-2 response cytokines and TNF-α.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3941002. 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

ATOPIC DERMATITIS		
Objectives	***Endpoints***	***Estimands***
Primary Objective	***Primary Endpoint***	***Primary Estimands***
• *To compare the efficacy of PF-07038124 versus vehicle on percent change from baseline in Eczema Area and Severity Index (EASI) in participants with mild or moderate atopic dermatitis (AD).*	• *Percent change from baseline in EASI total score at Week 6.*	• *Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the investigational product (IP) on a continuous endpoint; without the benefit of additional prohibited medications during treatment and regardless of participant compliance with the IP dosing.*
Secondary Objectives:	***Secondary Endpoints***	***Secondary Estimands***

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ATOPIC DERMATITIS		
Objectives	***Endpoints***	***Estimands***
• *To compare the efficacy of PF-07038124 versus vehicle, using Investigator's Global Assessment (IGA) score assessment as endpoint in participants with mild or moderate AD.*	• *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 study visit time points specified in the SoA.*	• *Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant compliance with the IP dosing.*
• *To compare the efficacy of PF-07038124 versus vehicle, using measures of disease severity and symptoms as endpoints in participants with mild or moderate AD.*	• *Proportion of participants achieving EASI 75 (75% improvement from baseline) at study visit time points specified in the SoA.*	• *Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant compliance with the IP dosing.*
• *To compare the efficacy of PF-07038124 versus vehicle, using measures of patient reported outcomes (PRO), in participants with mild or moderate AD.*	• *Proportion of participants having ≥4 points of reduction in weekly averages of Peak Pruritus Numerical Rating Scale (PP-NRS) from baseline at study visit time points specified in the SoA.*	• *Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless*

ATOPIC DERMATITIS		
Objectives	***Endpoints***	***Estimands***
		of a participant compliance with the IP dosing.
• *To compare the efficacy of PF-07038124 versus vehicle, on measures of disease and symptom severity in participants with mild or moderate AD.*	• *Change from baseline in EASI total score at study visit time points specified in the SoA.* • *Proportion of participants achieving IGA score of clear (0) or almost clear (1) at study visit time points specified in the SoA.* • *Percent change from baseline in affected Body Surface Area (BSA) at study visit time points specified in the SoA.*	• *All continuous secondary endpoints will be analyzed descriptively and using estimand E1 described above, when appropriate.* • *All categorical secondary endpoints will be analyzed descriptively and using estimand E2 described above, when appropriate.*
• *To characterize the safety and tolerability of PF-07038124 versus vehicle in participants with mild or moderate AD.*	• *Incidence of treatment emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in vital signs, electrocardiogram (ECG), and laboratory tests.* • *Incidence of severity grades in skin tolerability at times indicated in SoA.*	• *There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.*

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PSORIASIS		
Objectives	***Endpoints***	***Estimands***
Primary:	***Primary:***	***Primary:***
• *To compare the efficacy of PF-07038124 versus vehicle on change from baseline in Psoriasis Area and Severity Index (PASI) score in participants with mild to moderate plaque psoriasis.*	• *Change from baseline in PASI score at Week 6.*	• *Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the investigational product (IP) alone on a continuous endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.*
Secondary:	***Secondary:***	***Secondary:***
• *To compare the efficacy of PF-07038124 versus vehicle on Physician Global Assessment (PGA) score in participants with mild to moderate plaque psoriasis.*	• *Proportion of participants with PGA score clear (0) or almost clear (1) (on a 5-point scale) and ≥2 points improvement from baseline at Week 6* and *at study visit time points specified in the SoA.*	• *Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.*
• *To compare the efficacy of PF-07038124 versus vehicle on the proportion of participants with mild to*	• *Proportion of participants achieving PASI 75 (75% or greater improvement from baseline) at study visit time points specified in the SoA.*	• *Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder*

PSORIASIS		
Objectives	***Endpoints***	***Estimands***
moderate plaque psoriasis achieving PASI 75.		*endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.*
• *To compare the efficacy of PF-07038124 versus vehicle, using measures of patient reported outcomes (PRO), in participants with mild or moderate plaque psoriasis.*	• *Proportion of participants who achieved a Psoriasis Symptoms Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item at study visit time points specified in the SoA.*	• *Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.*
• *To compare the efficacy of PF-07038124 versus vehicle on measures of disease and symptom severity in participants with mild to moderate plaque psoriasis.*	• *Change from baseline in PASI scores at study visit time points specified in the SoA (except Week 6).* • *Percent change from baseline in PASI scores at study visit time points specified in the SoA.* • *Proportion of participants with PGA score clear (0) or almost clear improvement from baseline at time points specified in the SoA.* • *Percent change from baseline in BSA at study visit time points specified in the SoA.*	• *All other continuous secondary endpoints will be analyzed descriptively and using estimand E1 described above when appropriate.* • *All other categorical secondary endpoints will be analyzed descriptively and using estimand E2 described above when appropriate.*

