Protocol C2501004

A PHASE 2, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, STUDY TO EVALUATE THE SAFETY AND EFFICACY OF PF-06826647 IN PARTICIPANTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

Statistical Analysis Plan
(SAP)

Version: 3.0

Author: PPD

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version	Version Date	Specific Changes
1.0	18 Dec 2019	N/A
2.0	19 Jun 2020	• Section 4.5: has been added specifying COVID-19 data handling. • Section 6.2.4: the endpoint PP-NRS ≥4 has been removed. • Section 6.4: has been edited. • Appendix 2.1: visit windows has been adjusted. • Appendix 4: SAS codes have been adjusted.
3.0	29 Nov 2020	Changes were made per the planned analyses reduction on some Secondary CCI [redacted] • Section 2.1.2: removed the not applicable endpoints for Estimand E2. • Section 3.1.2: deleted the abosolute values for PP-NRS and PSI as the secondary endpoints, only kept change from baseline. • CCI [redacted] • Section 6.2.3: added the detailed analysis for change and percent change from baseline of PASI at Week 16. • Section 6.2.4 and Section 6.2.5: updated the analyses per the planned reduction. • Appendix 1: updated and corrected the summary of analyses for efficacy endpoints. Other changes: • Corrected some typos. • Appendix 2.1: added footnotes to clarify some special cases for Week 16 and Week 18, adjusted the Week 40 visit window, clarified the handling of multiple obsevations in a same window. • Appendix 2.3: deleted.

2. INTRODUCTION

PF-06826647 is a potent tyrosine kinase 2 (TYK2) inhibitor with a good selectivity profile over other human kinases and is being investigated in participants with plaque psoriasis. Based on its cytokine inhibition profile, PF-06826647 is expected to target the T-helper

1 (Th1), T-helper 17 (Th17), and Types I interferon signaling pathways directly by inhibiting TYK2. This should provide therapeutic benefit in the treatment of inflammatory conditions driven by Th1/Th17 and interferon immune responses.

The purpose of this multicenter, placebo controlled double blind study is to provide additional efficacy, safety, tolerability CCI *data regarding PF-06826647 in the oral treatment of moderate to severe plaque psoriasis. It is intended to enable dose selection for the future development of PF-06826647.*

The most common variant of psoriasis or plaque psoriasis, is a chronic inflammatory autoimmune skin disease characterized by red, scaly, raised plaques. Chronic plaque psoriasis is a common skin disorder with a worldwide prevalence of 2% and afflicts an estimated 7.4 million Americans. Although psoriasis primarily affects the skin and is not a life threatening disease, it can profoundly impact the patient's quality of life (QoL) resulting in impairment akin to other major diseases, such as diabetes, cardiovascular disease, and psoriatic arthritis.[1]

The Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3 and TYK2, is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for immune cell function, survival, activation, and proliferation. TYK2 pairs with JAK1 to mediate type I interferon (IFN) signaling and with JAK2 to transmit interleukin (IL) IL-12 and IL-23 signaling. Both of these key cytokines are implicated in the pathophysiology of plaque psoriasis. IL-12 and IL-23 require TYK2 for signal transduction, indicating that inhibition of TYK2 mediated signaling could be efficacious in the treatment of these inflammatory conditions.

Over activation of Th17 and the main effector cytokines of Th17 cells has been linked to various inflammatory diseases, including psoriasis (see the protocol) *Th17 cells are elevated in psoriatic lesions, along with levels of proinflammatory cytokines, including IL-17A, IL-17F, IL-17C, which are expressed by Th17 cells and are likely mediators of inflammation and tissue damage* (see the protocol). *Human genetic studies implicate the Th17 pathway in psoriasis, and have uncovered likely risk alleles which include genes involved in IL-23 signaling and genes that function downstream of the IL-17 receptor. In addition to genetic evidence, several effective psoriasis therapies target Th17 cytokine production, suggesting a central role of Th17 and IL-17 in the disease. The newest and most effective therapeutics are directed to the cytokines and cytokine signaling of interleukin-23/type 17 T cell (IL-23/T17) axis. Additionally, the TYK2-selective inhibitor, BMS-986165, recently showed efficacy in a Phase 2 psoriasis study. Thus, there is strong rationale for targeting the Th17 pathway in the treatment of psoriasis.*

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C2501004. 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	*Endpoints*	*Estimands*
Primary:	***Primary:***	***Primary:***
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 90.	• *Proportion of participants achieving PASI 90 (90% or greater improvement from Baseline) at Week 16.*	*Estimand E1:* *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 participant's compliance with the IP dosing.* *Population: Participants with moderate to severe plaque psoriasis as defined by the inclusion and exclusion criteria without the benefit of additional prohibited medication regardless of compliance.* *Intercurrent Events: A) Prohibited medication –response will be considered negative for participants after receiving prohibited medication. B) Withdrawal and all other events leading to missing data will be treated as in A). C) Inadequate compliance – participants data will be used as recorded.* *Population level summary: The difference in proportions between treated and placebo response rates.*
Secondary:	***Secondary:***	***Secondary:***
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 75.	*Key secondary endpoint:* • *Proportion of participants achieving PASI 75 (75% or greater improvement from Baseline) at time points specified in the Schedule of Activities (SoA).*	*The binary secondary endpoints, when appropriate, will be analyzed descriptively and using estimand E1.*
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on PGA score in participants with moderate to severe plaque psoriasis.	• *Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement from*	