PSORIASIS		
Objectives	***Endpoints***	***Estimands***
• *To assess safety and tolerability of PF-07038124 in participants with mild to moderate plaque psoriasis.*	• *Incidence of treatment emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in vital signs, electrocardiogram (ECG), and laboratory tests.* • *Incidence of severity grades in skin tolerability at times indicated in SoA.*	• *There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.*

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2.1.1. Primary Estimand(s)

The primary estimands of this study will use the treatment policy strategy and estimate the treatment difference without the benefit of additional prohibited medications during treatment and regardless of participant compliance with the IP dosing. This estimand (Estimand 1) for AD and Psoriasis are defined according to the primary objectives and are in alignment with the primary endpoints.

For AD, it includes the following 4 attributes:

- Population: Participants with mild or moderate AD as defined by the inclusion and exclusion criteria; without the benefit of receiving prohibited medications during treatment and regardless of compliance.

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

- Intercurrent event(s): A) Prohibited medication – all scores in participants who receive prohibited medication post randomization will be omitted from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the IP treatment. B) Withdrawal and all other events leading to missing data will be treated similarly assuming participants have efficacy values similar to control participants. C) Inadequate compliance – participants data will be used as recorded.

- Population-level summary: The percent change from baseline mean difference between treated and vehicle in EASI score.

For Psoriasis, it includes:

- Population: Patients with mild to moderate plaque psoriasis as defined by the inclusion and exclusion criteria of the study who do not take prohibited medications during treatment and regardless of compliance.

- Variable: Change from baseline PASI score at Week 6.

- Intercurrent events: A) Prohibited medication – all scores in participants who receive prohibited medication post randomization will be omitted from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the IP treatment. B) Withdrawal and all other events leading to missing data will be treated similarly as in A). C) Inadequate compliance – participants data will be used as recorded.

- Population-level summary: The mean difference between treated and vehicle control arms of the change from baseline PASI score.

2.1.2. Secondary Estimand(s)

Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant compliance with the IP dosing.

All continuous secondary endpoints will be analyzed descriptively and using estimand E1 described above, when appropriate.

All binary secondary endpoints will be analyzed descriptively and using estimand E2 described above, when appropriate.

- Population: Participants with mild or moderate AD or Psoriasis as defined by the inclusion and exclusion criteria; without the benefit of receiving prohibited medications during treatment and regardless of compliance.

- Variables: Proportion of participants achieving IGA score of clear (0) or almost clear (1) and a reduction from baseline of ≥2 points at Week 6 for AD; Proportion of participants with PGA score clear (0) or almost clear (1) (on a 5-point scale) and ≥2 points improvement from baseline at Week 6 for Psoriasis; and other categorical secondary endpoints.

- Inter-current Events: A) Prohibited medication – response will be considered negative for participants who receive prohibited medication post-randomization. B) Withdrawal and all other events leading to missing data will be treated similarly assuming that participants no longer receive benefit from the IP and hence will be treated as failure for endpoint above. C) Inadequate compliance – participants data will be used as recorded.

- Population level summary:

  The difference in proportions between IP treated and vehicle response rates.

2.1.3. Additional Estimand(s)

There is no defined estimand for other endpoints, and they will be analyzed using Pfizer data standards as applicable.

2.2. Study Design

This is a phase 2a, randomized, double blind, vehicle controlled, parallel group, multicenter study on the efficacy, safety, tolerability and PK of PF-07038124 0.01% QD versus vehicle control in the treatment of adult participants with mild to moderate AD or mild to moderate plaque psoriasis. In this study the efficacy of PF-07038124 ointment versus vehicle will be assessed in two different indications – there is a separate vehicle control group for each indication.

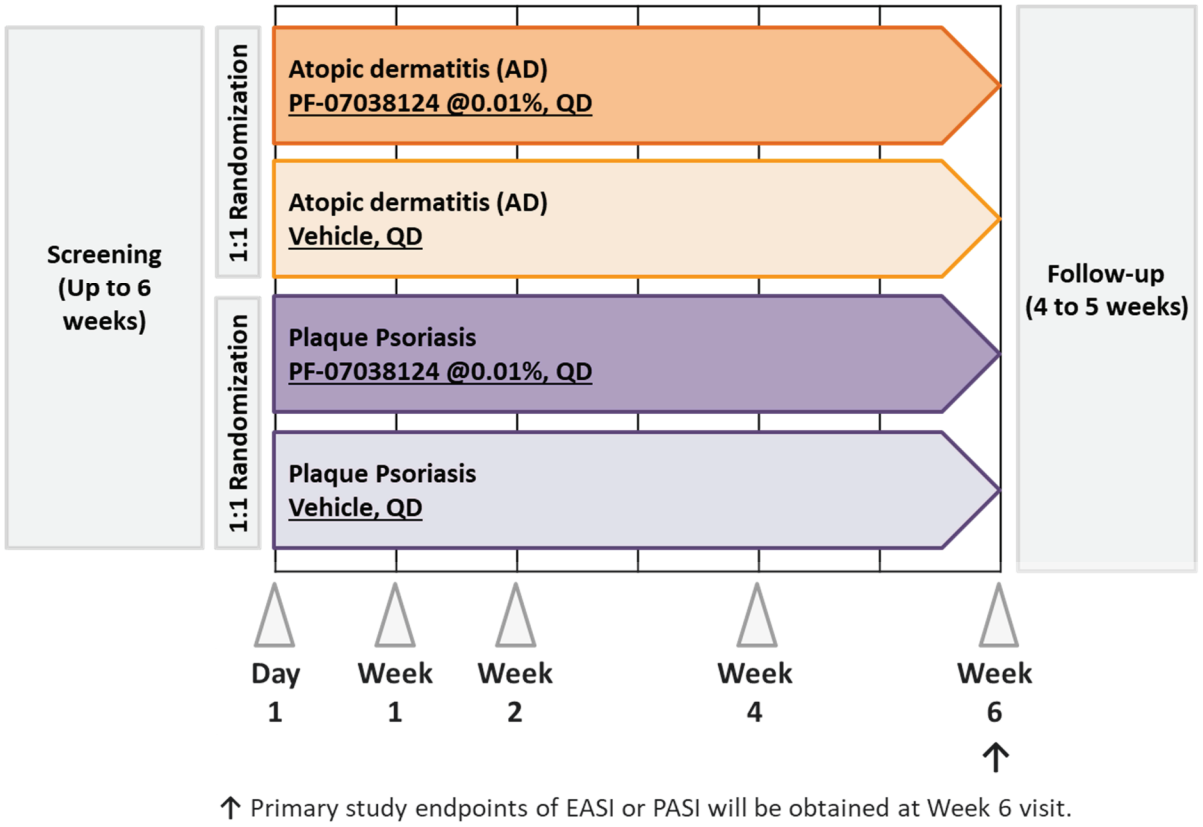
A total of approximately 88 participants with AD or psoriasis will be randomly assigned to study intervention in this basket trial design.

For AD, a maximum of approximately 56 participants will be randomly assigned to study intervention such that approximately 42 evaluable participants complete the study. Assuming a 25% drop out rate, approximately 28 participants will be randomized to either PF-07038124 or vehicle control to achieve approximately 21 completers in each group. Randomization will be stratified by baseline disease severity (mild [Investigator's Global Assessment or IGA = 2] vs. moderate [IGA = 3]). Up to 25% of AD participants will have an IGA score of 2 at baseline.

For psoriasis, a maximum of approximately 32 participants will be randomly assigned to study intervention such that approximately 24 evaluable participants complete the study. Assuming a 25% drop out rate, approximately 16 participants will be randomized to PF-07038124 or vehicle control to achieve 12 completers in each group. Randomization will be stratified by baseline disease severity (mild [Physician Global Assessment or PGA = 2] vs. moderate [PGA = 3]). Up to 25% of participants will have a PGA score of 2 at baseline.

The total duration of study participation will be approximately 17 weeks, including a screening period of up to 6 weeks, a double-blind, placebo-controlled treatment period of 6 weeks, and a safety follow-up period of 4-5 weeks from last dose of study drug to last study visit. The study intervention arms and duration for AD and psoriasis participants are the same.

Figure 1 Study Design Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- *Percent change from baseline in EASI total score at Week 6* (see Protocol Section 3.1). The baseline will be defined as the EASI total score on Day 1 predose.

- *Change from baseline in PASI score at Week 6* (see Protocol Section 3.2). The baseline will be defined as PASI score on Day 1 predose.