Objectives	***Endpoints***	***Estimands***
	baseline at time points specified in the SoA. • *Proportion of participants with PGA score clear (0) or almost clear (1) at time points specified in the SoA.*	
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 50 and PASI 100.	• *Proportion of participants achieving PASI 50 (50% or greater improvement from Baseline), PASI 100 (100% from Baseline) at time points specified in the SoA.*	
To compare the efficacy of multiple dose levels of PF-06826647 versus placebo on PGA and PASI scores in participants with moderate to severe plaque psoriasis.	• *Change from baseline and percent change from baseline in PASI scores at 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 continuous endpoint; without the benefit of additional prohibited medications, regardless of participant's compliance with the IP dosing.* *Population: Participants with moderate to severe plaque psoriasis as defined by the inclusion and exclusion without the benefit of additional prohibited medications regardless of compliance.* *Intercurrent Events: A) Prohibited medication – all scores after participants receive prohibited medication 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.*

Objectives	***Endpoints***	***Estimands***
To compare the effect of multiple dose levels of PF-06822647 versus placebo in Peak-Pruritus Numerical Rating Scale score in participants with moderate to severe plaque psoriasis.	• *Absolute score and change from baseline in Peak-Pruritus Numerical Rating Scale score at time points specified in the SoA.*	*Population level summary:* *The mean difference between treated and placebo arms of the change from baseline PASI score.* *All continuous endpoint, when appropriate will be analyzed descriptively and using estimand E2 described above when appropriate.*
To assess the safety and tolerability of PF-06826647 in participants with moderate to severe plaque psoriasis.	• *Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events.* • *Change from baseline in clinical laboratory values (chemistry, hematology & lipids).* • *Incidence of clinically significant changes in ECG (heart rate, QT, QTc, PR and QRS intervals).* • *Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements).*	*There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.*
To compare the efficacy of multiple dose levels PF-06826647 versus placebo on measures of disease and symptom severity in participants with moderate to severe plaque psoriasis.	• *Absolute score and change from baseline Psoriasis Symptom Inventory at time points specified in the SoA.*	*This endpoints will be analyzed descriptively and using estimand E2 described above when appropriate.*
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Study Objectives, Endpoints and Estimands -- Extension Treatment Period

Objectives	*Endpoints*	*Estimands*
Primary:	***Primary:***	***Primary:***
To assess the safety and tolerability of PF-06826647 in participants with moderate to severe plaque psoriasis.	• *Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events.* • *Change from baseline in clinical laboratory values (chemistry, hematology & lipids).* • *Incidence of clinically significant changes in ECG (heart rate, QT, QTc, PR and QRS intervals).* • *Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements).*	*Not Applicable, will be analyzed descriptively and according to the Pfizer standard.*

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2.1.1. Primary Estimand(s)

The primary estimand will provide a population level estimate of the treatment effect of PF-06826647 on the proportion of participants with moderate to severe plaque psoriasis achieving PASI 90 (90% or greater improvement from Baseline) under the hypothetical scenario that prohibited medications are not used regardless of dosing compliance.

- Population: *Participants with moderate to severe plaque psoriasis as defined by the inclusion and exclusion criteria without the benefit of additional prohibited medication regardless of compliance.*

- Variable: *Proportion of participants achieving PASI 90 (90% or greater improvement from Baseline) at Week 16.*

- Intercurrent *events: A) Prohibited medication –response will be considered negative for participants after receiving prohibited medication. B) Withdrawal and all other events leading to missing data will be treated as in A). C) Inadequate compliance – participants data will be used as recorded.*

- Population-level summary: *The difference in proportions between treated and placebo response rates.*

The primary estimand strategy will be applied to the following secondary endpoints:

- Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement (daily and weekly) at time points specified in the SoA.
- Proportion of participants with PGA score clear (0) or almost clear (1) at time points specified in the SoA.
- Proportion of participants with PSI overall score ≤8 with 0 or 1 for every individual domain time points specified in the SoA.
- The primary estimand will also be used for PASI 75 response at all time points specified in the Schedule of Activities.

2.1.2. Secondary Estimand(s)

The secondary estimand will provide a population level estimate of the treatment effect of PF-06826647 on continuous endpoints, especially the change from baseline and the percent change from baseline in PASI scores under the hypothetical scenario that prohibited medication is not used regardless of dosing compliance.

- Population: *Participants with moderate to severe plaque psoriasis as defined by the inclusion and exclusion without the benefit of additional prohibited medications regardless of compliance.*
- Variable: Change from baseline or the percentage change from baseline in PASI at Week 16.
- *Intercurrent Events: A) Prohibited medication – all scores after participants receive prohibited medication 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 placebo arms of the change from baseline/percentage change from baseline PASI score.

2.1.3. Additional Estimand(s)

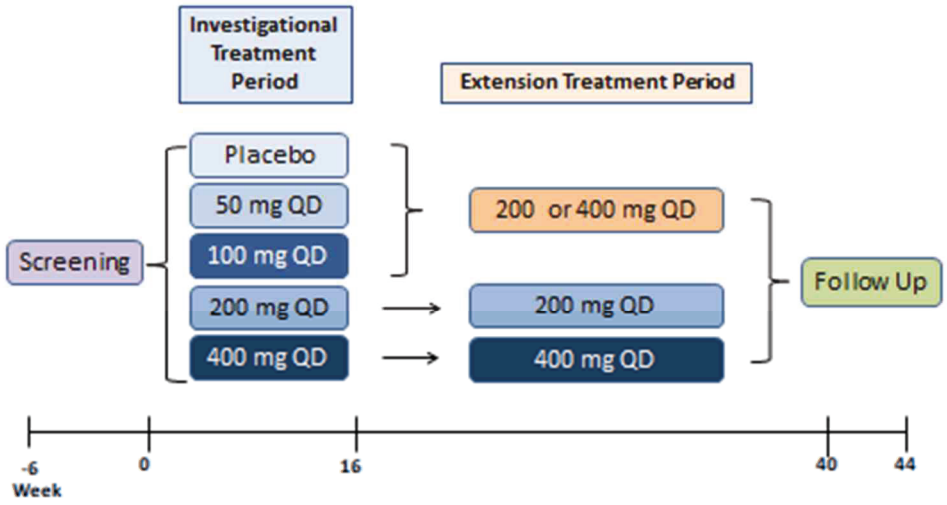
There is no defined estimand for other endpoints, and they will be analyzed using Pfizer data standards as applicable.

2.2. Study Design

This is a Phase 2b, randomized, double blind, placebo controlled, parallel group, multicenter study in participants with moderate to severe plaque psoriasis. After a screening period of - up to 6 weeks, eligible participants will be randomized in a 2:1:1:2:2 ratio such that participants will receive placebo or either one of four PF-06826647 daily dose levels (50 mg, 100 mg, 200 mg or 400 mg) every day during the Investigational Treatment Period for 16 weeks in a blinded fashion. All participants completing the 16 week Investigational Period will continue on to a 24 week non-placebo controlled Extension Treatment Period with double blind oral daily treatment, if per the Investigator judgment the participant is compliant with study procedures and continued participation presents no safety risks. The participants continuing into the Extension Treatment Period that were originally randomized to the 200 mg and 400 mg treatment groups will continue on their respective doses, while those randomized to one of the other treatment groups (including placebo) will be randomly assigned (at study baseline) to receive either 200 mg or 400 mg during the Extension Treatment Period. Participants who discontinue prior to Week 16 visit will enter the Follow-Up period and will not be eligible for the Extension Period.

Approximately 160 participants (40 participants in each of the following arms: placebo, 200 mg, and 400 mg; and 20 participants in each of the following arms: 50 mg and 100 mg) will be randomly assigned to a treatment group in order to ensure a minimum of 128 evaluable participants completing Week 16 (assuming a 20% dropout rate).

2.3. Schema



The total duration of study participation will be approximately 50 weeks, including up to 6 weeks Screening Period, 16 week Investigational Treatment Period, the 24 week Extension Treatment Period and a Follow-Up visit 4 weeks after the Extension Treatment Period.

Investigators, participants, and the sponsor study team (with the exception of the sponsor supply chain lead) will be blinded as to investigational drug.

If a participant is withdrawn from IP treatment, the participant will proceed with the Early Termination (ET) and Follow up visits per Schedule of Activities. If a participant uses prohibited medication, guidance in Section 10.8 of the protocol should be followed.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Investigational Treatment Period

3.1.1. Primary Endpoint(s)

- Proportion of participants achieving PASI 90 (90% or greater improvement from Baseline) at Week 16.

3.1.2. Secondary Endpoint(s)

- Proportion of participants achieving PASI 75 (75% or greater improvement from Baseline) at time points specified in the Schedule of Activities (SoA) of the protocol.
- 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.
- Proportion of participants with PGA score clear (0) or almost clear (1) at time points specified in the SoA.
- Proportion of participants achieving PASI 50 (50% or greater improvement from Baseline), PASI 100 (100% from Baseline) at time points specified in the SoA.
- Change from baseline and percent change from baseline in PASI scores at time points specified in the SoA.
- Change from baseline in Peak-Pruritus Numerical Rating Scale score at time points specified in the SoA.
- Proportion of participants with PSI overall score ≤8 with 0 or 1 for every individual domain time points specified in the SoA.
- Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events.
- Change from baseline in clinical laboratory values (chemistry, hematology & lipids).

- Incidence of clinically significant changes in ECG (heart rate, QT, QTc, PR and QRS intervals).

  Note: For heart rate, the clinically significant abnormal criteria are < 40 or > 120 beats per minute (bpm).

- Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements).

- Change from baseline Psoriasis Symptom Inventory at time points specified in the SoA.

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3.2. Extention Treatment Period

3.2.1. Primary Endpoint(s)

- Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events.
- Change from baseline in clinical laboratory values (chemistry, hematology & lipids).
- Incidence of clinically significant changes in ECG (heart rate, QT, QTc, PR and QRS intervals).
- Change from baseline in vital signs (blood pressure, pulse rate and temperature measurements).