3.2. Secondary Endpoint(s)

For AD:

- *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 study visit time points specified in the SoA.*
- *Proportion of participants achieving EASI 75 (75% improvement from baseline) at study visit time points specified in the SoA.*
- *Proportion of participants having ≥4 points of reduction in weekly averages of Peak Pruritus Numerical Rating Scale (PP-NRS) from baseline at study visit time points specified in the SoA.*
- *Change from baseline in EASI total score at study visit time points specified in the SoA.*
- *Proportion of participants achieving IGA score of clear (0) or almost clear (1) at study visit time points specified in the SoA.*
- *Percent change from baseline in affected Body Surface Area (BSA) at study visit time points specified in the SoA.*
- *Incidence of treatment emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in vital signs, electrocardiogram (ECG), and laboratory tests.*
- *Incidence of severity grades in skin tolerability at times indicated in SoA.*

For Psoriasis:

- *Proportion of participants with PGA score clear (0) or almost clear (1) (on a 5-point scale) and ≥2 points improvement from baseline at Week 6 and other study visit time points specified in the SoA.*
- *Proportion of participants achieving PASI 75 (75% or greater improvement from baseline) at study visit time points specified in the SoA.*

- *Proportion of participants who achieved a Psoriasis Symptoms Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item at study visit time points specified in the SoA.*
- *Change from baseline in PASI scores at study visit time points specified in the SoA (except Week 6).*
- *Percent change from baseline in PASI scores at study visit time points specified in the SoA.*
- *Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement from baseline at time points specified in the SoA.*
- *Percent change from baseline in BSA at study visit time points specified in the SoA.*
- *Incidence of treatment emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in vital signs, electrocardiogram (ECG), and laboratory tests.*
- *Incidence of severity grades in skin tolerability at times indicated in SoA.*

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3.4. Baseline Variables

In general, for all analyses, baseline will be defined based on observations collected prior to first dose. Baseline values for demographics and hight 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 the last measurement before first dose on Day 1. If a value is missing on Day 1, then the last available observation

before Day 1 will be used. For the PP-NRS score, baseline will be defined as the average of all values recorded between Day -7 and Day -1.

3.5. 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).

3.5.1. 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.

3.5.2. Laboratory Data

The laboratory tests will be performed at time points identified in the Schedule of Activities. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns at the investigator's discretion.

3.5.3. Vital Sign

Vital signs (blood pressure, pulse, and oral or tympanic temperature) will be measured after a minimum of 5 minutes rest as indicated in the Schedule of Activities.

3.5.4. Electrocardiograms

Single 12-lead ECGs should be collected at times specified in the Schedule of Activities.

The baseline ECG values (the last measurement prior to receive study treatment on Day 1) will serve as each subject's baseline values.

Only categorical summaries of the ECG data according to sponsor data standard will be provided.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Population	Description
Modified Intention to Treat (mITT) or Full Analysis Set (FAS)	*All participants randomly assigned to IP and who apply at least 1 dose of IP.*
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Safety Analysis Set	*All participants randomly assigned to IP and who apply at least 1 dose of IP. Participants will be analyzed according to the product they actually have received.*

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis 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

Statistical inference will be made on the primary endpoints: (percentage change from baseline in EASI score at Week 6 and change from baseline in PASI score at Week 6). The null hypothesis is that there is no difference PF-07038124 its corresponding vehicle arm (ie, AD vehicle and Psoriasis vehicle). The alternative hypothesis is that the PF-07038124 arm being tested is superior to its

corresponding vehicle at Week 6 in AD and/or Psoriasis patients. The study will be considered positive for AD and/or Psoriasis, if either one or both null hypotheses are rejected.

The sample size calculation is based on the primary endpoint (percentage change from baseline in EASI score at Week 6). A total of 56 randomized participants in 1 treatment group and 1 vehicle group (28/arm) will provide approximately 90% power to detect a difference of 50 in percentage change from baseline with a common standard deviation 48% between PF-07038124 and a vehicle arm, controlling the two-sided error rate alpha 0.05. These calculations allow for a 25% dropout rate leaving 42 evaluable participants (21/arm).

For the key secondary endpoint, IGA response rate of clear or almost clear and ≥2 points improvement at Week 6, assuming 20% rate for vehicle and 55% rate for the treatment, this sample size provides 66% power controlling the two-sided error rate alpha 0.05.

The sample size is based on the primary efficacy endpoint, PASI change from baseline at Week 6. With an assumed standard deviation of 4.2 and treatment difference of 4.5, a total of 32 randomized participants in 2 treatment groups (16/arm) will provide approximately 80% power for the comparison of active versus vehicle group at a two-sided significance of 0.1. This calculation allows for an approximate 25% dropout rate, that is 12 participants evaluable per arm at Week 6, where evaluable is defined as included in the mITT set.