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3.3. Baseline Variables

Baseline will be defined as the last available measurement prior to randomization on Day 1, if a Day 1 measurement is not available, the value from the Screening visit can be used. For the PRO endpoints baseline will be defined as the average of all values/values recorded on Day 1 or the last available screening vists when missing Day 1 measurement.

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 (after the first application of IP) 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 6.8.1).

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, uric acid, albumin, total protein, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides.

3.4.3. Vital Signs, including Height and Weight

Vital sign measurements are body temperature, pulse rate, and blood pressures.

Weight is collected at pre- and post-treatment.

3.4.4. Physical Examinations

Complete physical examinations consist of assessments of the general appearance, skin, head, eyes, ears, nose, throat,cardiovascular, respiratory (lung), gastrointestinal, and neurological systems.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

4.1. Full Analysis Set (FAS)

As specified in the protocol, the analysis of the efficacy, patient reported outcome CCI [redacted] endpoints will be performed for the modified intent-to-treat (mITT) population, defined as all randomized subjects who receive at least 1 dose of investigational product (PF-06826647 or placebo). This population is also called the Full Analysis Set (FAS).

4.2. Safety Analysis Set

The safety analysis set (SAS) will be all subjects who receive at least 1 dose of investigational product. The final safety database will include all reported safety data at the time of database release.

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4.4. Treatment Misallocations and Missing Data

If a subject was:

- Randomized but not treated: the subject will appear on the subject evaluation table as randomized but not treated; this is the extent of how much the subject will be reported;
- Treated but not randomized: the subject will be reported under the treatment they actually received for all safety analyses, but will not be included in the efficacy analyses;
- Randomized but took incorrect treatment: If a subject received the incorrect treatment for the whole duration of the study, then the subject will not be reported for any efficacy analysis, but will be summarized under the treatment they actually received for all safety analyses; if a subject received the incorrect treatment at only some dosing occasions then the subject will be reported under their randomized treatment group for both efficacy and safety analyses. If sufficient doses were incorrect and therefore deemed a major protocol deviation, the subjects may be excluded as sensitivity analysis.

For the continuous PRO variables such as pruritus NRS, CCI [redacted] rules suggested by the developers of these instruments will be followed in calculating the missing values. If these rules are not enough for imputing a value, then the missing values will be handled in the same way as non-PRO variables.

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
Full analysis set	All participants randomly assigned to IP and who apply at least 1 dose of IP.
CCI [redacted]	[redacted]
Safety	All participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. A randomized but not treated participant will be excluded from the safety analyses.

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 Categorical Endpoint Set	This set will include all patients in the mITT population. All data for a subject after the initiation of prohibited medications, withdrawl of either study drug or the study itself will be set to a failure. Any additional missing data will be recorded as a failure. Subjects will have either a success or failure in the dataset for all scheduled visits.
Secondary 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 secondary estimand requires multiple imputation which will be performed on this dataset, the multiple imputations themselves will not be saved in the database.
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.

4.5. Handling of Missing Data due to COVID-19 Pandemic

Due to the COVID-19 pandemic, as part of control measures some of the important endpoint data, such as PASI and PGA scores, are being collected via remote visit. If data are available for those visits, then those will be incorporated in the analysis; any incomplete data or missing data collected via remote visit will be removed from the primary analysis. Hence no non-responder imputation will be done on missing binary data collected via remote visit.

All participants that are discontinued due to COVID-19 will be removed from the primary and secondary efficacy endpoint analyses.

All missing data due to COVID-19 pandemic will be used 'as is' for the sensitivity analysis and the safety analysis.

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis will be performed when all randomized subjects have either completed their 16-week study participation period or withdrawn early or should the study be stopped prematurely due to any reason, and the database is released. *An interim analysis may be performed for making internal business decisions regarding future study planning. In that case, before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in the IRC charter.*

5.1. Hypotheses and Decision Rules

Statistical inference will be made on the primary endpoint: Proportion of participants achieving PASI 90 (90% or greater improvement from Baseline) at Week 16 based on an analysis of the Primary Estimand Endpoint Set. The global null hypothesis is that there is no difference between any arm of PF-06826647 and placebo arm. The alternative hypothesis is that one of the PF-06826647 arms being tested is superior to the placebo arm at Week 16. The study will be considered positive, if this null hypothesis is rejected.

Since test statistic corresponding to each of the PF-06826647 arms are indendepent with each others satisfying the distributional assumption about the use of Hochberg step-up procedure, the familywise error-rate will be controlled in strong sense at the 1-sided 0.05 level for these tests with a Hochberg step-up procedure (Hochberg, A sharper Bonferroni procedure for multiple significance testing 1988)[3] (Hochberg and Tamhane, Multiple Comparison Procedures 1987)[4] (Marcus, Peritz and Gabriel 1976). The p-values from the 3 comparisons will be ordered from smallest to largest, p[1], p[2], and p[3]. Testing will begin with the largest p-value, p[3], if significant at the 0.05 level that comparison and all other comparisions will be declared significant. If it is not significant, p[2] will be compared to an alpha of 0.05/2, if p[2] $\leq$0.05/2 it and all remaining hypotheses will be declared significant. If not significant, the process will continue using 0.05/3.

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

Landmark (cross-sectional) analyses of key binary endpoints will calculate and test for risk differences using the method of (Chan and Zhang 1999).[2] Covariates will not be included in the primary analyses. Risk differences and 90% confidence intervals will be presented.

For all key binary endpoints such as PASI75, PASI90 and PGA scores etc that are measured repeatedly over time, will be analyzed using generalized linear mixed effect model (GLMM) with treatment group (defined as factor variable), visit, treatment group by visit interaction and subjects as the random effect. An unstructured covariance matrix will be used to fit such model. In case, if the model fails to converge, a covariance structure such as compound symmetry or autoregressive model may be used. Bayesian information criterion (BIC) will be used to assess the goodness of fit of the models. The model with the smallest BIC will be selected for inference. P-values and inference for relative risks between treatments will be provided based on the link function of logit.

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.

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

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 (Weeks 1 2, 4, 6, 8, 12 and 16), 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-06826647 treated groups and placebo group 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 Efficacy Set by treatment group and will include the following: 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

The primary analysis will use the primary estimand binary 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. For continuous endpoint data, each landmark analysis (eg, Cross sectional analysis by week) missing data 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 (Missing Not At Random)--option) will impute missing placebo observations under the assumption data are missing at random (MAR) and impute missing treatment observations assuming they are similar to corresponding placebo patients. Imputation will use the full conditional specification (FCS) method, the imputed data for the placebo arm will be combined for the analysis.

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

6. ANALYSES AND SUMMARIES

Analysis will be done pairwise between each of the PF-06826647 treated groups and the placebo group. An analysis with point estimates of the difference, the associated 90% confidence intervals and p-values will also be reported.

A summary of analyses for clinical efficacy endpoints is provided in Appendix 1. Visit windows to be used for all efficacy analyses and some relevant safety analyses are detailed in Appendix 2.1.

6.1. Primary Endpoint(s)

6.1.1. Proportion of Participants Achieving PASI90 at Week 16

6.1.1.1. Main Analysis

- Estimand strategy: Primary Estimand (Section 2.1.1) 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 4.1) using data prepared in the description of the Primary Estimand Categorical Endpoint Set.

- Analysis methodology: Risk differences will be analyzed using the method of (Chan and Zhang 1999)[2] in PROC BINOMIAL.

- Intercurrent events and missing data: These have been accounted for in the preparation of the Primary Estimand Categorical Endpoint Set (Section 4.4). This prepared data set has no missing values.

- Proprotions, risk differences and 90% confidence intervals will be presented.

6.1.1.2. Sensitivity/Supplementary Analyses

- Estimand strategy: Primarily this estimand is intended to provide an estimate of the treatment effect in the population level assunming missing data are either MCAS (Missing Completely at Random) or MAR (Missing at Random). Applicable statistics will be calculated at Week 16.

- Population: mITT.

- Analysis methodology: GLMM and descriptive statistics.

- Missing Data: Observed Data.

6.2. Secondary Endpoint(s)

6.2.1. Proportion of Participants Achieving PASI75

6.2.1.1. Main Analysis

- Estimand strategy: Primary Estimand (Section 2.1.1) 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. Applicable statistics will be calculated at time points specified in the SoA.

- Analysis set: mITT (Section 4.1) using data prepared in the description of the Primary Estimand Categorical Endpoint Set.

- Analysis methodology: Risk differences will be analyzed using the method of (Chan and Zhang 1999)[2] in PROC BINOMIAL.

- Intercurrent events and missing data: These have been accounted for in the preparation of the Primary Estimand Categorical Endpoint Set (Section 4.4). This prepared data set has no missing values.

- Proprotions, risk differences and 90% confidence intervals will be presented.

6.2.1.2. Sensitivity/Supplementary Analysis

- Estimand strategy: Primarily this estimand is intended to provide an estimate of the treatment effect in the population level assunming missing data are either MCAS (Missing Completely at Random) or MAR (Missing at Random). Applicable statistics will be calculated at time points specified in the SoA.

- Population: mITT.
- Analysis methodology: GLMM and descriptive statistics.
- Missing Data: Observed Data.

6.2.2. Proportion of Participants with PGA 0/1, PGA 0/1 and ≥2 Points Improvements

6.2.2.1. Main Analysis

- Estimand strategy: Primary Estimand (Section 2.1.1) 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 4.1) using data prepared in the description of the Primary Estimand Categorical Endpoint Set.
- Analysis methodology: Risk differences will be analyzed using the method of (Chan and Zhang 1999)[2] in PROC BINOMIAL.
- Intercurrent events and missing data: These have been accounted for in the preparation of the Primary Estimand Categorical Endpoint Set (Section 4.4). This prepared data set has no missing values.
- Proprotions, risk differences and 90% confidence intervals will be presented.

6.2.2.2. Sensitivity/Supplementary Analysis

- Estimand strategy: Primarily this estimand is intended to provide an estimate of the treatment effect in the population level assunming missing data are either MCAS (Missing Completely at Random) or MAR (Missing at Random). Applicable statistics will be calculated at time points specified in the SoA.
- Population: mITT.
- Analysis methodology: GLMM and descriptive statistics.
- Missing Data: Observed Data.