For the key secondary endpoint, PGA response rate of clear or almost clear and ≥2 points improvement at Week 6, assuming 20% rate for vehicle and 65% rate for the treatment, this sample size provides 61.9% power controlling the two-sided error rate alpha 0.05.

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

Landmark (cross-sectional) analyses of key binary endpoints will be analyzed by first treating missing data as non-responders and then applying Chan and Zhang's exact confidence interval (CI) method[1].

For all binary endpoints, a summary based on the mITT 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.

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5.2.2. Analyses for Continuous Endpoints

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, 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 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-07038124 treated group and the corresponding vehicle group will be derived from the model for AD and Psoriasis patients separately. 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 n, mean, median, standard deviation, minimum and maximum.

5.2.3. Analyses for Categorical Endpoints

NA.

5.2.4. Analyses for Time-to-Event Endpoints

NA.

5.3. Methods to Manage Missing Data

5.3.1. Efficacy Data

The primary analysis will use the primary estimand continuous endpoint set. For each landmark analysis (eg, cross sectional analysis by week) missing data, except missing due to COVID-19 pandemic, will be imputed using a control based imputation method. PROC

MI will first be called at the visit and a control based method (implemented with the 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.

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, except missing due to COVID-19 pandemic, will have been set to a non-responder. Summaries will use the Observed Efficacy Set and will report results on an observed case (OC) basis.

If a subject misses a visit due to COVID-19, he/she will be excluded from the analysis for that visit; If a subject discontinues treatment or withdraws from the study due to COVID-19, he/she will be excluded from the analyses after the treatment discontinuation visit or study withdrawal visit, respectively.

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6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Percentage Change from Baseline in EASI Score at Week 6 & Change from Baseline PASI Score at Week 6

6.1.1.1. Main Analysis

- Estimand strategy: Primary Estimand (Section 2.1.1). 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 full analysis set.
- Analysis methodology: Percent change from baseline will be analyzed using an ANCOVA with the observed (or imputed) Week 6 change from baseline EASI score as the dependent variable with treatment arm and baseline EASI score as the independent variables. Same method will be used for change from baseline PASI score at Week 6.
- Intercurrent events and missing data: Data 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). A thousand (1000) 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.

6.1.1.2. Sensitivity/Supplementary Analyses

Sensitivity Analyses:

- To assess the impact of baseline distribution, the main analysis will be repeated with the ANCOVA model replaced by an ANOVA model (excluding baseline as a covariate).

Supplementary Analyses:

- Mixed model repeated measures (MMRM) models will be used (assuming missing data are missing at random). The fixed effects of treatment, visit, and treatment by visit interaction will be included. Visit will be modeled as a categorical covariate.

6.2. Secondary Endpoint(s)

6.2.1. IGA/PGA Responses at Week 6

6.2.1.1. Main Analysis

- Estimand strategy: Secondary estimand (Section 2.1.2) use a composite endpoint strategy. 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 Secondary Estimand Categorical Endpoint Set.
- Analysis methodology: Risk differences will be analyzed using the method of Chan and Zhang (1999). Confidence Interval of binomial proportion will be reported using Blyth-Still-Casella method.
- Intercurrent events and missing data: These have been accounted for in the preparation of the Secondary Estimand Categorical Endpoint Set (Section 5.3). This prepared data set has no missing values.
- Proportions, risk differences and 90% confidence intervals will be presented.

6.2.2. Other Binary Secondary Endpoints

EASI 75, PP-NRS response Rate, IGA of clear or almost clear, PASI 75, PGA of clear or almost clear andPSI response rate will be analyzed the same way as described in Section 6.2.1.

6.2.3. Other Continuous Secondary Endpoints

Change from baseline EASI, Percent change from baseline in affected BSA (in AD patients), Change from baseline PASI (except Week 6), Percent change from baseline PASI, Percent change from baseline in affected BSA (in Psoriasis patients)

6.2.3.1. Main Analysis

- Estimand strategy: Primary Estimand (Section 2.1.1). 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 and absolute change from baseline at week 6 will be analyzed using an ANCOVA with the observed endpoint data as the dependent variable with treatment arm and baseline endpoint value as the independent variables.
- Intercurrent events and missing data: Data prohibited medication will be excluded and set to missing. For ANCOVA analysis at week 6, missing data which will be multiply imputed using a control-based strategy as described in (Section 5.3). A thousand (1000) 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.