6.2.3. Change and Percent Change From Baseline in PASI Score at Week 16

6.2.3.1. Main analysis

- Estimand strategy: Seconday 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 4.1) using data prepared in the description of the Seconday Estimand Continuous Endpoint Set.
- Analysis methodology: ANCOVA model with treatments arms and baseline score as dependent variable.
- Intercurrent events and missing data:These have been accounted for in the estimand (Section 2.1.2) and missing data will be imputed using a contro based imputation method (Section 5.3).
- Mean difference of change/percent change from baseline PASI score and 90% confidence intervals will be presented.

6.2.3.2. Sensitivity/Supplementary Analysis

- Estimand strategy: Primarily this estimand is intended to provide an estimate of the treatment effect in the population level assuming missing data are either MCAS (Missing Completely at Random) or MAR (Missing at Random). Applicable statistics will be calculated at time points specified in the SoA.
- Population: mITT.
- Analysis methodology: MMRM and descriptive statistics.
- Missing Data: Observed Data.

6.2.4. Secondary Endpoints: Continuous Data

Analyses of all continuous endpoints such as PASI, CCI PP-NRS, PSI, CCI [redacted] etc for their percentage change or absolute change from baseline or absolute values:

- Estimand strategy: Primarily this estimand is intended to provide an estimate of the treatment effect in the population level assuming missing data are either MCAS (Missing Completely at Random) or MAR (Missing at Random). Applicable statistics will be calculated at time points specified in the SoA.
- Population: mITT.
- Analysis methodology: MMRM and descriptive statistics.
- Missing Data: Observed Data.

6.2.5. Secondary Endpoint: Binary Data

Analyses of all binary endpoints such as PASI 50, PASI 75, PASI 90, PASI 100, PGA (0/1), PGA (0/1 and ≥2), CCI [redacted] PSI (≤8 and 0/1), CCI [redacted] for their proportions of participants will be as follows:

6.2.5.1. Main Analysis

- Estimand strategy: Primary estimand (Section 2.1.1) 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 4.1) using data prepared in the description of the Primary Estimand Categorical Endpoint Set.

- Analysis methodology: Risk differences will be analyzed using the method of (Chan and Zhang 1999)[2] in PROC BINOMIAL.

- Intercurrent events and missing data: These have been accounted for in the preparation of the Primary Estimand Categorical Endpoint Set (Section 4.4). This prepared data set has no missing values.

- Proprotions, risk differences and 90% confidence intervals will be presented.

6.2.5.2. Sensitivity/Supplementary Analyses

- Estimand strategy: Primarily this estimand is intended to provide an estimate of the treatment effect in the population level assunming missing data are either MCAS (Missing Completely at Random) or MAR (Missing at Random). Applicable statistics will be calculated at time points specified in the SoA.

- Population: mITT.

- Analysis methodology: GLMM and descriptive statistics.

- Missing Data: Observed Data.

6.3. Clinical Laboratory Values, ECG

The following endpoints will be summarized using available data and not modeled.

Change from baseline in clinical laboratory values, Change from baseline in ECG parameters (hear rate, QT, QTc, PR and QRS intervals). Estimand strategy: No estimand is applicable. Summary statistics will be calculated at time points specified in the SoA.

- Population: Safety Analysis Set.

- Analysis methodology: Summary statistics.

- Missing Data: Observed Data.

CCI [redacted]

6.5. Skin Biopsy

NA.

6.6. Subset Analyses

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

6.7. Baseline and Other Summaries and Analyses

6.7.1. 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: age, gender, race, ethnicity, height, weight, body mass index, disease duration, baseline PASI score, baseline PGA. CCI [redacted] etc.

6.7.2. Study Conduct and Participant Disposition

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

6.7.3. 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.

6.7.4. Concomitant Medications and Nondrug Treatments

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

6.8. Safety Summaries and Analyses

The analysis population for safety is described in Section 4.4. 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 10.2 of the protocol.

All the tables, listings and graphs for adverse events, lab parameters and vital sign and ECG will follow Pfizer standards.

6.8.1. Adverse Events

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. 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 are at least 4 subjects with an event in in any treatment group.

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

There will be no adjustment for multiple comparisons or stratification factors in the analyses unless specified. For tier-1 and 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 5.2.1. For tier-1 events p-values may be included in the presentations. 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.

6.8.2. Laboratory Data

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

6.8.3. Vital Signs

Vital signs will be summarized at all visits per SoA.

6.8.4. Electrocardiograms

ECG parameters, if applicable, will be summarized at baseline, Week 4, Week 16/End of Treatment visits and at Week 40.

6.8.5. Physical Examination

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

7. INTERIM ANALYSES

7.1. Introduction

There will be an interim analyses for this study. *Interim analyses will be performed to assess efficacy and safety after at least 60% of the planned participants, ie, approximately 80 participants, complete their study participation through Week 12. Interim analysis results will be used for internal business decisions regarding future study planning or stopping for futility. Before the interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in the internal review committee (IRC) charter.*

7.2. Interim Analyses and Summaries

A separate interim analysis plan may be developed, if needed.