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CCI [redacted]

6.5. Subset Analyses

There are no subset analyses are planned.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Demographic and baseline characteristics will be summarized by randomized treatment group for all randomized and treated subjects. Continuous variables will be summarized using mean and standard deviation. Categorical variables will be summarized using relative frequency. Key demographic and baseline variables to be summarized include: geographic region, age, gender, race, ethnicity, height, weight, body mass index, disease duration, baseline EASI score, baseline IGA, baseline PASI score, baseline PGA, baseline BSA score etc.

6.6.2. Study Conduct and Participant Disposition

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

6.6.3. Study Treatment Exposure

A summary of dosing compliance by treatment group will be provided.

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

6.6.4. Concomitant Medications and Nondrug Treatments

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

6.7. 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 8.2.5 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 5.2.1.

6.7.1. 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 5.2.1.

There will be no adjustment for multiple comparisons or stratification factors in the analyses unless specified. 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.

6.7.2. 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.

6.7.3. Vital Signs

Vital signs will be summarized at baseline, Weeks 2, 4, and 6/End of Treatment visits.

6.7.4. Electrocardiograms

Categorical summary tables will be summarized by treatment and time post-dose using sponsor reporting standards. Baseline is as defined in Section 3.5.4. A listing of ECG comments on findings and normal/abnormal results will be provided.

6.7.5. Physical Examination

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

7. INTERIM ANALYSES

No interim analyses are planned.

8. REFERENCES

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

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Efficacy Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Week 6 PCFBL in EASI / CFBL in PASI	Primary Analysis	FAS	MI	ANCOVA
PCFBL in EASI / CFBL in PASI	Sensitivity Analysis	FAS	OC	MMRM
Week 6 IGA / PGA Response	Secondary Analysis	FAS	NRI	Chan & Zhang
Week 6 CFBL in EASI / PCFBL in PASI / PCFBL in BSA	Secondary Analysis	FAS	MI	ANCOVA
EASI 75 / PP-NRS Rate / IGA of clear or almost clear / PASI 75 / PGA of clear or almost clear	Secondary Analysis	FAS	NRI	Chan & Zhang

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PCFBL= Percent change from baseline; CFBL= Change from baseline; ANCOVA = Analysis of Covariance; NRI = Non Responder Imputation; OC = Observed Cases.

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

Visit windows will be used for efficacy variables, and for any safety data that display or summarize by study visit. For other endpoints (e.g., ECG, vital signs), 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≤18
4	Week 3	22	19≤day≤25
5	Week 4	29	26≤day≤36
6	Week 6	43	37≤day≤57
7	FUP/EOS	N/A	day ≥58
* 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 before 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 equally distant from the Target Day in absolute value, the later visit should be used.

Appendix 3. Endpoint Derivations

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)		

[redacted]

[redacted]

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

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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.

Investigator's Global Assessment (IGA)

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

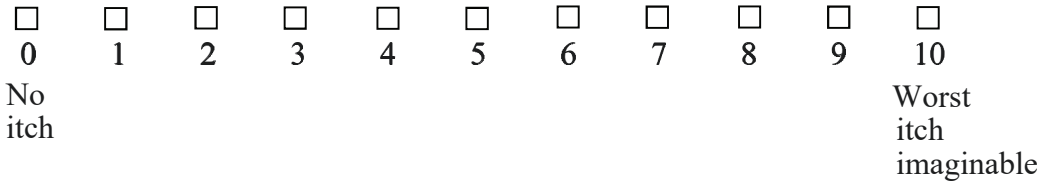
IGA Score

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.

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?



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[redacted]

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[redacted]

Psoriasis Area Severity Index (PASI)
The Psoriasis Area and Severity Index quantifies the severity of a subject's psoriasis based on both lesion severity and the percentage of body surface area affected. Lesion severity: the basic characteristics of psoriatic lesions - erythema, induration and scaling - provide a means for assessing the severity of lesions. Assessment of these three main signs is performed separately for four areas of the body: head, upper limbs, trunk, and lower limbs. Average erythema, induration and scaling are rated for each body area according to a 5-point scale: 0, no involvement; 1, slight; 2, moderate; 3, marked; 4, very marked.

Body surface area (BSA) involvement: the extent (%) to which each of the four areas of the body is affected by psoriasis is assigned a numerical score according to the following area scoring criteria: 0, no involvement; 1, >0 to 9%; 2, 10 to 29%; 3, 30 to 49%; 4, 50 to 69%; 5, 70 to 89%; 6, 90 to 100%. Details see Table 5 of the protocol.

Derivation of PASI score
In each area, the sum of the severity rating scores for erythema, induration and scaling is multiplied by the score representing the percentage of this area involved by psoriasis, multiplied by a weighting factor (head 0.1; upper limbs 0.2; trunk 0.3; lower limbs 0.4). The sum of the numbers obtained for each of the four body areas is the PASI.

PASI = 0Ah(Eh + Ih + Sh) + 0.2Au(Eu + Iu + Su) + 0.3At(Et + It + St) + 0.4Al(El + Il + Sl)

where A = area of involvement score; E = erythema; I =induration; S = scaling; h = head;
u = upper limbs; t = trunk; l = lower limbs

The PASI score can vary in increments of 0.1 units from 0.0 to 72.0, with higher scores representing increasing severity of psoriasis.

PASI C /75/CCI response
At least C /75/CCI % reduction in PASI relative to baseline PASI Score.

Body Surface Area (BSA)
Assessment of body surface area involved in psoriasis is performed separately for four areas of the body: head, upper limbs, trunk, and lower limbs. The percentage surface area affected by psoriasis is estimated by means of the "handprint method", where the full hand of the subject (ie, the subject's flat hand, thumb and fingers) represents approximately 1% of the total BSA2 and a set percentage of each of the four areas of the body:

- 1 handprint corresponds to approximately 10% of the head/neck;
- 1 handprint corresponds to approximately 5% of the arm/upper limbs;
- 1 handprint corresponds to approximately 3.3% of the trunk;
- 1 handprint corresponds to approximately 2.5% of the lower limbs.

The extent (%) to which each of the four areas of the body is affected is captured on the CRF (to 2 decimal places, as necessary). A weighting factor is applied to each of the four areas in calculation of the total body surface area affected: head x0.1; upper limbs x0.2; trunk x0.3; lower limbs x0.4, as the four areas correspond to approximately 10%, 20%, 30% and 40% of the total BSA, respectively. The sum of the weighted percent involvement obtained for each of the four body areas is the overall psoriatic BSA.

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.

Physician Global Assessment (PGA)

The Physician Global Assessment of psoriasis is scored on a 5-point scale, reflecting a global consideration of the erythema, induration and scaling across all psoriatic lesions. Average erythema, induration and scaling are rated separately over the whole body according to a 5-point severity scale, scored from 0 to 4, with appropriate morphologic descriptors. The severity rating scores are summed and the average taken - the total average is rounded to the nearest whole number score to determine the PGA. The 5-point scale for PGA is: 0, "clear"; 1, "almost clear"; 2, "mild"; 3, "moderate"; 4 "severe".

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Details on C-SSRS Mapping
Columbia-Classification Algorithm of Suicide Assessment (C-CASA)

Table 1. C-CASA Suicidality Events and Codes

Event Code	Event
1	Completed suicide
2	Suicide attempt
3	Preparatory acts towards imminent suicidal behavior
4	Suicidal ideation
5	Self-injurious behavior, intent unknown
6	Not enough information, fatal
7	Self-injurious behavior, no suicidal intent
8	Other, accident, psychiatric; mental
9	Not enough information, non fatal

* Note: Event Codes 5, 6, 8 and 9 are not applicable to prospectively collected data

Table 2. C-SSRS Mapped to C-CASA - Suicidality Events and Codes

C-CASA Event Code	C-CASA Event	C-SSRS Response
1	Completed suicide	As captured in the safety database
2	Suicide attempt	"Yes" on "Actual Attempt"
3	Preparatory acts towards imminent suicidal behavior	"Yes" on any of the following: • "Aborted attempt", or • "Interrupted attempt", or • "Preparatory Acts or Behavior"
4	Suicidal ideation	"Yes" on any of the following: • "Wish to be dead", or • "Non-Specific Active Suicidal Thoughts", or • "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act", or • "Active Suicidal Ideation with Some Intent to Act, without Specific Plan", or • "Active Suicidal Ideation with Specific Plan and Intent"
7	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?"

Appendix 4. Sample SAS Code for Estimand 1

```
libname c3941002  "/Volumes/app/…… /data_vai" ;

data ps;
        set c3941002.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 upcase(avisit)='WEEK 6';
regimen = "QD";
if trtan = 1 then dose=0;
if trtan = 2 then dose=0.01;
        keep subjid dose regimen chg aval base;

run;

proc means data=ex1;

        class regimen dose;

        var chg aval;

run;

proc sort data=ex1 out=ex2;

   *data must be sorted by regimen before usin proc mi;

        by regimen dose;

run;

*imputing aval=observed so range of endpoint 0-72 can be included in;

*mi procedure;

proc mi data=ex2 seed=1022 nimpute=1000 out=outimp  max=72 min=0;

        by regimen;

        class dose;
```

```
        monotone reg(aval= base/details);
        mnar model( aval/modelobs = (dose="0"));
        var base   aval;
run;
proc univariate data=outimp;
var aval;
histogram ;
run;
data outimp1;
        set outimp;
        chg = aval - base;**calculate chg from baseline
run;
proc sort data = outimp1 out = outimp2;
   by _imputation_ regimen dose subjid;
run;


proc mixed data=outimp2;
```

```
        by _imputation_;
        class dose regimen;
        model chg = base dose*regimen;
        lsmeans dose*regimen/ diff alpha=.1 ;
        ods output diffs=diffs lsmeans=lsmeans;
run;

data diffsout;
         set diffs;
         **only keep within regimen contrasts vs placebo;
         where regimen = _regimen and dose = 0;
run;
**now use mianalyze on lsmean differences;
**First sort by group, regimen and _dose (dose = 0 for all groups);
proc sort data=diffsout out=diffsout1;
         by regimen _dose _imputation_;
run;
```

```
**now mianalyze by regimen 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 regimen _dose;
     modeleffects estimate;
     stderr stderr;
     ods output parameterestimates=parameterestimates;
run;
```

Appendix 5. Sample SAS Code for Estimand 2 – Risk Difference using Chan and Zhang (1999)

PROC BINOMIAL DATA=<DATASET> GAMMA=0 ALPHA=<Value>;

PD/EX ONE STD;

PO <POPULATION VARIABLE>;

OU <OUTCOME VARIABLE>;

RUN;

Appendix 6. Sample SAS Code for the Confidence Interval of a Binomial Proportion (Blyth-Still-Casella)

PROC BINOMIAL DATA=<DATASET> ALPHA=<value>;

BI/BS;

OU <RESPONSE VARIABLE>;

RUN;

Appendix 7. Sample SAS Code for MMRM

```
proc mixed data=_dsnin order=internal alpha=0.1;
    by PARAMN;
    class SUBJID AVISITN TRTPN;
    model PCHG = BASE TRTPN AVISITN  TRTPN*AVISITN /solution ddfm=kr;
    repeated AVISITN/ subject =SUBJID type=un r rcorr; /**try UN first, if not converged, will use CS***/
    lsmeans TRTPN*AVISITN / diff cl alpha=0.1;
    ods output lsmeans=lsmeans diffs=diffs;
run;
/*For one-sided P-value calculation, the LOWER tail side should be used. */;
```

Appendix 8. 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
CCI	[redacted]
CCI	[redacted]
BCG	bacille Calmette-Guerin
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CAT	computerized axial tomography
CC	[redacted]
CD	Crohn's disease
CFR	Code of Federal Regulations

Abbreviation	Term
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CC [redacted]	[redacted]
CLIA	Clinical Laboratory Improvement Amendments
CCI [redacted]	[redacted]
CMV	Cytomegalovirus
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia suicide severity rating scale
CT	clinical trial
DILI	drug-induced liver injury
CCI [redacted]	[redacted]
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

Abbreviation	Term
EOT	end of treatment
ePRO	electronic patient reported outcome
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
F	bioavailibility
FDA	Federal Drug Administration
FSH	follicle-stimulating hormone
Fu	fraction unbound
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B visrus
HCVAb	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
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
IFN-α	Interferon alpha
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IgG	immunoglobulin G

Abbreviation	Term
IGRA	Interferon Gamma Release Assay
IL-	interleukin
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

Abbreviation	Term
NOAEL	no-observed-adverse-effect level
NRS	Numerical Rating Scale
NTIS	Night time itch scale
PASI	Psoriasis area and severity index
PCD	primary completion date
PCP	primary care physician
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PG	polypropyle glycol
CCI [redacted]	[redacted]
PI	principal investigator
PK	pharmacokinetic(s)
CCI [redacted]	[redacted]
PPD	Purified Protein Derivative
PP-NRS	Peak Pruritus Numerical Rating Scale
PR	pulse rate
PRO	Patient reported outcomes
PSAAD	Pruritis and Symptoms Assessment for Atopic Dermatitis
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

Abbreviation	Term
RBC	red blood cell
CCI	[redacted]
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
C CI	[redacted]
TB	tuberculosis
TBili	total bilirubin
TdP	Torsade de Pointes
TEAE	treatment emergent adverse events
CCI	[redacted]
TNF	tumor necrosis factor
TYK2	Tyrosine Kinase 2
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
UVA	ultraviolet A light
UVB	ultraviolet B light
VZV	varicella zoster virus
WBC	white blood cell

[redacted]

[redacted]

Abbreviation	Term
WOCBP	woman of childbearing potential