8. REFERENCES

1. Casella G. Refining binomial confidence intervals. Can J Statist 1986; 14: 113–129.

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

3. Hochberg, Y. 1988. ". A sharper Bonferroni procedure for multiple significance testing." *Biometrika* 75: 800-802.

4. Hochberg, Y., and AC. Tamhane. 1987. *Multiple Comparison Procedures.* New Yrok: Wiley.

5. Marcus R, Peritz E, Gabriel KR. On closed testing procedure with special reference to ordered analysis of variance. *Biometrika*, 1976, **63**:655–660.

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Proportion of achieving PASI90 at Week 16	Main Analysis	FAS	Prohibited medication/withdrawal and all other missing data will be treated as tratment failure	Chan and Zhang
Binary endpoints for PASI 75, PASI 90, PGA (0/1 and ≥2), PGA (0/1) at all time points	Sensitivity/Supplementary Analysis	FAS	Observed data	GLMM
Binary endpoints for PASI 75, PASI 90, PGA (0/1 and ≥2), PGA (0/1), CCI [redacted] PSI (≤8 and 0/1), CCI [redacted]	Main Analysis	FAS	Prohibited medication/withdrawal and all other missing data will be treated as treatment failure	Chan and Zhang
Continuous endpoints for PASI	Main Analysis	FAS	Multiple Imputation	ANCOVA
Continuous endpoints for PASI, CCI [redacted] PP-NRS, PSI, CCI [redacted]	Sensitivity/ Supplementary Analysis	FAS	Observed data	MMRM

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.

Visit No.	Visit Label	Target Day	Visit Window[d]
1	Screening	N/A	-42 ≤ day ≤ -1
2	Baseline[a]	1	day = 1
3	Week 1	8	2≤day≤11
4	Week 2	15	12≤day≤21
5	Week 4	29	22≤day≤35
6	Week 6	43	36≤day≤49
7	Week 8	57	50≤day≤70
8	Week 12	85	71≤day≤98
9	Week 16[b]	118	99≤day≤ MIN (129, first dosing day at Week 18 -1)
10	Week 18[b]	127	MIN (129, first dosing day at Week 18 -1)+1≤day≤133
11	Week 20	141	134≤day≤154
12	Week 24	169	155≤day≤182
13	Week 28	197	183≤day≤210
14	Week 32	225	211≤day≤238
15	Week 36	253	239≤day≤266
16	Week 40[c]	281	267≤day≤305

a. 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.

b. If the nominal week 16 assessments happened at the same day as Week 18 dosing, for all the efficacy and safety endpoints analyses by visit, that day will be counted as Week 16 visit, but for the dosing and compliance analysis, that day will be counted as Week 18 visit.

c. For the last on treatment visit of Week 40, we extended the visit window to include more data collected in the study. And here day 305 is the day before the scheduled target day of follow-up visit (309±3).

d. For multiple observations fall into a same window, following algorithm will be takento identify the observation for analysis:

   1. The observation closest to the targeted day will be used.
   2. If the observations are with equal distant from the targeted day in absolute value, the one after the targeted day will be used.

   All observations will, however, be included in the listings.

Appendix 2.2. Endpoint Derivations

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%. For 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 50/75/90/100 response

At least 50/75/90/100% reduction in PASI relative to baseline PASI Score.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

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".

CCI [redacted]

[redacted]

[redacted]

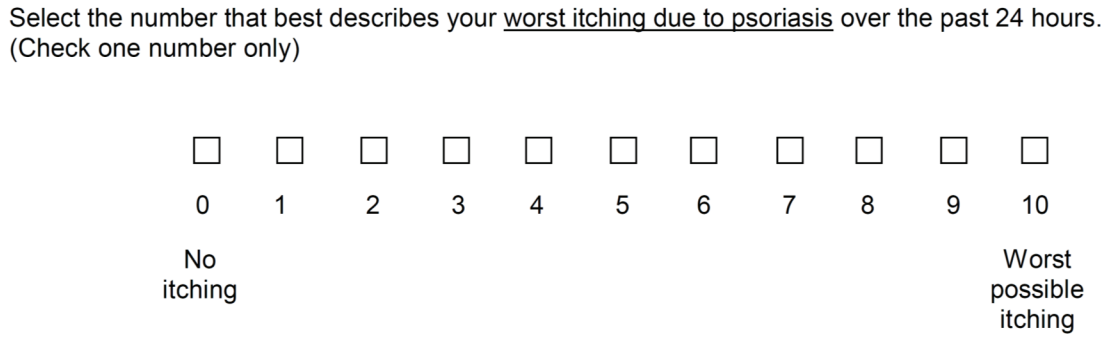
[redacted]

CCI [redacted]

CCI [redacted]

Peak Pruritus Numerical Rating Scale (PP-NRS)

The intensity of pruritus will be assessed by a numerical rating scale (NRS), an 11-category numeric rating scale from 0 to 10. Pruritus will be evaluated by asking participants to assign a numerical score representing the worst imaginable itch over the last 24 hours on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. This item will be administered to all participants.



CCI [redacted]

CCI

Appendix 3. Statistical Methodology Details

Hochberg Testing Procedure

Consider testing null hypotheses H01, …H06 and let pi, i=1,…,6 denote the corresponding 1-sided p-values from the individual pairwise comparisons against the placebo arm prior to multiplicity adjustment. Furthermore, let [1], ….[6] denote the order of the p-values so that p[1] ≤p[2] ≤…. P[6]. The procedure starts with the largest p-value p[6] as follows:

1. If p[6] < α reject all null hypotheses, otherwise go to next step.
2. If p[5] < α/2 reject hypotheses H0[1] through H0[6], otherwise go to next step.
3. If p[k] < α/(6-k +1), reject hypotheses H0[1] through H0[k].
4. If p[1] < α/6, reject H0[1], otherwise stop and do not reject any hypotheses.

Alternatively, the unadjusted raw p-values can be read into Proc Multtest and adjusted using the HOC option in SAS's PROC MULTTEST.

```
data pvals;
  Input Test$ Raw_P;
Datalines;
Test1 .xxxxx
Test2 .xxxxx
…..
Test6 .xxxxx
;
Proc multtest pdata=pvals hoc out=new;
run;
```

Appendix 4. SAS Code for Estimand 2 –Change from Baseline in PASI Score

```
libname C2501004  "/Volumes/app/…… /data_vai" ;

data adps;
set C2501004.adps;
if paramcd="PASI0246" and 2<avisitn<=9 and ANL01FL="Y" ;
keep subjid avisitn aval base trtan paramcd anl01fl;
run;

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

*Multiple Imputation;
**data already has one record per subject per visit even if;
**data is missing. Proc Mi needs missing values in order to impute;
data _data1;
set ADPS;
where avisitn=9;
run;

proc sort data=data1 out=data1 miss;
by trtan;
run;

*imputing aval=observed so range of endpoint 0-72 can be included in;
*mi procedure;
proc mi data=data1_miss seed=2501004 nimpute=1000 out=outimp;
class trtan;
monotone regpmm(aval= base/details k=5);
mnar model( aval/modelobs = (trtan="1"));
var base aval;
run;
proc univariate data=outimp;
var aval;
histogram;
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 = data1;
```

```
by imputation trtan usubjid;
run;


proc mixed data=data1 order=data;
by imputation;
class trtan;
model CHG = trtan base;
lsmeans trtan/ diff alpha=.1;
ods output lsmeans=mmmrm diffs=dmmrm(where=(trtan=1));
run;

**now use mianalyze on lsmean;
**First sort by trtan;
proc sort data=mmmrm out=lsout1;
by trtan _imputation_;
run;
**now mianalyze by trtan;
**NB mianalyze only uses estimates and standard errors not CI limits etc.;
proc mianalyze data=lsout1 alpha=.1;
**specify alpha for 90% CIs here;
by trtan;
modeleffects estimate;
stderr stderr;
ods output parameterestimates=lsmean;
run;
**now use mianalyze on lsmean differences;
**First sort by trtan;
proc sort data=dmmrm out=diffsout1;
by trtan _imputation_;
run;
**now mianalyze by trtan;
**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 trtan;
modeleffects estimate;
stderr stderr;
ods output parameterestimates=diff;
run;
```

Appendix 5. SAS Code for the Generalized Linear Mixed Model for Binary Longitudinal Data

```
PROC GLIMMIX DATA =<DATA>   METHOD=RMPL;
   CLASS SUBJID TRTPN VISIT;
   MODEL RESPONSE (EVENT = "1") = TRTPN VISIT TRTPN * VISIT / ALPHA = 0.1
DIST=BINARY LINK=LOGIT;
   RANDOM VISIT /SUBJECT = SUBJID TYPE=UN RESIDUAL;
   LSMEANS TRTPN * VISIT / ILINK COV DIFF CL;
RUN;
```

Appendix 6. SAS Code for Estimand 1 – Risk Difference using (Chan and Zhang 1999)[2]

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

PD/EX ONE STD;

PO <POPULATION VARIABLE>;

OU <OUTCOME VARIABLE>;

RUN;

Appendix 7. 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 8. List of Abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BA	bioavailability
BE	bioequivalence
BIC	Bayesian information criterion
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward
BP	blood pressure
BSA	Body Surface Area
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
CCI	[redacted]
DMC	data monitoring committee
EAC	event adjudication committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
FAS	full analysis set
FCS	full conditional specification
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLIMMIX	generalized linear mixed-effects model with repeated measures
GLMM	generalized linear mixed effect model
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HDL	high density lipoprotein
ICD	informed consent document
ICH	International Council for Harmonisation
IRC	internal review committee
IST	independent statistical team

Abbreviation	Term
ITT	intent-to-treat
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MCAS	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
MNAR	missing not at random
N/A	not applicable
NNB	number needed to benefit
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level
CCI	[redacted]
OC	observed case
PASI	Psoriasis Area Severity Index
PD	pharmacodynamic(s)
PGA	Physician Global Assessment
PK	pharmacokinetic(s)
CCI	[redacted]
PP	per-protocol
PPAS	per-protocol analysis set
PP-NRS	Peak Pruritus Numerical Rating Scale
PRO	patient-reported outcome
PT	preferred term
CCI	[redacted]
QoL	quality of life
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RCDC	reverse cumulative distribution curve
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SGS	Statistical Guidance Standards
SoA	schedule of activities

Abbreviation	Term
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TA	therapeutic area
TEAE	Treatment-Emergent Adverse Event
ULN	upper limit of normal
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary